Am J Surg Pathol • Volume 42, Number 9, September 2018

Poorly Differentiated Nonkeratinizing Squamous Cell Carcinoma of the Thymus

Clinicopathologic and Molecular Genetic Study of 25 Cases

汇报人：康媛媛

指导老师：王璐

胸腺的解剖学及组织学

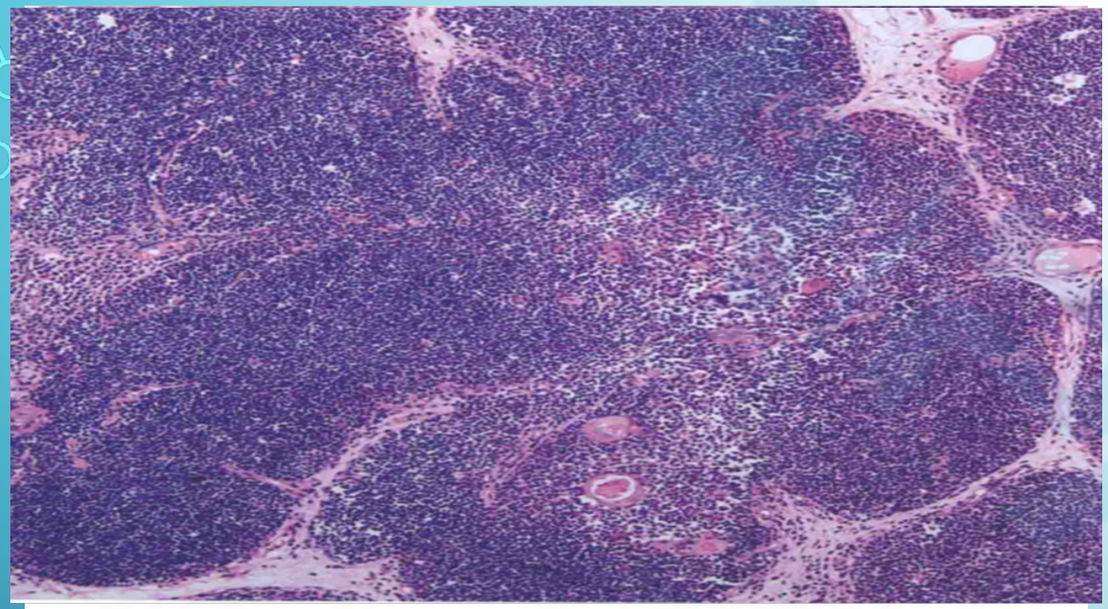


图 1-1-1 · 15 岁男性胸腺组织，皮质和髓质分布大致相等

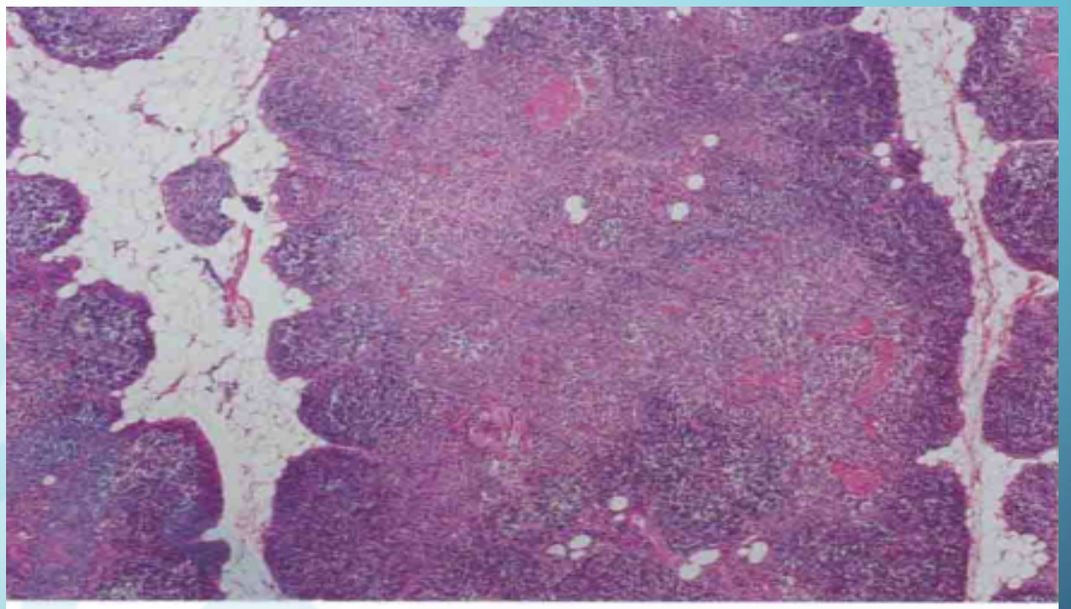


图 1-1-2 · 46 岁男性胸腺组织，皮质有明显萎缩

- 胸腺是一个淋巴上皮性器官，位于胸腔前纵膈上部胸骨柄后方，分左右两叶；
- 胸腺胎儿末期开始发育，青春期后逐渐萎缩，并逐步被脂肪组织取代；

皮质主要由上皮性网状支架和未成熟的淋巴细胞（胸腺细胞）构成。

髓质淋巴细胞少而稀疏，上皮性网状细胞多而显著。尚有散在的圆形的胸腺小体。

胸腺上皮性肿瘤的WHO分类

- **Thymoma**

Type A thymoma, including atypical variant 8581/3*

Type AB thymoma 8582/3*

Type B1 thymoma 8583/3*

Type B2 thymoma 8584/3*

Type B3 thymoma 8585/3*

Micronodular thymoma with lymphoid stroma 8580/1*

Metaplastic thymoma 8580/3

Other rare thymomas

Microscopic thymoma 8580/0

Sclerosing thymoma 8580/3

Lipofbroadenoma 9010/0*

Thymic carcinoma

Squamous cell carcinoma 8070/3

Basaloid carcinoma 8123/3

Mucoepidermoid carcinoma 8430/3

Lymphoepithelioma-like carcinoma 8082/3

Clear cell carcinoma 8310/3

Sarcomatoid carcinoma 8033/3

Adenocarcinomas

Papillary adenocarcinoma 8260/3

Thymic carcinoma with adenoid cystic carcinoma-like features 8200/3*

Mucinous adenocarcinoma 8480/3

Adenocarcinoma NOS 8140/3

NUT carcinoma 8023/3*

Undifferentiated carcinoma 8020/3

Other rare thymic carcinomas

Adenosquamous carcinoma 8560/3

Hepatoid carcinoma 8576/3

Thymic carcinoma, NOS 8586/3

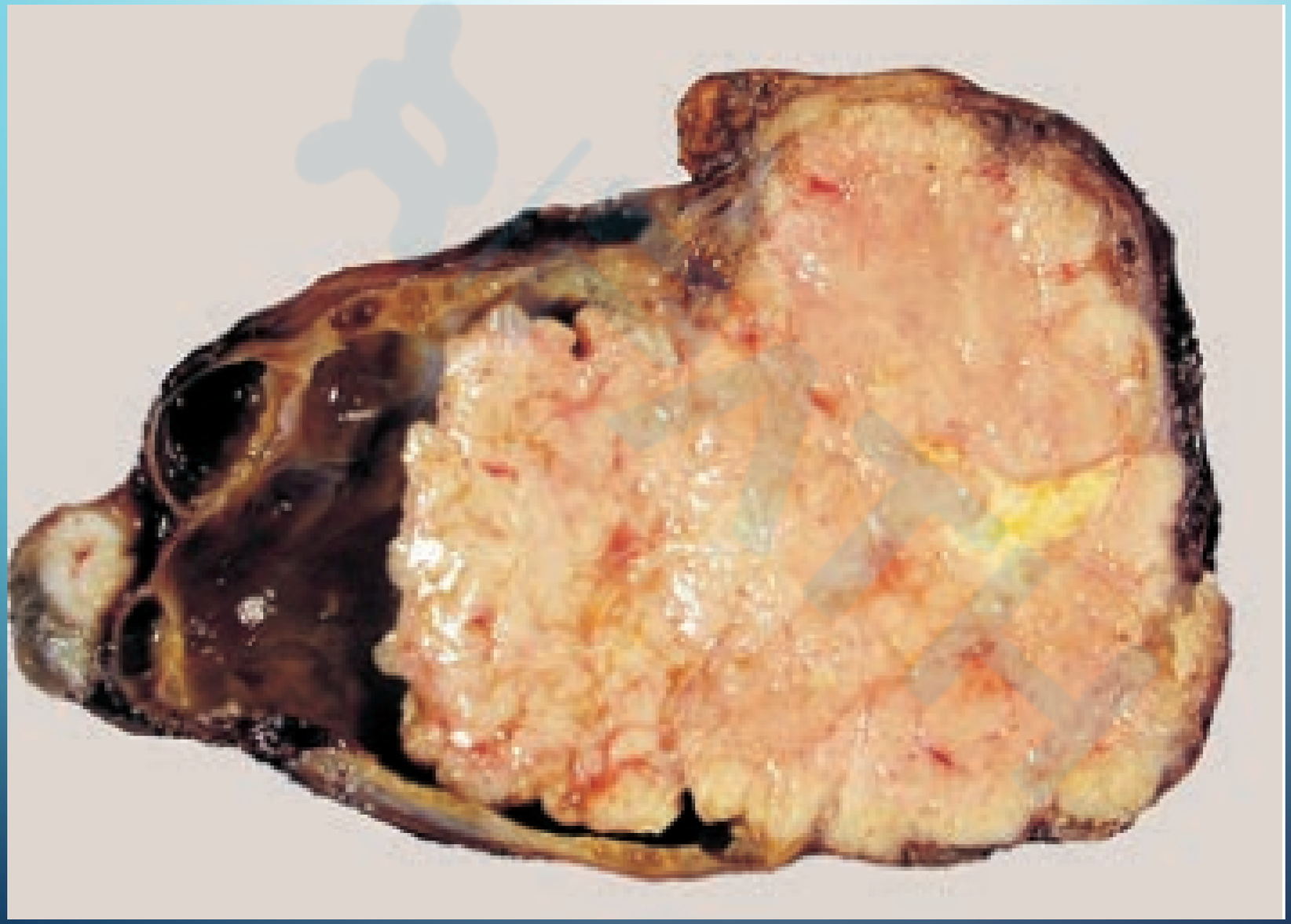
•定义

胸腺淋巴上皮瘤样癌（LELTC）是一种胸腺原发的未分化或低分化鳞状细胞癌，伴有显著的淋巴细胞、浆细胞浸润，形态学类似于鼻咽癌。

•临床特征

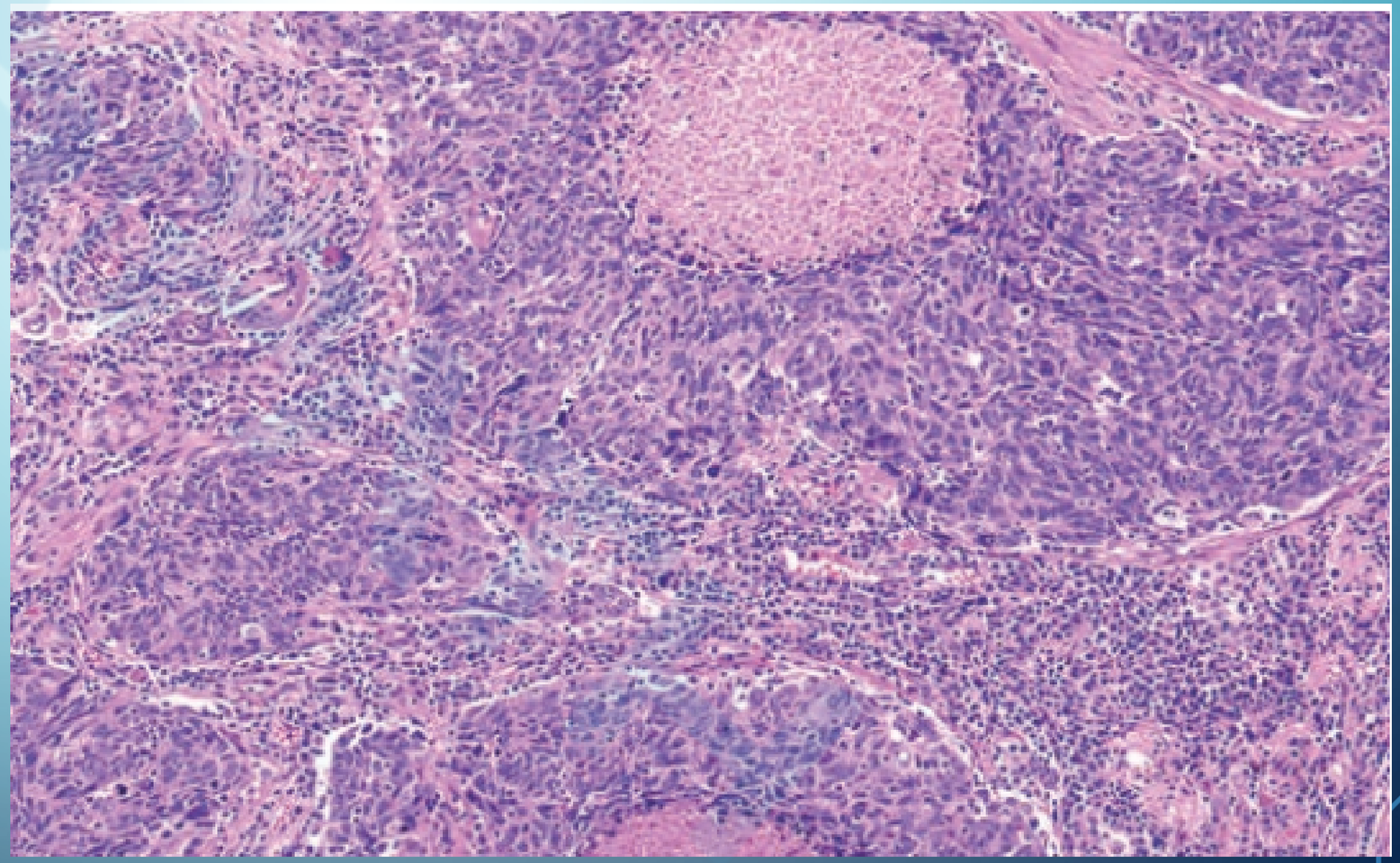
大多数症状为纵膈肿块的压迫症状，如胸痛、咳嗽、呼吸困难等，上腔静脉综合症可发生在较晚期疾病患者。与重症肌无力、纯红再障或低配血无关，罕见合并增生性骨关节病、多肌炎或肾病综合征； 肿瘤体积一般较大，且可见局部侵袭，CT可显示肿瘤常见坏死。

- 肿瘤大体



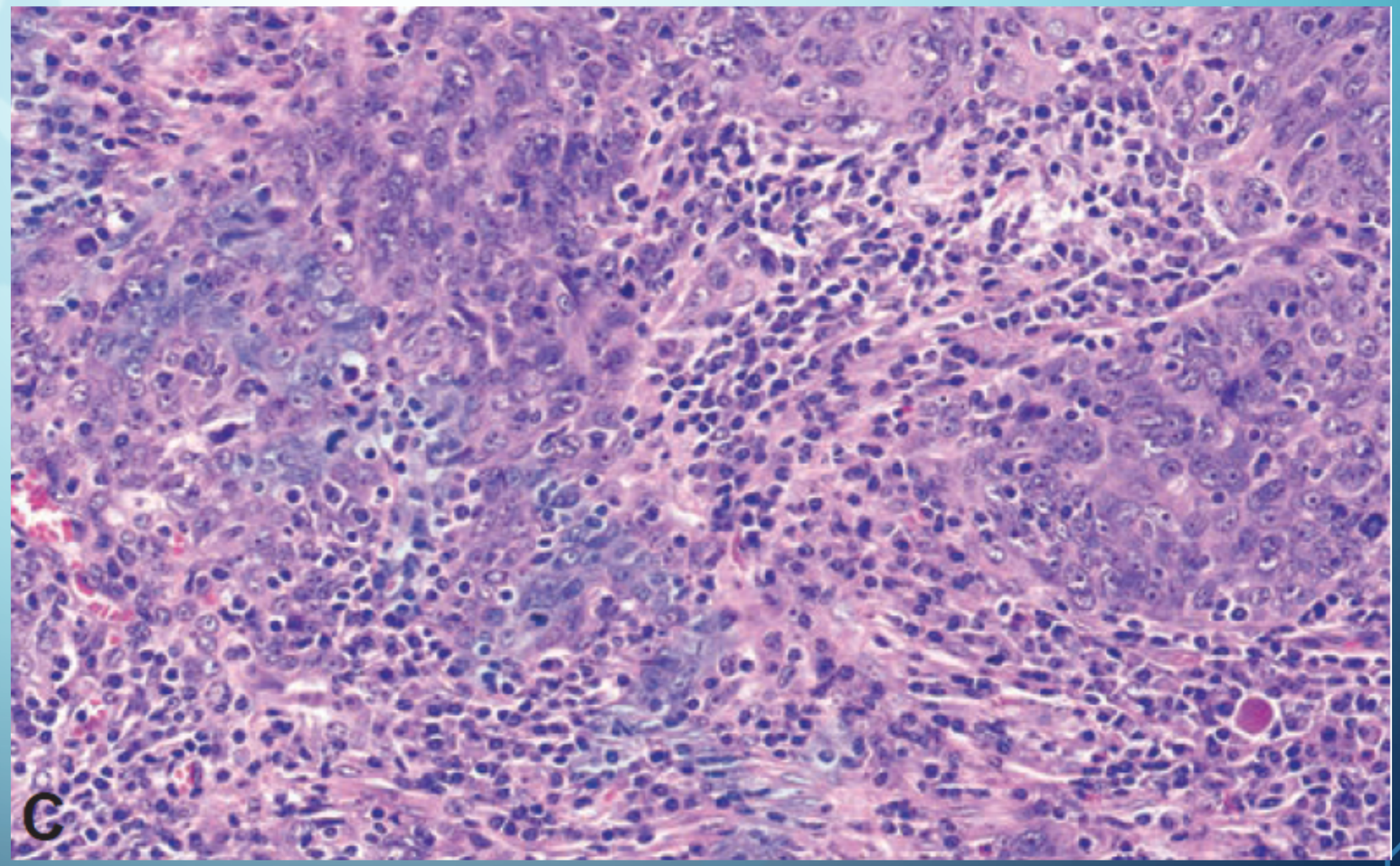
镜下特点

- 肿瘤细胞呈不规则岛状或巢状，间质伴有丰富的淋巴细胞和浆细胞浸润。凝固性坏死很常见。



镜下特点

- 癌细胞界限不明显，呈合体样。
- 大的泡状核，一个或多个明显的核仁。细胞分布不均匀、部分拥挤，出现重叠。



免疫组化

- 肿瘤细胞阳性标记：

  AE1/AE3(+)、P63（+）、CD5（+）、CD117（+）。

- 肿瘤细胞阴性标记：

  CK7、CK20。

材料与方法

- 研究人群

总共25例原发性胸腺癌患者，由Department of Pathology at the Beth Israel Deaconess Medical Center 提供。

- 免疫组化

  AE1/AE3、降钙素、Calretinin、CD117、CD20、CD3、CD5、CEA、Chromogranin、CK18、CK19、CK5/6、CK7、EREB、Ki67、MOC31、P16、P40、P53、P63、PAX8、SYN、TDT、TTF1、NUT.

- 电子显微镜

- DNA原位杂交

- 荧光原位杂交

- NGS

结　果

TABLE 2. Patient Demographics and Clinical Follow-up

Case	Sex/Age (y)	Clinical	Stage	Margins/LNs	Histology	Tx	Follow-up
1	M/56	Incidental	I	Negative margins; 0/4 LN	LELCA with associated cystic changes	NA	A&W @ 8 y, then LFU
2	M/55	Incidental	II	Negative margins	LELCA with microinvasion into mediastinal fat	Surgery only	A&W, NED @ 16 y
3	F/47	Upper back pain	IV	Positive, widely invasive to lung+7/9 LN mets	LELCA	NA	Metastases to lung and mediastinal LN at presentation—LFU
4	F/57	Fatigue	II	Negative margins 0/9 LN	LELCA	Surgery only	A&W, NED ×12 y
5	M/55	Incidental	I	Negative margins	LELCA	Rx	Two recurrences @ 4 & 6 y; A&W at 8 y
6	M/57	Incidental	III	Positive	Desmoplastic, arising in SCT	Rx	Died of disease @ 1 y w/mets to sacrum
7	M/74	Right diaphragm paresis, dysphagia	III	Positive, 3/6 LN+ Invasion of lung, pleura and pericardium	Desmoplastic, arising in atypical thymoma (B3)	Rx	AWD @ 3 y with brain mets
8	M/48	Shortness of breath, pleuritic pain	NA	NA	LELCA w/ foci of squamous differentiation	NA	LFU
9	M/62	Shoulder pain and swelling	II	Negative margins, 0/5 LN	Mixed w/ foci of squamous differentiation	Rx Tx	A&W, NED @ 3 y
10	M/56	Incidental	II	NA	Mixed	NA	Local recurrence @ 4 y.
11	M/67	Weight loss	II	Negative margins	Desmoplastic+transition with atypical SCT	NA	A&W, NED @ 6 y.
12	F/51	Incidental during workup for metastatic disease	I	NA	LELCA with transitions with atypical thymoma (B3)	NA	DOD @ 3 y w/ local recurrence and mets to mediastinal lymph nodes and parascapular soft tissue
13	F/61	Incidental during cardiac evaluation	I	Negative margins, 0/16 LN	LELCA w/ transitions to SCT+glandular component	NA	A&W NED @ 5 y.

14	M/60	Incidental on CTS for myasthenia gravis	II	Negative margins	LELCA w/ transitions to B1 thymoma+glands +ribbons	No Tx	A&W NED 7 y.
15	M/61	NA	II	Negative margins 0/2 LN	Desmoplastic with spindling and basaloid areas	Rx Tx	A&W NED @ 2 y.
16	M/68	Incidental during routine CTS	II	Negative margins	Desmoplastic	Rx Tx	A&W NED @ 4 y
17	M/82	Chest pain, mass on CTS	II	Positive in anterior, medial and lateral margins	Desmoplastic with florid squamous differentiation+SCT	NA	DOD @ 1 y with metastases
18	M/64	Incidental	I	Negative margins	LELCA with squamous foci	Rx Tx	Recent case
19	M/65	Incidental	I	Negative margins	Desmoplastic w/ transitions with SCT	Rx Tx	A&W NED @ 4 y
20	M/85	Incidental	III	Negative margins, 0/6 LN	Desmoplastic with squamous foci	Rx Tx	A&W NED @ 1.5 y
21	M/20	Cough, shortness of breath	IV	Positive, 4/50 LNs +	LELCA EBER^{+}	Rx Tx +chemo	AWD @ 1 y
22	M/75	Incidental	II	Negative margins	Mixed	None	LFU
23	M/36	Shortness of breath	III	Positive+lung invasion and lung metastases	Desmoplastic with spindling and transitions to atypical SCT	Palliative tx, sent to hospice	Multiple lung metastases @ diagnosis; rapid deterioration, LFU
24	F/56	Cough	I	Negative margins	Mixed with transitions to SCT	Rx Tx	A&W NED at 1.5 y
25	F/67	Cough and chest pain	III	Positive	LELCA	No Tx	Patient died due to complications of peritonitis @ 1 mo

A&W indicates alive and well; AWD, alive with disease; CTS, computerized tomography scan; DOD, dead of disease; F, female; LFU, lost to follow-up; LN, lymph nodes; M, male; Mets, metastases; NA, information not available; NED, no evidence of disease; Rad tx, radiation therapy; SCT, spindle cell thymoma; Tx, treatment.

- 临床研究结果

➢ 共25例患者，其中19名男性和6名女性，男女比例为3:1，年龄20 - 85岁(平均60岁) 。

➢肿瘤直径在2.0 - 13.5 cm之间(中位:6.0 cm)，均通过影像学检查发现，典型表现为前纵隔肿块。临床包括无症状偶然发现、胸痛、呼吸短促、体重减轻等。

➢17/25个肿瘤较小(小于5.0 cm)，局限于被膜内(改良Masaoka I期)，或少量浸润周围脂肪(改良Masaoka II期)，除第12例和第17例外，其余均预后较好。

➢7例为III期以上肿瘤，除第20例切缘阴性无病生存外，其余6例均提示预后不良，其中两例死亡。

- 大体

肿瘤质地较硬，切面呈淡红色或黄白色，部分被纤维包膜分割呈分叶状。肿瘤切面可见坏死、出血和囊性变。

- 组织学

所有病例均有相似的组织、细胞学特征，见下图：

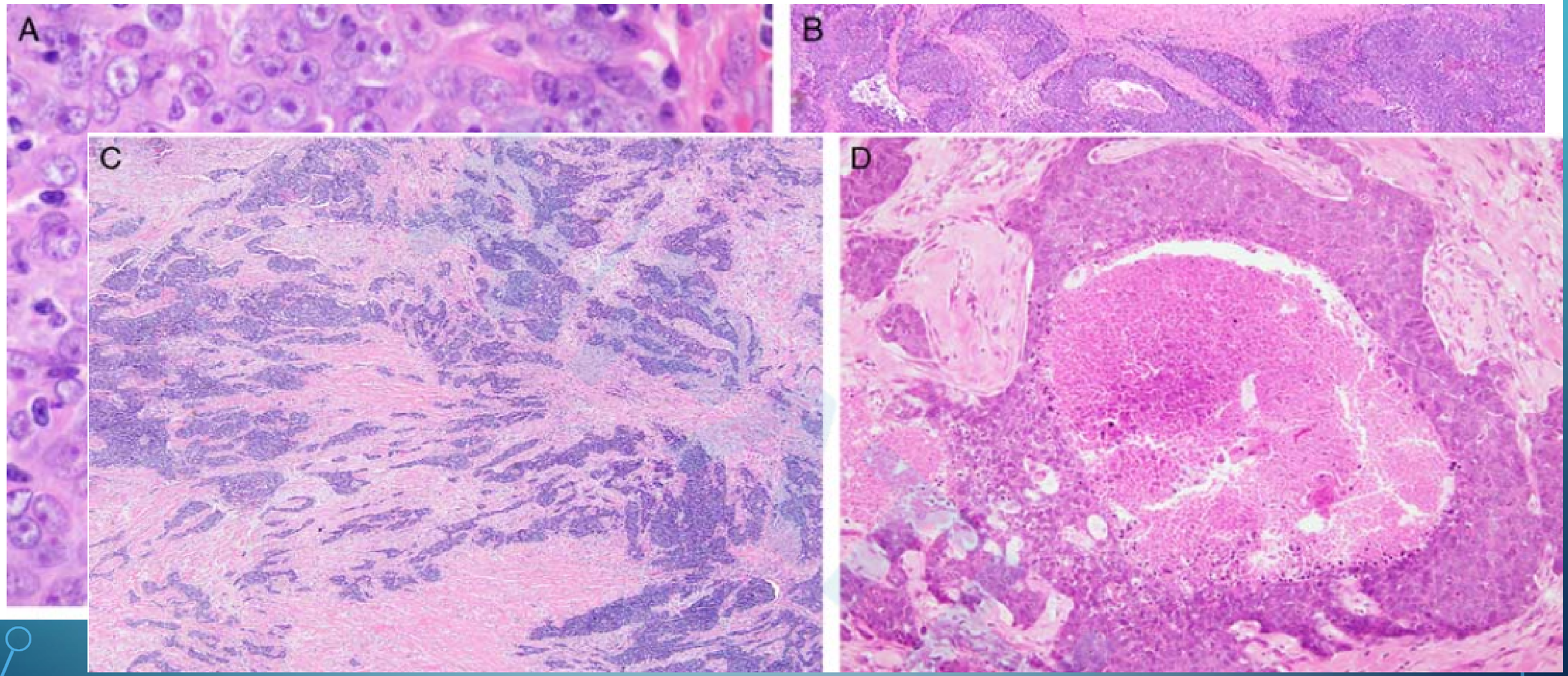


FIGURE 1. A, Representative high-power magnification of PDNKSCC showing sheets of large round to oval tumor cells with vesicular nuclei and open chromatin pattern, and prominent eosinophilic nucleoli. The cytoplasm is indistinct and there is frequent overlapping of nuclei. Scattered apoptotic cells are present as well as mitotic figures (center). B, PDNKSCC with anastomosing cord-like pattern of growth. C, Small infiltrative islands of tumor cells are seen. D, Island of tumor cells with large central, comedo-like area of necrosis. This feature was observed at least focally in all cases in the study.

肿瘤的组织学生长模式：

1.淋巴上皮瘤样模式:12例患者肿瘤细胞排列成不规则的索和岛状，被含有密集淋巴细胞浸润的结缔组织间质分隔，间质炎细胞为成熟T淋巴细胞和B淋巴细胞以及浆细胞和少量组织细胞。4例患者可见淋巴滤泡形成。

2.促结缔组织增生性模式:10例患者肿瘤细胞排列成不规则索状和岛状，被致密的纤维间质条带分隔，炎症浸润很少或没有浸润

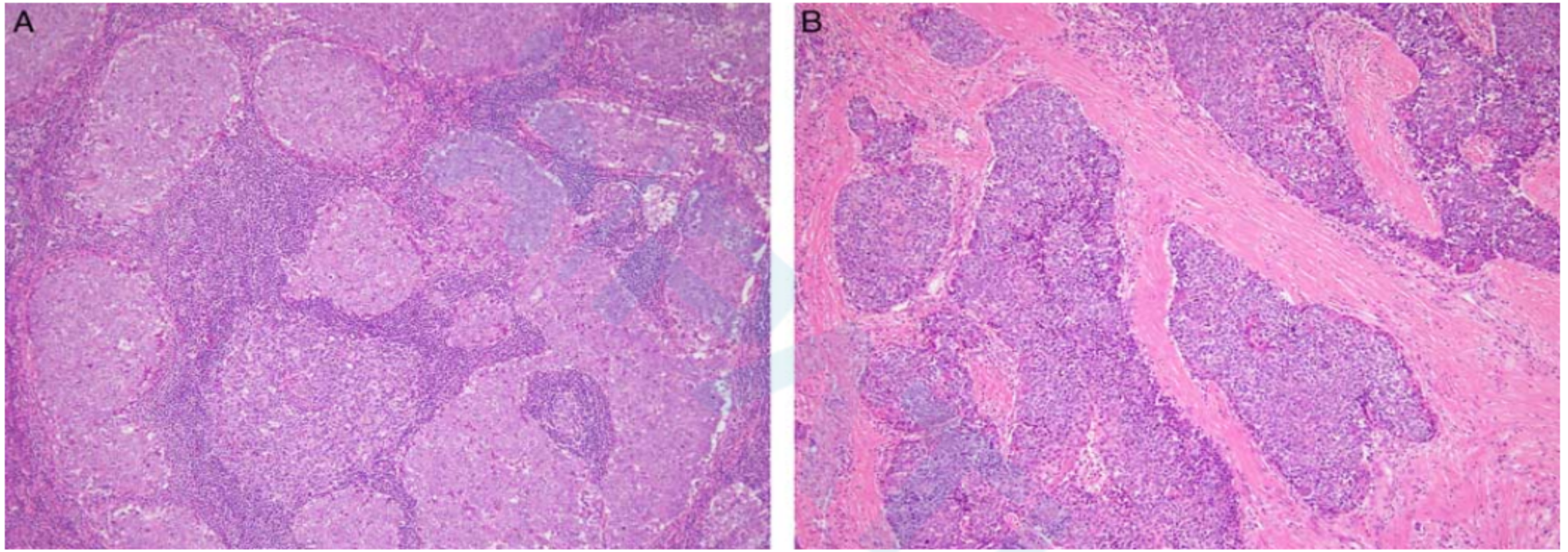


FIGURE 2. A, Lymphoepithelioma-like pattern of growth in PDNKSCC of the thymus shows irregular islands of tumor cells surrounded by a dense lymphoplasmacytic stroma. B, Desmoplastic pattern of growth in PDNKSCC of the thymus shows islands of tumor cells separated by a lymphocyte-poor connective tissue stroma.

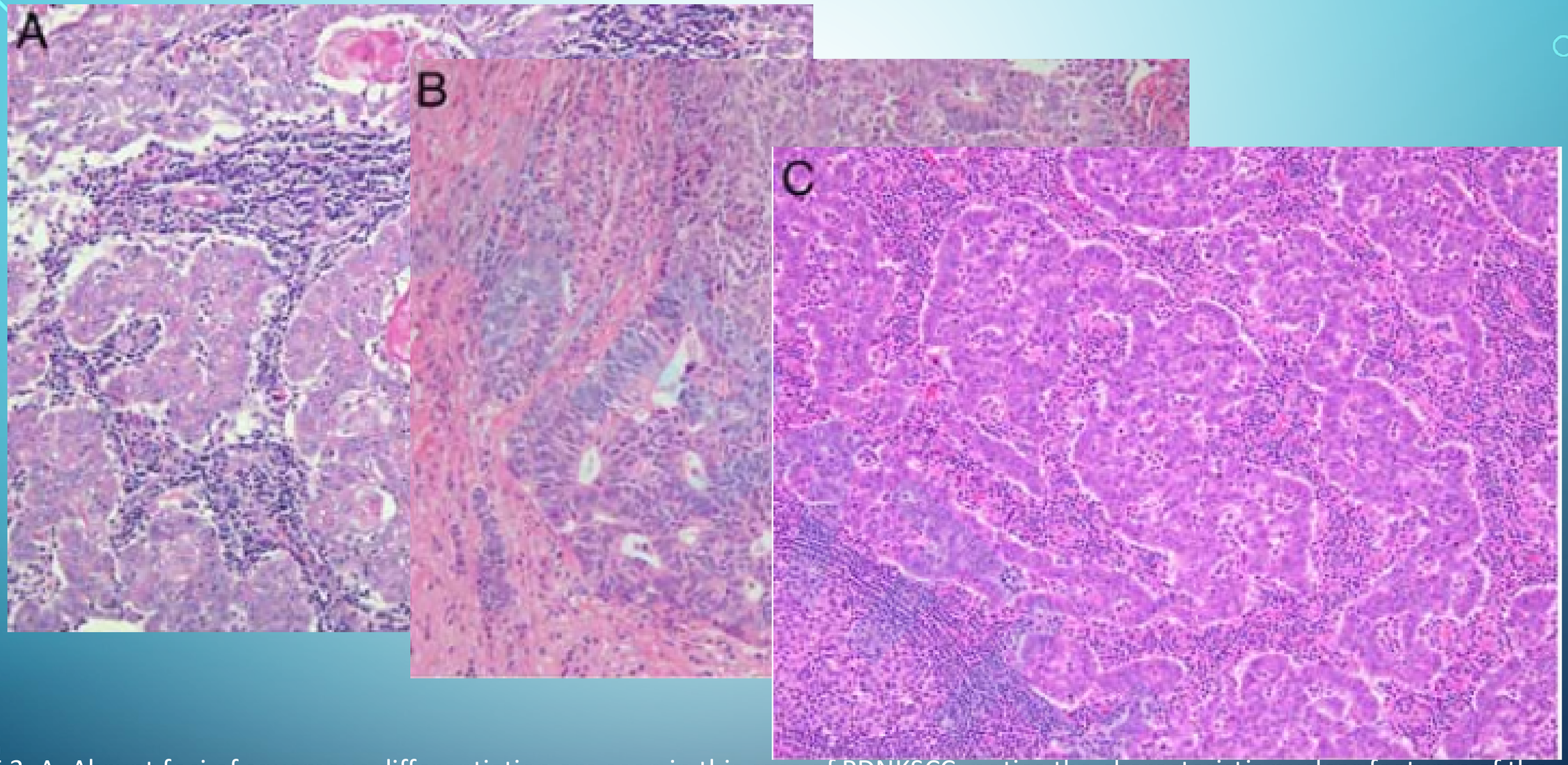


FIGURE 3. A, Abrupt foci of squamous differentiation are seen in this case of PDNKSCC; notice the characteristic nuclear features of the atypical cells surrounding the foci of squamous differentiation. B, Foci of glandular differentiation in PDNKSCC showing wellformed glandular lumens in continuity with a olid area containing sheets of atypical cells. C, Ribbon-like pattern of growth in PDNKSCC of thymus showing abundant lymphoid stroma. These areas merged with other areas displaying more conventional trabecular and solid growth patterns. D,

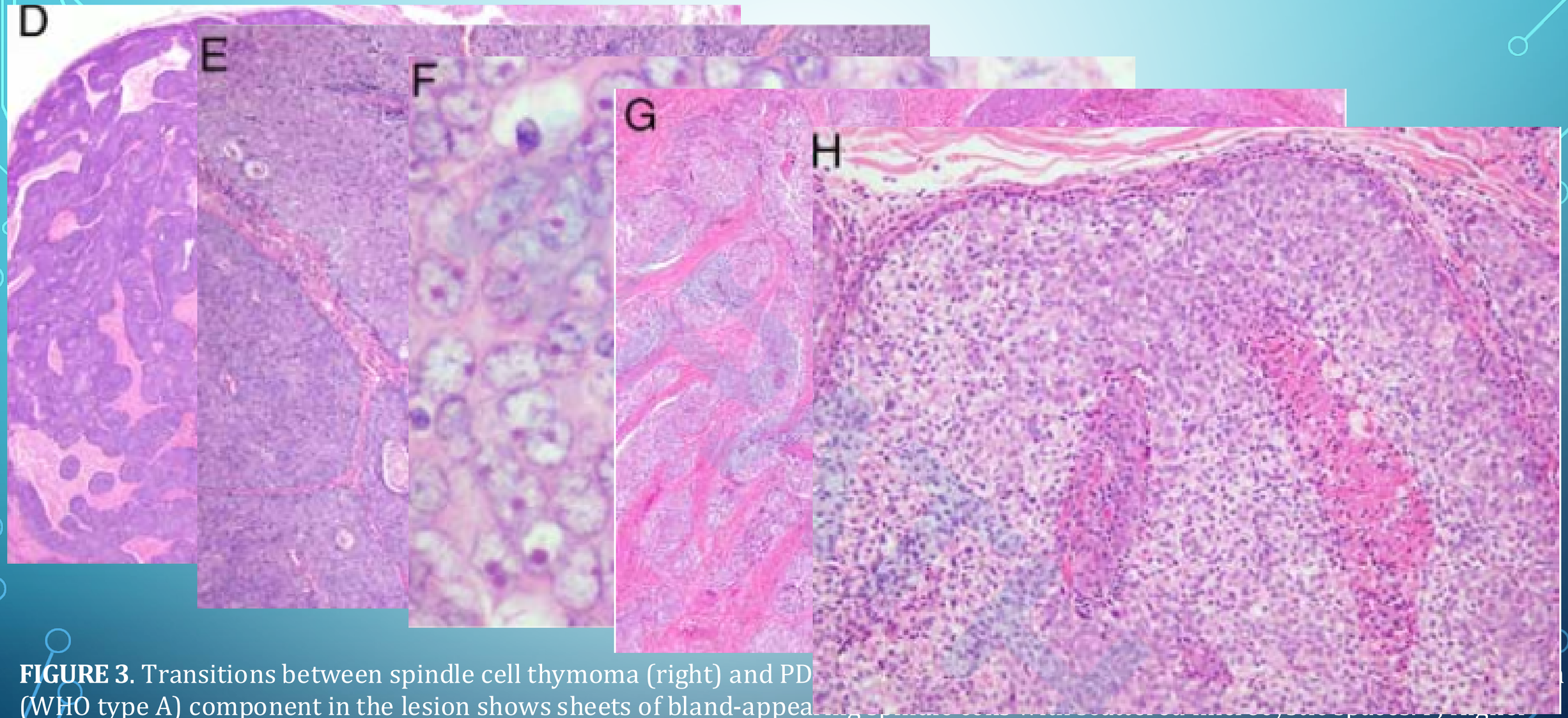


FIGURE 3. Transitions between spindle cell thymoma (right) and PD
(WHO type A) component in the lesion shows sheets of bland-appea
magnification from the PDNKSCC component shows the characteristic cells with round to oval, vesicular nuclei, and prominent eosinophilic nucleoli. G, Composite tumor showing transitions between atypical thymoma (left) and PDNKSCC (right). H, Higher magnification from the atypical thymoma (WHO type B3) component in this tumor showing sheets of large cohesive cells with sharp cell membranes and hyperchromatic nuclei with nuclear membrane irregularities.

免疫组化结果

- 阳性标记

  AE1/AE3、CK18、CK19、MOC31、p40、p63所有病例均+

  CD117（21/25）+

  CD5 （20/25）+

  PAX-8仅1/22+

  MIB-1平均显示35%的核染色(范围:15% - 40%)

  P16显示胞浆弥漫阳性和灶状核阳性

  P53、CEA、CK7、神经内分泌标记偶见阳性

- 阴性标记

  NUT、降钙素和TTF1

- 间质淋巴细胞:CD3+、CD20+，TDT-

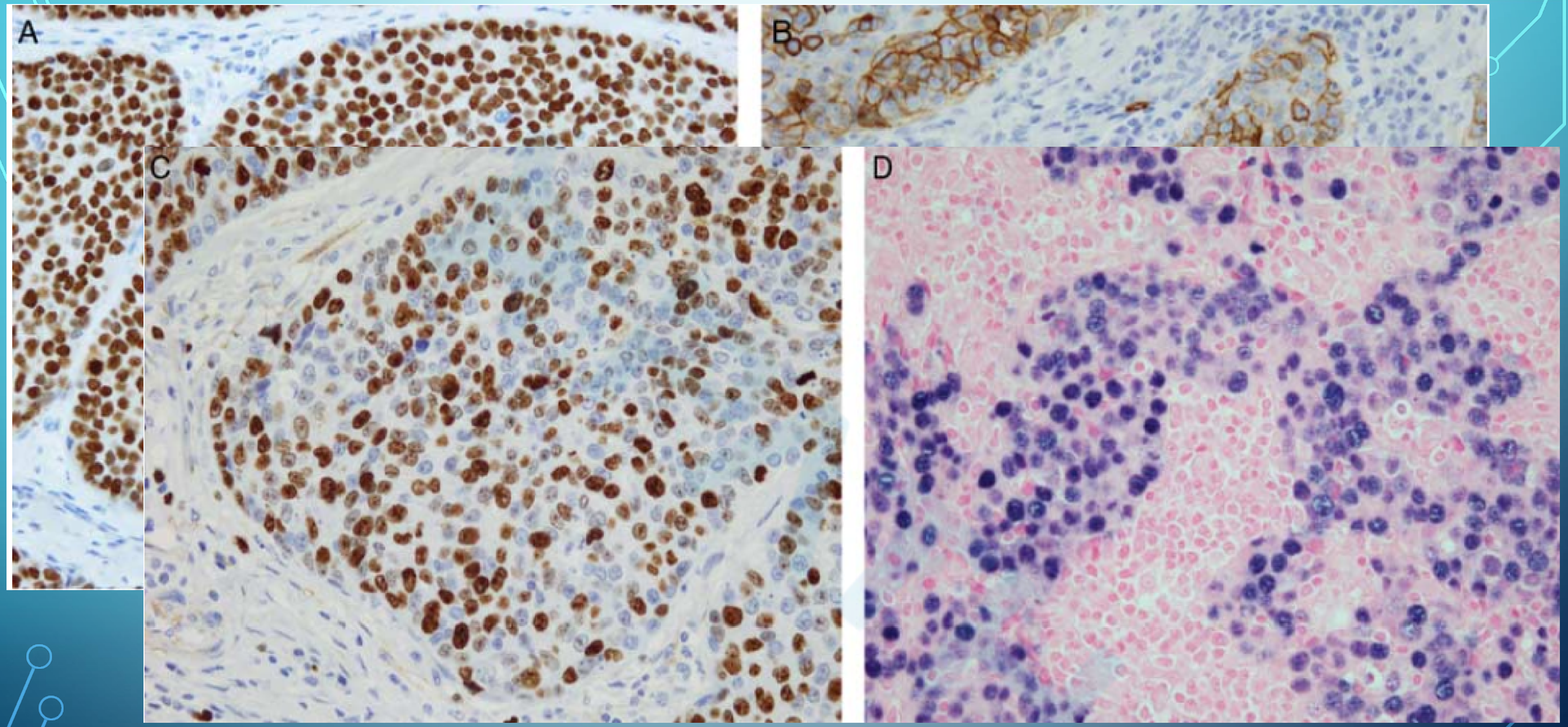


FIGURE 4. A, Immunohistochemical staining for p63 shows strong nuclear positivity in nearly all the cells in PDNKSCC of the thymus. B, Immunohistochemical staining for p16 shows cytoplasmic and focal nuclear positivity in the tumor cells. C, Immunohistochemical staining for MIB1 proliferation marker shows increase in the proliferation fraction in > 50% of the tumor cells. D, DNA in situ hybridization for EBER shows strong nuclear positivity in the tumor cells (blue signal) (case no. 21).

超微结构

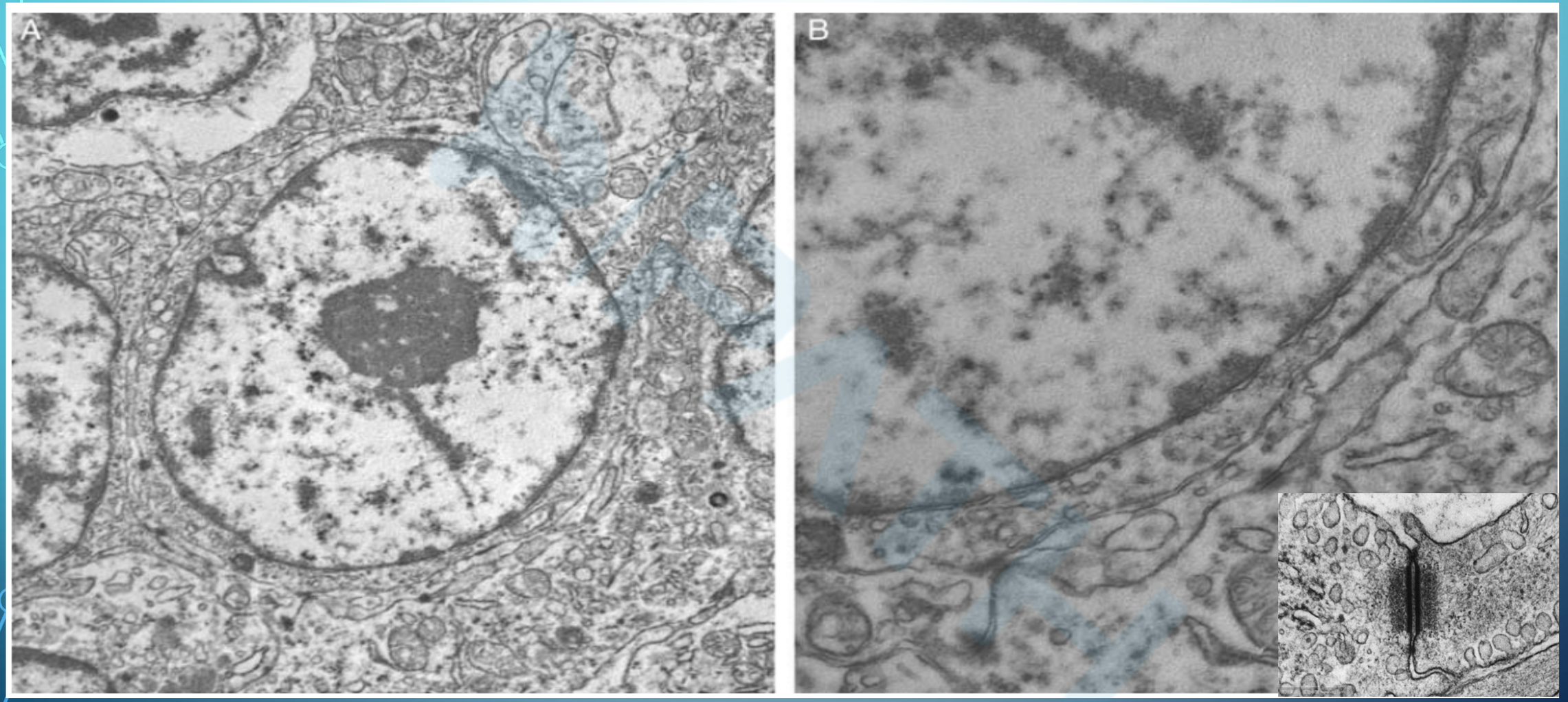


FIGURE 5. A, Ultrastructural appearance (case 4) shows a large, round tumor cell with centrally placed nucleolus surrounded by a scant rim of cytoplasm with scant organelles. There is margination of the nuclear chromatin to the periphery of the nuclear envelope with central clearing of chromatin, which imparts the cell with its distinctive vesicular appearance. B, Ultrastructural detail from the cell membrane (same cell) showing multiple small, primitive desmosomal-type cell junctions.

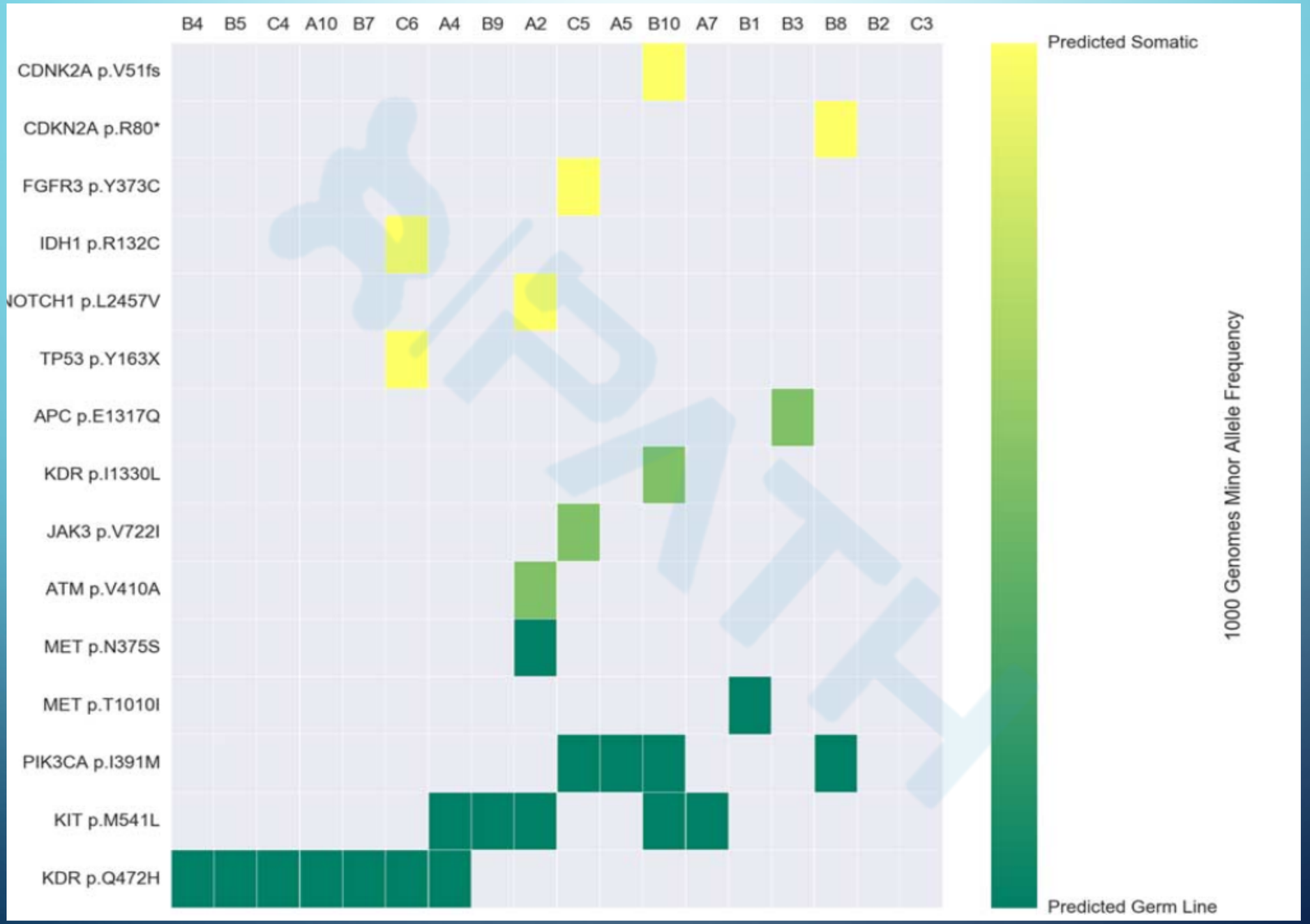
- 原位杂交仅一例显示EBER阳性

- FISH结果

  16例患者均行NUT-BRD4检测，所有病例均未发现NUT-BRD4融合，而在用于对照的病例中，53%的细胞核出现融合。

- NGS结果

  见下图


B4
B5
C4
A10
B7
C6
A4
B9
A2
C5
A5
B10
A7
B1
B3
B8
B2
C3
CDNK2A p.V51fs
CDKN2A p.R80*
FGFR3 p.Y373C
IDH1 p.R132C
NOTCH1 p.L2457V
TP53 p.Y163X
APC p.E1317Q
KDR p.I1330L
JAK3 p.V722I
ATM p.V410A
MET p.N375S
MET p.T1010I
PIK3CA p.I391M
KIT p.M541L
KDR p.Q472H
Predicted Somatic
Predicted Germ Line
1000 Genomes Minor Allele Frequency

- 临床随访

➢共随访患者20例；

➢14例患者在确诊后1.5 - 16年内均存活，无疾病迹象(中位生存率:4y;平均:5.5 y)；

➢大多数幸存者肿瘤相对较小(小于5cm直径)，诊断处于I期和II期，手术切缘清晰；

➢5例处于晚期，切缘均为阳性，因肿瘤转移至骨、脑、胸壁、肺、淋巴结而死亡。

讨　论

- 胸腺癌被定义为原发性胸腺上皮肿瘤，在组织学上它们具有与许多其他上皮肿瘤相同的形态学特征。因此，胸腺癌的诊断通常是排除性的；

- 在作者的研究中，已经证明这些肿瘤与NUT-BRD4易位、EBV或任何常见和已知的驱动基因易位无关。

- 突然出现的角化病灶、电镜肿瘤细胞的原始桥粒连接的超微结构特征、 p40/p63核阳性证实了该肿瘤与鳞状细胞谱系之间的联系。胸腺瘤和胸腺癌同时存在于同一病变范围内，支持了胸腺癌可以由先前的胸腺瘤转化而来。

- 预后因素

通过上述研究发现胸腺上皮肿瘤最重要的预后决定因素是分期，而非组织学。因此，早期发现、完全切除和边缘干净，预后更好。

- 鉴别诊断

1. PDNKSCC与NUT中线癌

➢组织形态学， 该肿瘤与NUT癌形态学有交叉，但合体样细胞，空泡状核和突出的核仁可做鉴别；

➢免疫组化CD5、CD117和FESH检测NUT-BRD4有助于鉴别。

2. PDNKSCC与转移性鼻咽非角化型鳞状细胞癌

- 鼻咽癌纵膈转移罕见；
- 组织形态两者无法区分；
- 免疫组化和EBV检测可以帮助鉴别，鼻咽非角化型鳞状细胞癌EBV 100%+，PDNKSCC EBV-/+。

3. PDNKSCC与转移性鳞状细胞癌

- 病史及影像学；
- 形态学，PDNKSCC特殊的组织学结构及合体细胞样、泡状核和很少角化；
- 免疫组化， CD117和CD5标记可供鉴别。

THANKS!