Am J Surg Pathol , Volume 42, Number 3, March 2018

Clinicopathologic Features and Prognostic Impact of Lymph Node Involvement in Patients With Breast Implant-associated Anaplastic Large Cell Lymphoma

汇报人：许秀丽
指导教授：郭双平

BI-ALCL

- **Dfinition**： **This provisional entity is a T-cell lymphoma with morphological and immunophenotypic teatures indistinguishable from those of ALK-negative anaplastic large cell lymphoma (ALCL), arising primarily in assocaition with a breast implant.**
- **Prognosis: Most patients have excellent outcomes, often after excision alone. The median overall survival is 12 years.**

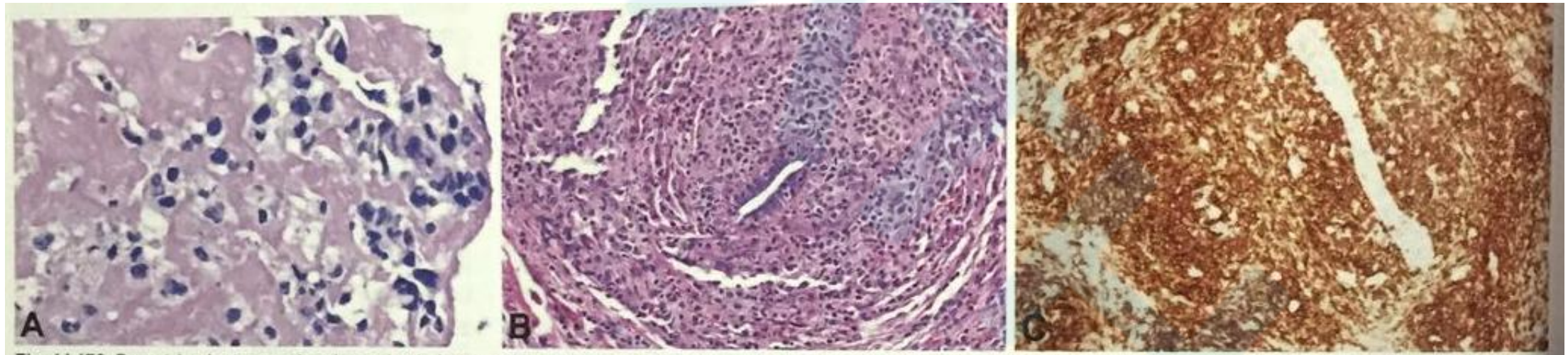


Fig. 14.176 Breast implant–associated anaplastic large cell lymphoma. **A** The tumour cells have pleomorphic nuclear features. This case had invasion of the capsule and underlying breast, shown in B and C. **B** Some tumours may show invasion of the breast, which is associated with a more aggressive clinical course. **C** Neoplastic cells with strong staining for CD30 surround a duct in the breast.

PURPOSE

- (1) describe the histopathologic features of lymph nodes involved by BI-ALCL;
- (2) determine the relationship between the depth of tumor infiltration into the fibrous capsule and LNI;
- (3) assess the prognostic importance of LNI by lymphoma in these patients.

MATERIALS AND METHODS

- Case Selection

  The clinical features of the **14** patients with BI-ALCL and LNI； **56** patients without LNI (control group).

- Pathologic Features

  BI-ALCL using previously defined criteria: lymphoma cells that were CD30+, anaplastic lymphoma kinase (ALK) negative and T-cell lineage

- Clinical Follow-up and Outcomes

RESULTS

TABLE 1. Clinical Characteristics of Patients With BI-ALCL and LNI (n = 14)

Case No.	References	Age (y)	Reason For Implants	Clinical Presentation	Extent of Periimplant Capsule Involvement	Timing of LNI*
1	Aladily[11]	63	Cancer	Effusion	Within	(+) 37
2	Alobeid et al[16]	68	Cancer	L axillary node	Within	(−) 5
3	Aladily[11]	57	Cosmetic	Effusion, mass	Beyond	Synchronous
4	Clemens et al[5]	52	Cosmetic	Mass	Beyond	Synchronous
5	Miranda et al[3]	40	Cosmetic	L axillary node	Beyond	(−) 36
6	George[17]	67	Cancer	Effusion	Within	(+) 6
7	Estes et al[18]	77	Cosmetic	Effusion, mass	Within	(+) 13
8	Miranda et al[3]	41	Cosmetic	Effusion, mass	Beyond	(+) 21
9	Unpublished	72	Cancer	Effusion, mass	Beyond	(+) 36
10	Clemens et al[5]	54	Cancer	Effusion, mass	Within	(+) 22
11	Acevedo-Banez et al[19]	50	Cancer	Mass	Beyond	Synchronous
12	Tardio and Granados[20]	51	Cancer	L axillary node, mass	Within	Synchronous
13	Laurent et al[21]	83	Cancer	Mass	Beyond	Synchronous
14	Unpublished	51	Cosmetic	R axillary node, mass	Beyond	Synchronous

Surgical therapy encompasses partial surgery, complete surgery.

*Timing of LNI:synchronous: LNI and periimplant capsule BI-ALCL diagnoses at the same time; (+ value): months after periimplant capsule diagnosis; (−value): months before periimplant capsule diagnosis.

†Clinical staging according to Clemens et al[5].

ASCT indicates autologous stem cell transplant; CR, complete remission; NA, not available.

- Partial information of 12 patients was included in earlier publications and 2 patients have not been reported previously (cases 9 and 14).
- The term "**capsule**" is defined as the fibrous tissue that develops around a breast implant.

TABLE 1. (*continued*)

Location of LNI	Clinical Stage Ann Arbor on Presentation	Clinical Stage MDACC† on Presentation	Management	Time Follow-up (mo)	Outcome	Cause of Death
Axilla	I	IB	Surgery, chemotherapy	100	CR	NA
Axilla bilateral	II	IIB	Surgery, chemotherapy	71	CR	NA
Supraclavicular, internal mammary	II	III	Surgery, chemotherapy, radiotherapy	100	CR	NA
Axilla, infraclavicular	II	III	Surgery, chemotherapy, radiotherapy	7	DOD	Mediastinal mass with bronchial compression
Axilla, supraclavicular, internal mammary, mediastinal, infraclavicular	II	III	Surgery, chemotherapy, radiotherapy, ASCT	100	CR	NA
Axilla, mediastinal, internal mammary	I	IB	Surgery, chemotherapy	14	CR	NA
Axilla	I	IB	Surgery, chemotherapy, radiotherapy	41	CR	NA
Axilla	I	IIA	Surgery, chemotherapy, radiotherapy	47	CR	NA
Axilla	I	IIA	Surgery	38	AWD	NA
Axilla	I	IIB	Surgery, chemotherapy	30	CR	NA
Axilla contralateral	IV	IV	Surgery, chemotherapy, radiotherapy	20	CR	NA
Axilla	II	IIB	Surgery, chemotherapy, radiotherapy	29	CR	NA
Axilla	II	III	Surgery, chemotherapy, immunotherapy	13	DOD	ALCL (manner of death not determined)
Axilla	II	III	Surgery, chemotherapy, radiotherapy	60	CR	NA

- **The median time of follow-up was 48 months (range, 7 to 100 mo).**
- **Outcome was available for all 14 patients: 11 (78.6%) achieved complete remission, 1 (7.1%) patient is alive with disease, and 2 (14.2%) died of BIALCL.**

TABLE 2. Clinical Characteristics of Patients With BI-ALCL and LNI (n = 14)

Age (y)	
Median	60
Range	40-83
	N (%)
Reason for implant (n = 14)	
Reconstructive for cancer	8 (57.1)
Cosmetic	6 (42.9)
Implant filling (n = 11)	
Silicone	8 (72.7)
Saline	2 (18.2)
Silicone/saline	1 (9.1)
Implant texture (n = 6)	
Yes	6 (100)
No	0
Time from implantation to diagnosis	
Median (y)	12
Range (y)	5-34
Side involved (n = 14)	
Left	3 (21.4)
Right	9 (64.3)
Bilateral	2 (14.3)
Clinical presentation (n = 14)	
Mass	10 (71.4)
Mass only	3 (21.4)
Mass+effusion	5 (35.7)
Mass+LNI	2 (14.3)
Effusion only	2 (14.3)
Enlarged lymph node	4 (28.6)
LNI+mass	2 (14.3)
Lymph node location (n = 14)	
Axillary	13 (92.9)
Axillary only	10 (71.4)
Axillary+infraclavicular	1 (7.1)
Axillary+mediastinal+internal mammary	1 (7.1)
Axillary+*	1 (7.1)
Supraclavicular, internal mammary	1 (7.1)
Timing of LNI (n = 14)	
At presentation	8 (57.1)
Metachronous	6 (42.9)
Ann Arbor stage at presentation (n = 14)	
I	6 (42.9)
II	7 (50.0)
III	0
IV	1 (7.1)
MDACC clinical stage at diagnosis (n = 14)	
IA	0
IB	3 (21.4)
IIA	2 (14.3)
IIB	3 (21.4)
III	5 (35.7)
IV	1 (7.1)
Extent of capsular involvement (n = 14)	
Within capsule	6 (42.9)
Beyond capsule	8 (57.1)
Outcome (n = 14)	
Complete remission	11 (78.6)
Dead of disease	2 (14.3)
Alive with disease	1 (7.1)
Cause of death (n = 2)	
ALCL related death	2
Bronchial compression	1 (50)
No details	1 (50)

*Axillary + supraclavicular, infraclavicular, internal mammary, and mediastinal.

TABLE 3. Pathologic Features of Patients With BI-ALCL and LNI (n = 14)

Case No.	References	Specimen Type	LN maximum Dimension (mm)	Tumor Burden (%)	Infiltration Pattern
1	Aladily[11]	Excision	20	70	S, P, I, D
2	Alobeid et al[16]	Excision	11.8	5	S, P, I
3	Aladily[11]	Excision	25	5	S, P, I
4	Clemens et al[5]	Dissection	40	60	S, P, I, D
5	Miranda et al[3]	Excision	17	5	HL-like
6	George[17]	Excision	8.9	30	S, P, I
7	Estes et al[18]	Excision	51	10	S
8	Miranda et al[3]	Dissection	13	30	S, I, D, NSHL-like
9	Unpublished	Excision	NA	1	S
10	Clemens et al[5]	Dissection	21	95	S, P, I, D
11	Acevedo-Banez et al[19]	Needle bx	12	20	S, I
12	Tardio and Granados[20]	Dissection	29	5	S, P, I
13	Laurent et al[21]	Dissection	25	10	S, I
14	Unpublished	Dissection	12	5	S, I

D indicates diffuse; I, interfollicular; NSHL-like, nodular sclerosis Hodgkin lymphoma-like; HL-like, Hodgkin lymphoma-like (excludes NSHL-like); LN, Lymph node; P, perifollicular; S, sinusoidal.

TABLE 3. *(continued)*

		Reactive features			
Cytomorphology	Hallmark Cells	Follicular Hyperplasia	Sinus Histiocytosis	Paracortical Hyperplasia	Eosinophils
Oval, lobated, anaplastic	Yes	Yes	Yes	Yes	Yes
Oval	No	Yes	No	Yes	Yes
Oval, lobated	Yes	Yes	No	No	Yes
Oval	No	Yes	Yes	No	Yes
Oval	No	Yes	Yes	Yes	Yes
Oval, anaplastic	Yes	Yes	Yes	No	Yes
Oval, lobated	Yes	Yes	Yes	No	Yes
Oval, lobated	No	Yes	Yes	Yes	Yes
Lobated	No	Yes	Yes	No	No
Oval, lobated	No	Yes	No	No	Yes
Oval, lobated	Yes	No	No	No	Yes
Lobated, anaplastic	Yes	Yes	Yes	Yes	No
Lobated	Yes	Yes	No	No	Yes
Oval	No	Yes	Yes	Yes	Yes

Tumor burden: percentage of tumor cells highlighted by CD30 divided by total cells in tissue sections.

TABLE 4. Pathologic Features of LNI of Patients With BI-ALCL (n = 14)

	N (%)
Specimen type	
Excisional biopsy	7 (50.0)
Lymph node dissection	6 (42.9)
Needle biopsy	1 (7.1)
Lymph node maximum dimension (n = 13)	
Median (mm)	23.6
Range (mm)	8.9-51
Lymphoma features	
Pattern of infiltration	
Sinusoidal	13 (92.9)
Perifollicular	7 (50.0)
Interfollicular	12 (85.7)
Diffuse	4 (28.6)
Hodgkin lymphoma like*	2 (14.3)
Tumor burden	
Median (%)	25
Range (%)	1-95
Cytomorphology	
Oval	13 (92.9)
Lobated	9 (64.3)
Anaplastic	5 (35.7)
Hallmark cells	7 (50.0)
Lymph node necrosis	5 (35.7)
Non-neoplastic features	
Follicular hyperplasia	13 (92.9)
Paracortical hyperplasia	5 (35.7)
Sinus histiocytosis	8 (57.1)
Eosinophils	13 (92.9)
Refringent material	1 (7.1)
Foamy histiocytes	1 (7.1)

*Hodgkin lymphoma-like: 1 nodular sclerosis HL-like, 1 mixed cellularity HL-like.

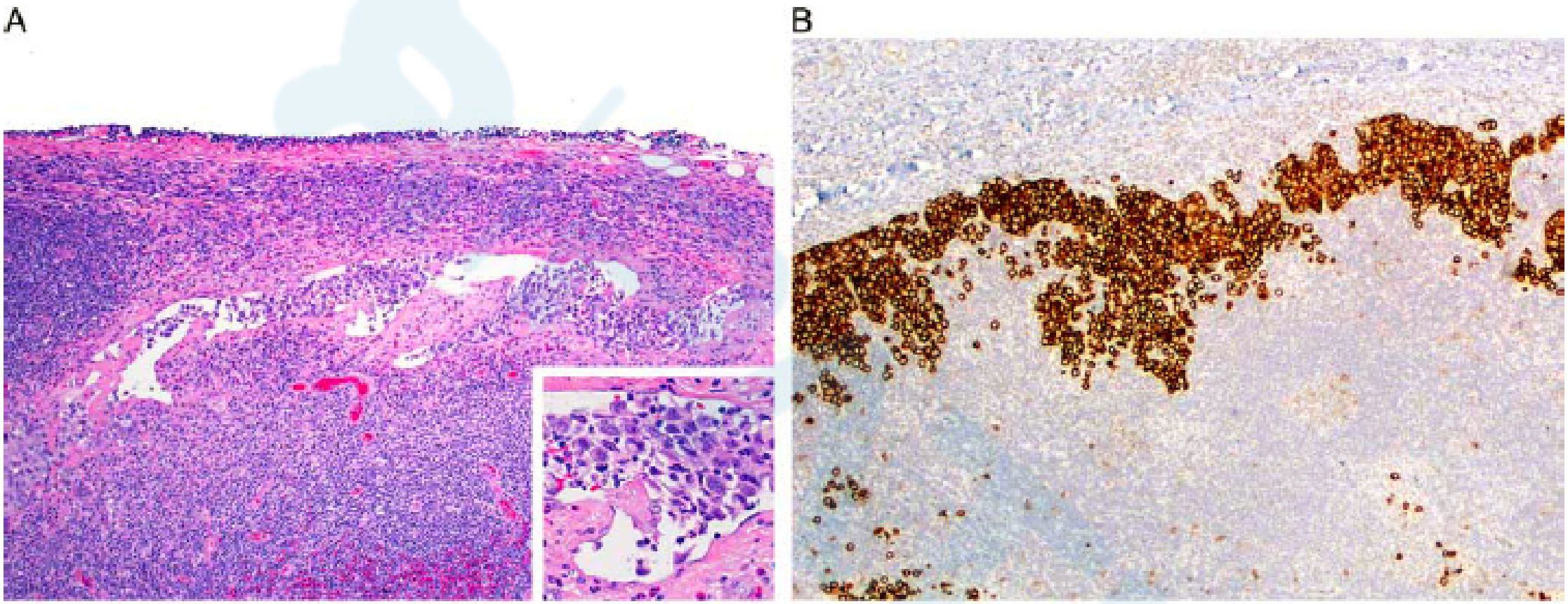
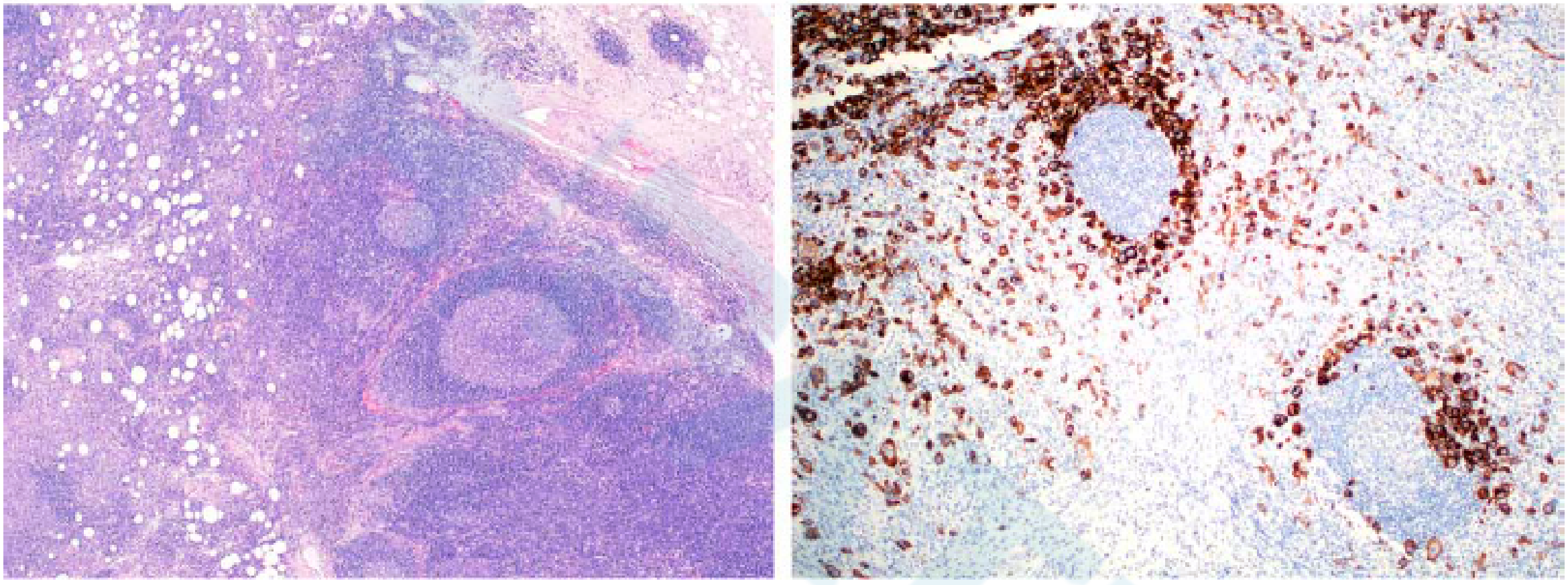
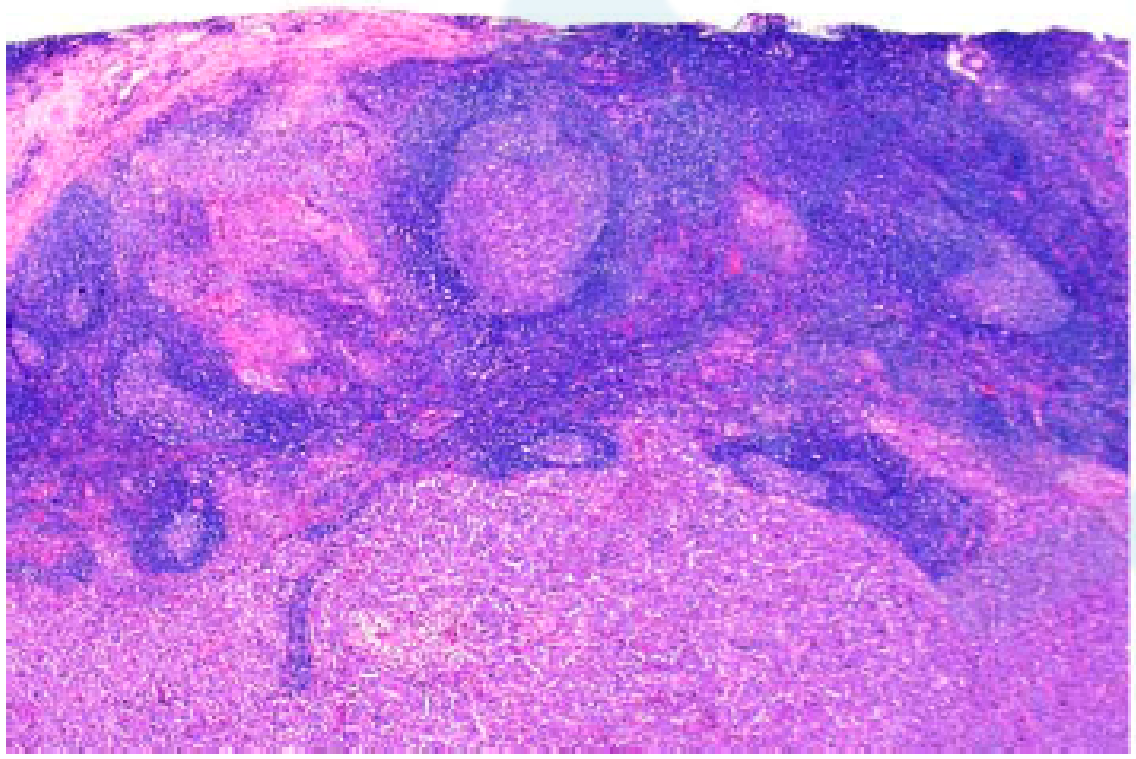


FIGURE 1. BI-ALCL: patterns of lymph node infiltration. A and B Sinusoidal pattern (case 7). A, A dilated subcapsular sinus of axillary lymph node contains clusters of lymphoma cells. Inset shows high magnification of cells within an open sinus (hematoxylin and eosin). B, Anti-CD30 immunohistochemistry with hematoxylin counterstain highlights the lymphoma cells within a dilated sinus.

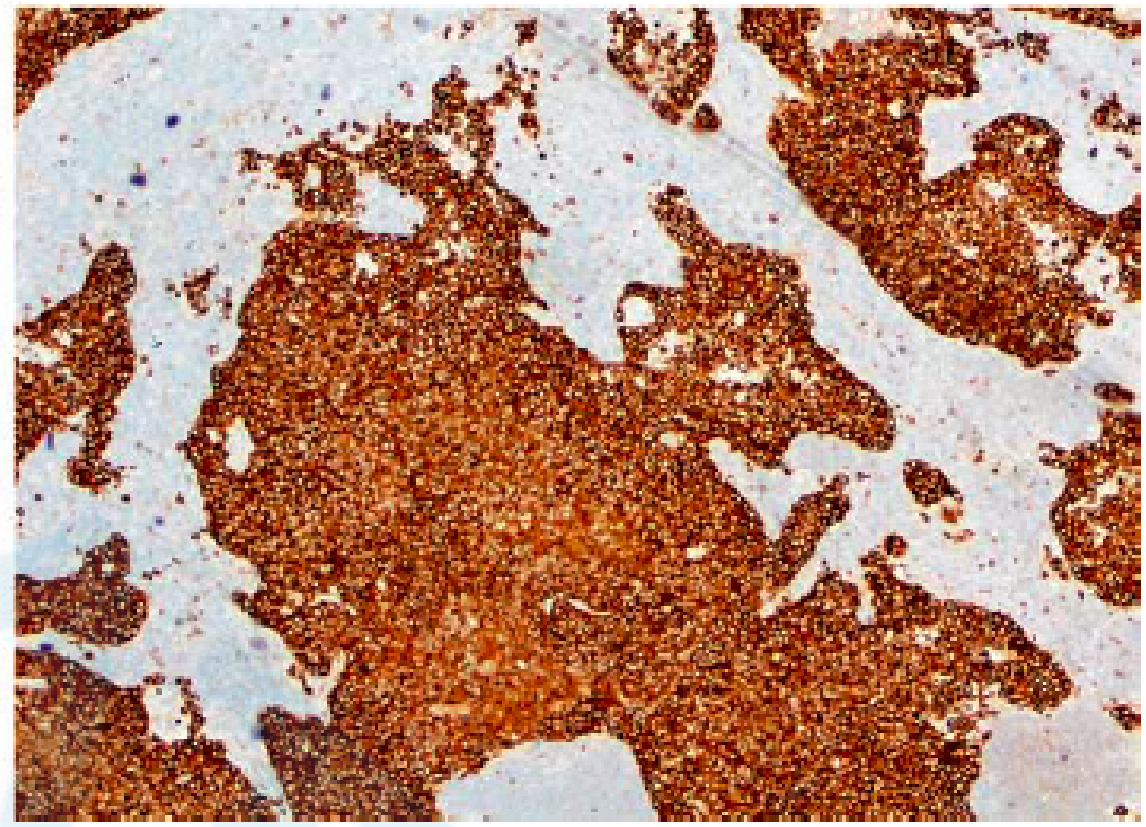


C and D, Perifollicular pattern (case 1). C, Lymph node displays hyperplastic lymphoid follicles partially surrounded by large lymphoma cells. D, The anti-CD30 immunohistochemistry highlights lymphoma cells around hyperplastic follicles (C, hematoxylin and eosin; D, anti-CD30 immunohistochemistry with hematoxylin counterstain)

E



F



E and F Diffuse pattern (case 10). E, The lymph node architecture is effaced by sheets of lymphoma cells (hematoxylin and eosin). F, Sheets of lymphoma cells are highlighted with anti-CD30 (anti-CD30 immunohistochemistry with hematoxylin counterstain).

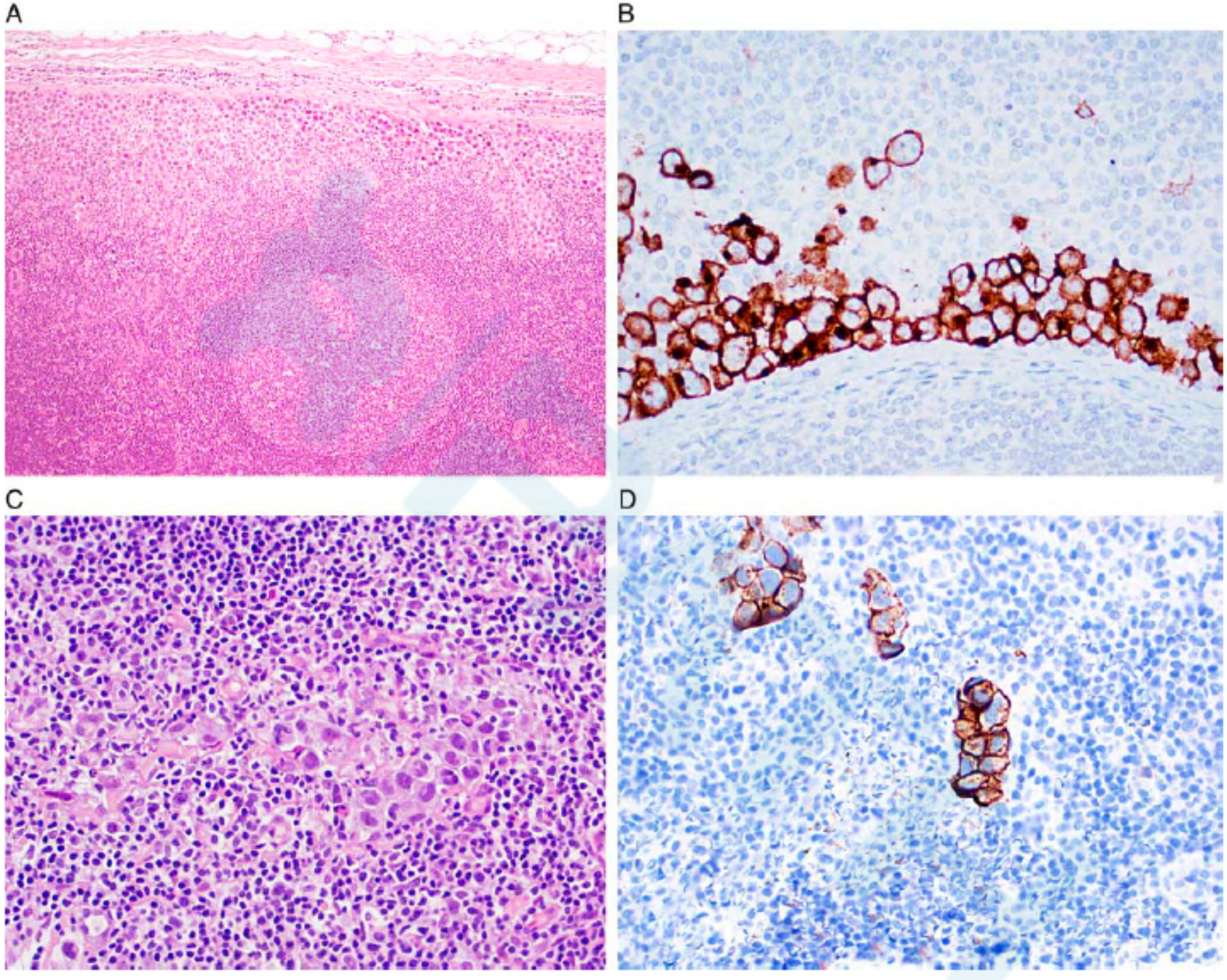


FIGURE 2. Cases of BI-ALCL with LNI with low tumor burden. A and B, **Case 2**. A, Lymph node with ~ 5% tumor burden involving the subcapsular sinus (hematoxylin and eosin). B, CD30 immunohistochemistry highlights lymphoma cells in the subcapsular sinus (anti-CD30 with hematoxylin counterstain). C and D, **Case 9**. C, 1% tumor burden in a sinusoidal pattern; only rare large cells are identified (hematoxylin and eosin). D, CD30 immunohistochemistry highlights scattered lymphoma cells with a sinusoidal pattern (anti-CD30 with hematoxylin counterstain).

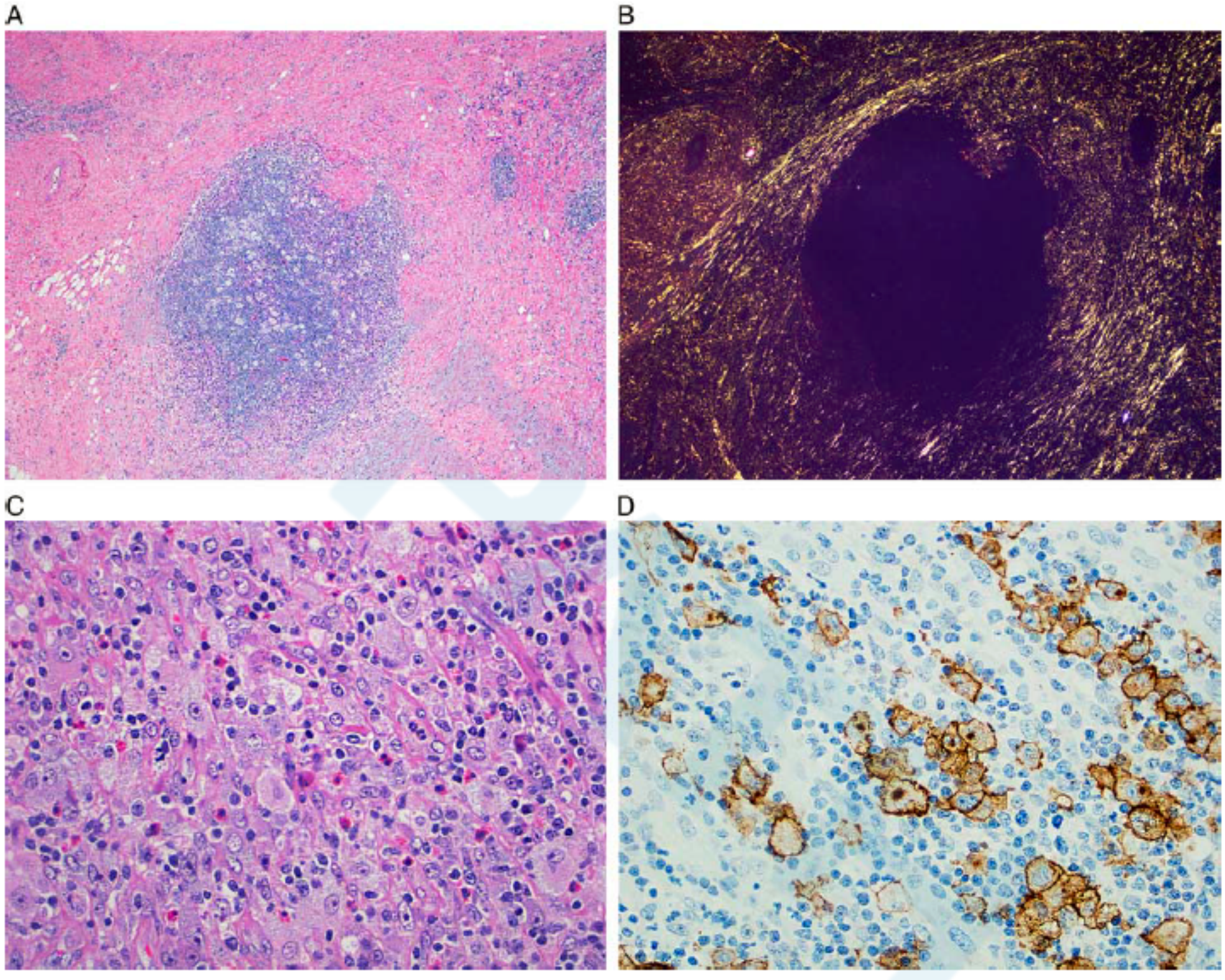


FIGURE 3. Nodular sclerosis Hodgkin lymphoma-like (NSHL-like) pattern (case 4). A, Lymphomatous nodule surrounded by sclerotic bands resembling NSHL (hematoxylin and eosin). B, The birefringent collagen is highlighted with polarized light. C, The cellular nodule is composed of a polymorphic infiltrate of small lymphocytes, histiocytes, eosinophils, and scattered large Hodgkin and Reed-Sternberg-like cells (hematoxylin and eosin). D, Immunohistochemistry for CD30 highlights the large neoplastic cells, mimicking CHL (anti-CD30 immunohistochemistry with hematoxylin counterstain).

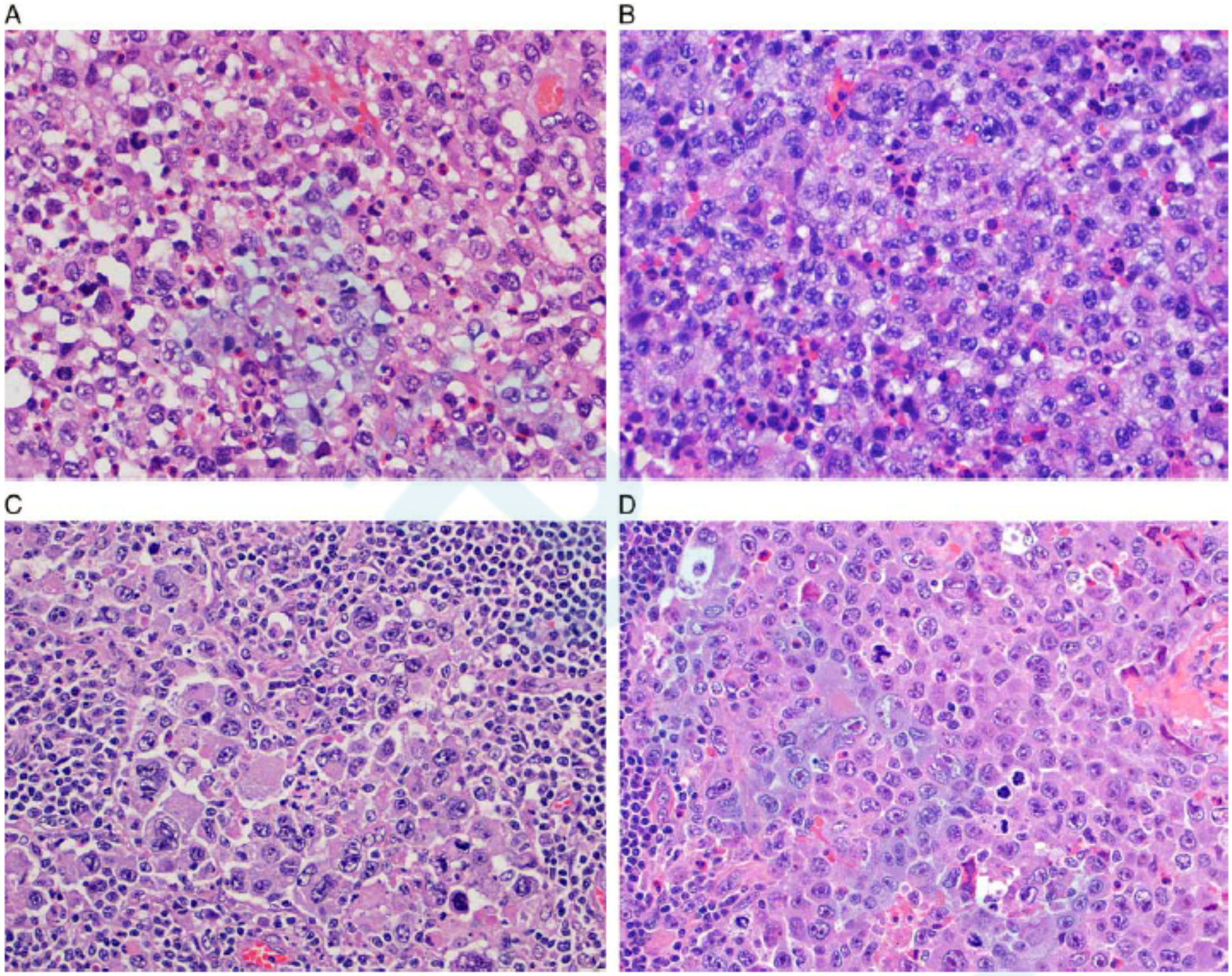


FIGURE 4. **BI-ALCL cytomorphology.** A, This case displays a predominance of cells with round to oval nuclei, vesicular chromatin and distinct nucleoli admixed with scattered eosinophils. B, This case displays a predominance of cells with lobulated nuclei, vesicular chromatin and irregular nuclear membrane with indentations. C, Most of the neoplastic cells are large and pleomorphic and have vesicular or hyperchromatic nuclei. D, This case illustrates a subset of lymphoma cells with cytomorphology of "hallmark cells" with nuclear indentations, abundant cytoplasm, and distinct paranuclear clearing (all figures stained with hematoxylin and eosin).

TABLE 5. Summary of the immunohistochemical and EBER Profile of BI-ALCL Cases With LNI (n = 14)

	(+) Cases (n [%])
CD2 (n = 7)	3 (42.9)
CD3 (n = 14)	0
CD4 (n = 13)	11 (84.6)
CD5 (n = 11)	2 (18)
CD7 (n = 9)	0
CD8 (n = 12)	1 (8.3)
CD15 (n = 9)	3 (33.3)
CD20 (n = 11)	0
CD30 (n = 14)	14 (100)
CD43 (n = 9)	8 (88.9)
CD45 (n = 11)	10 (90.9)
ALK (n = 14)	0
EBER (n = 9)	0
EMA (n = 7)	5 (71.4)
PAX5 (n = 6)	0

ALK indicates anaplastic lymphoma kinase; EBER, Epstein-Barr virus encoded RNA; EMA, epithelial membrane antigen; PAX5, paired-box protein 5.

- **The neoplastic cells were strongly positive for CD30 and were negative for ALK.**
- **All cases expressed at least 1 T-cell antigen including CD2, CD4, CD5, or CD43, but were negative for CD3.**
- **All tested cases were negative for CD20 (n = 11), PAX5 (n = 6), and Epstein-Barr virus encoded RNA (n = 11).**

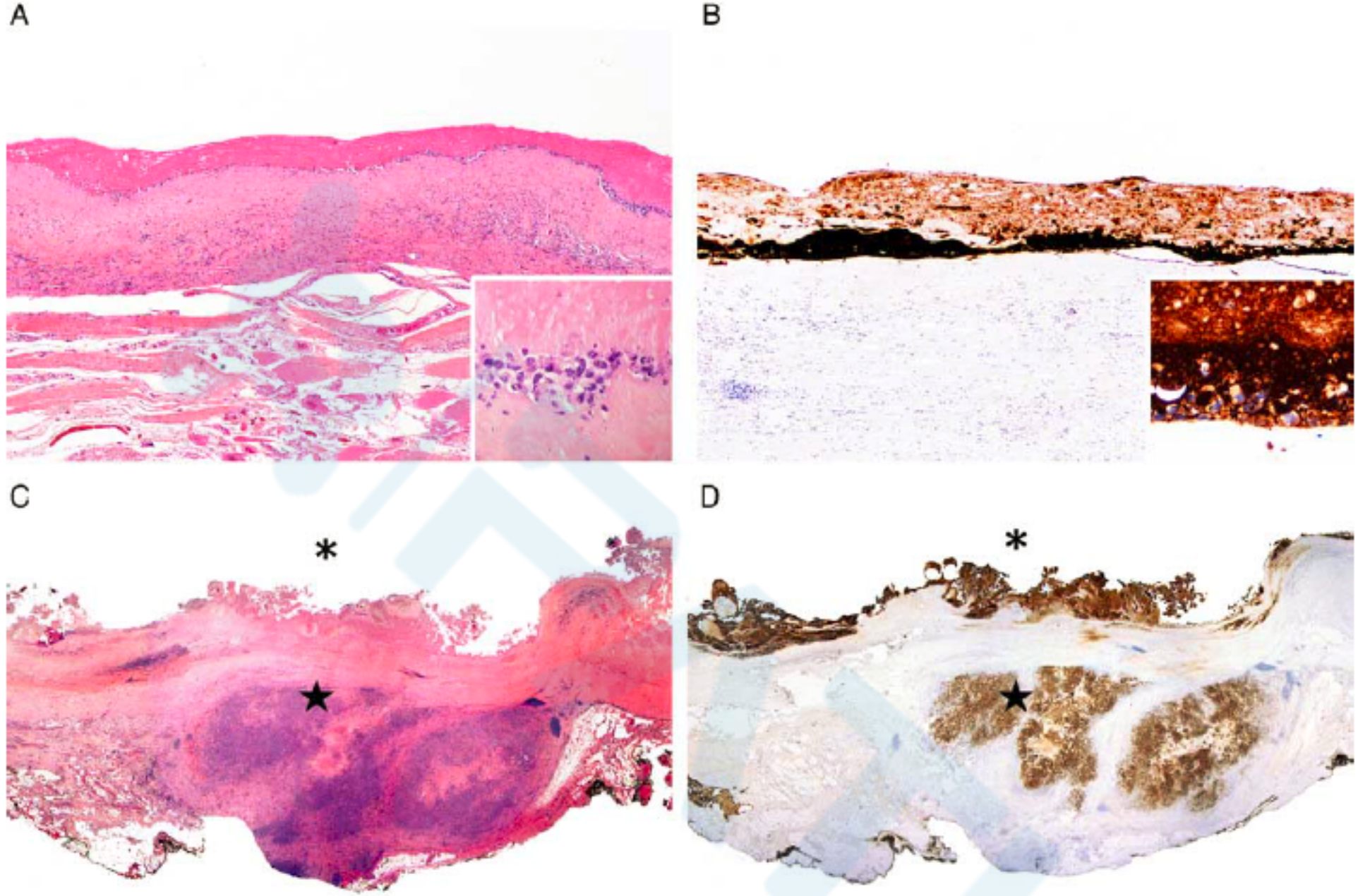


FIGURE 5. **Extent of lymphoma infiltration into the periimplant capsule.** A, Lymphoma confined to the luminal side of the capsule surrounding an implant. Large lymphoma cells are noted on the luminal surface of the capsule. Note in the inset that only rare lymphoma cells are viable, while most of the pink material corresponds to necrotic or ghost cells (hematoxylin and eosin). B, Anti-CD30 highlights the lymphoma cells on the luminal side of the capsule. Note in the inset that only rare lymphoma cells are viable and strongly reactive with CD30, while most of the CD30 reactivity corresponds to necrotic or ghost cells (anti-CD30 immunohistochemistry with hematoxylin counterstain). C, This illustration is a panoramic view of well-oriented capsulectomy specimen that displays lymphoma on the luminal surface of the capsule (asterisk), as well as lymphoma growing beyond the capsule (star) (hematoxylin and eosin). D, CD30 immunohistochemistry highlights abundant reactivity of viable as well as necrotic cells or ghost cells both at the luminal side (asterix) of the capsule as well as at the extracapsular extension (star) of BI-ALCL into surrounding soft tissue (anti-CD30 immunohistochemistry with hematoxylin counterstain).

TABLE 6. Clinical Management and Therapy of Patients With BI-ALCL and LNI (n = 14)

	N (%)
Chemotherapy (n = 14)	13 (92.8)
Radiotherapy (n = 13)	8 (61.5)
Surgery (n = 14)	14 (100)
ASCT (n = 12)	1 (8.3)
Salvage chemotherapy (n = 10)	4 (40)

ASCT indicates autologous stem cell transplant.

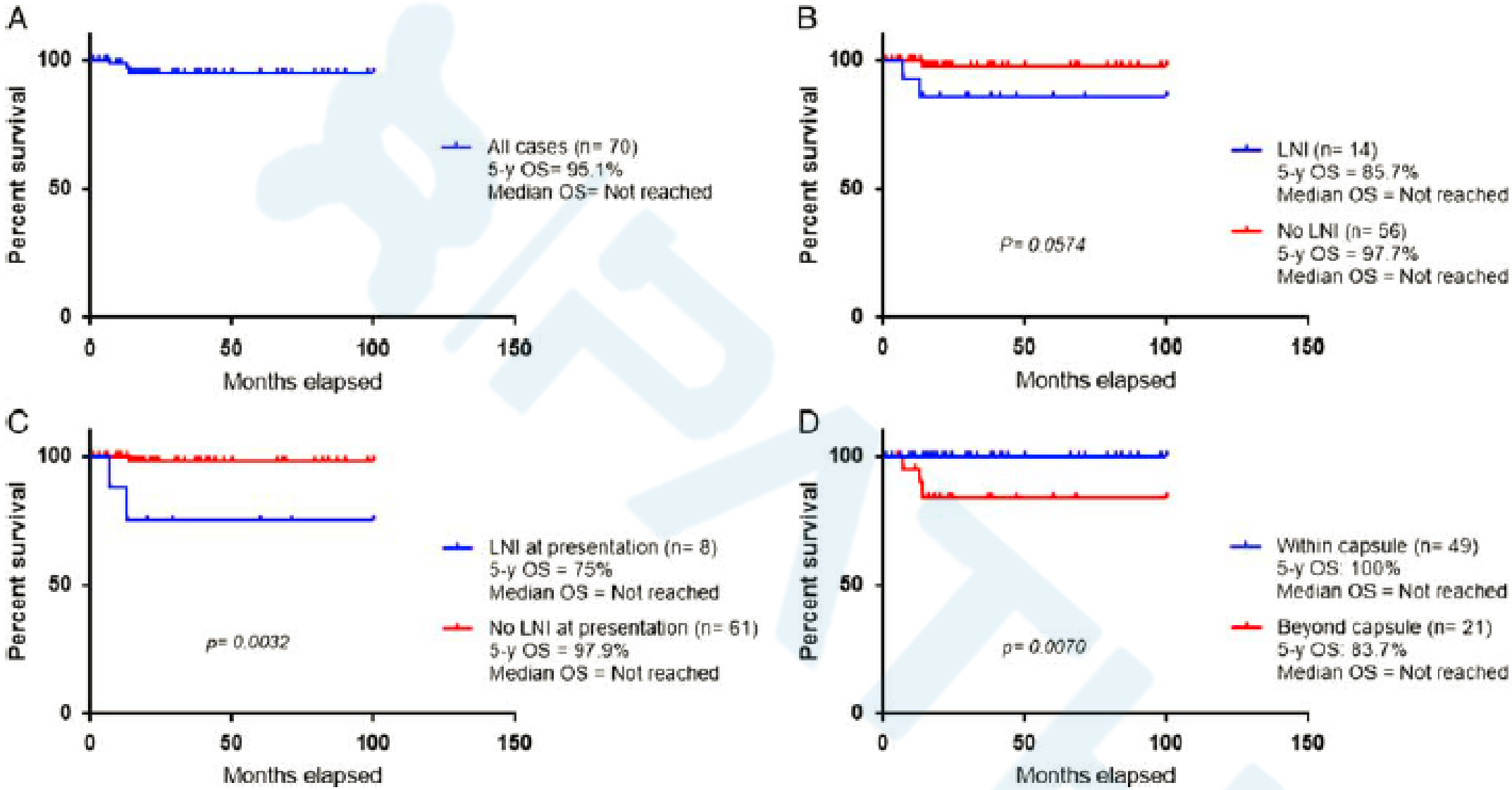


FIGURE 6. Survival curves. A, Five-year OS for the cohort of 70 patients with BI-ALCL, with and without LNI. B, Comparison of 5-year OS between patients with BI-ALCL, with (n = 14) and without LNI (n = 56). C, Comparison of 5-year OS between patients with BI-ALCL with (n = 8) and without (n = 61) LNI at presentation D, Comparison of 5-year OS of patients with BI-ALCL within (n = 49) and beyond the capsule (n = 21).

TABLE 7. Five-year OS of BI-ALCL Patients With and Without LNI

	5-Year OS (%)	*P*
BI-ALCL with and without LNI (n = 70) (Fig. 6A)	95.1	
BI-ALCL with and without LNI (Fig. 6B)		0.0574
With LNI (n = 14)	85.7	
Without LNI (n = 56)	97.7	
BI-ALCL with and without LNI at presentation (n = 69) (Fig. 6C)		**0.0032**
LNI at presentation (n = 8)	75	
No LNI at presentation (n = 61)	97.9	
BI-ALCL within vs. beyond capsule (Fig. 6D)		**0.007**
Within capsule (n = 49)	100	
Beyond capsule (n = 21)	83.7	

Significant *P*-values are shown in bold.

DISCUSSION

- The study provides the most important finding appears to be the degree of fibrous capsule (around the implant) involvement.
- Pathologists need to be particularly alert to not misdiagnosing nodal involvement by BI-ALCL as CHL.

In summary

- **Patients with tumor beyond the capsule surrounding the breast implant appear to have a higher risk of LNI than patients with tumor confined to the capsule.**

- **The immunohistochemical studies also may be misleading, as both HL and BI-ALCL contain large cells positive for CD30 that can be negative for CD3 and CD20. However, important clues to the diagnosis of BI-ALCL are the expression of CD45, positive in 90% of cases in this study, as well as the absence of PAX5. In contrast, CHL cells are CD45– and express PAX5 in most cases.**

- Patients with LNI have a lower 5-year OS compared with patients without LNI at presentation, however, most patients still achieve complete remission after therapy.

谢谢！