Primary Cutaneous CD4+ Small/Medium T-Cell Lymphoproliferative Disorders

A Clinical, Pathologic, and Molecular Study of 60 Cases Presenting With a Single Lesion: A Multicenter Study of the French Cutaneous Lymphoma Study Group

汇报人：张微晨

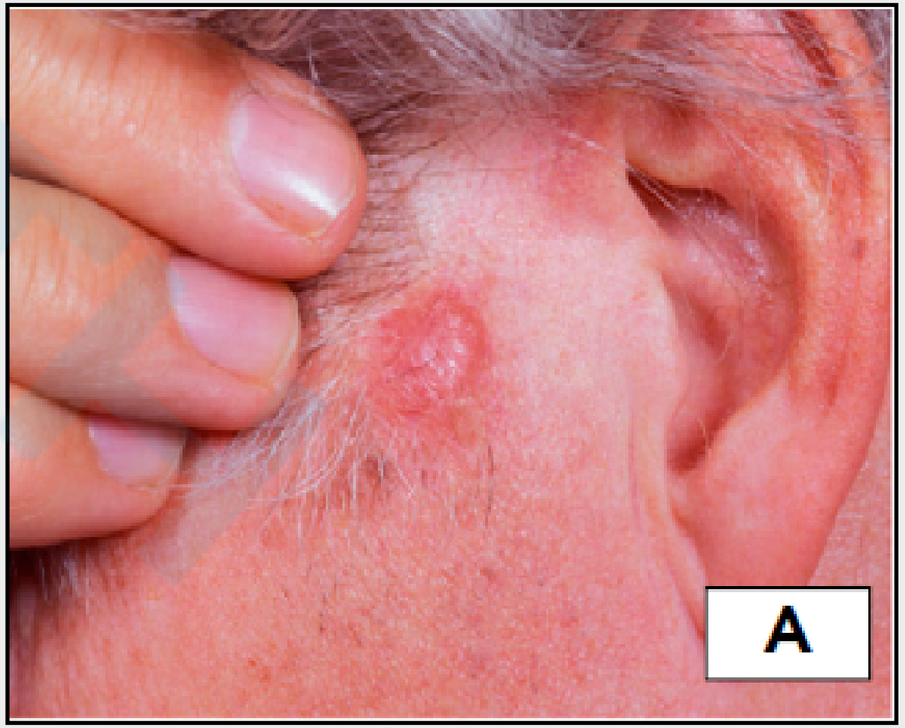
原发皮肤CD4+小/中等大T细胞淋巴组织增生性疾病

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSMLPD)

概述：原发皮肤CD4+小/中等大T细胞淋巴瘤是一种罕见的原发性皮肤T细胞淋巴瘤，占原发性皮肤肿瘤的2%-3%。2005年WHO-EORTC分类中，将其归为“皮肤外周T细胞淋巴瘤，非特指类型”的暂定亚型，因其惰性的临床过程和不确定恶性潜能，WHO（2017）淋巴肿瘤分类将其命名为原发皮肤CD4+小/中等大T细胞淋巴组织增生性疾病。

PCSMLPD

临床表现：病程较短，常以头颈部皮肤的单发无痛性结节/斑块为症状，缺乏系统性表现，实验室检查无异常，多灶性病变亦有报道。



PCSMLPD

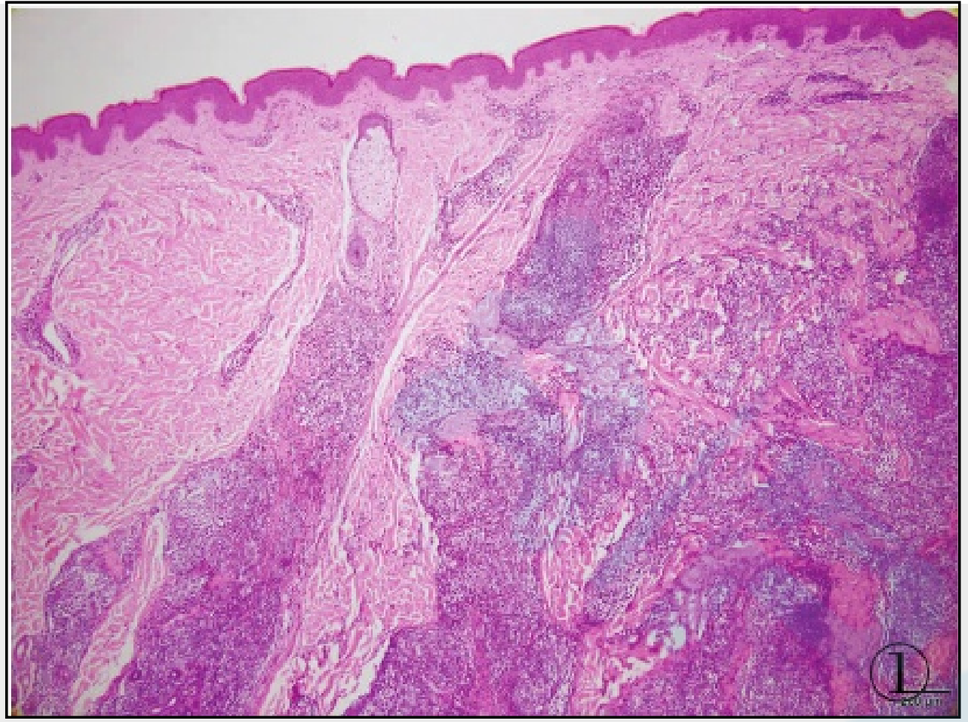
流行病学：发病年龄3-90岁，但多见于中老年人，中位年龄50-60岁，无明显性别优势。

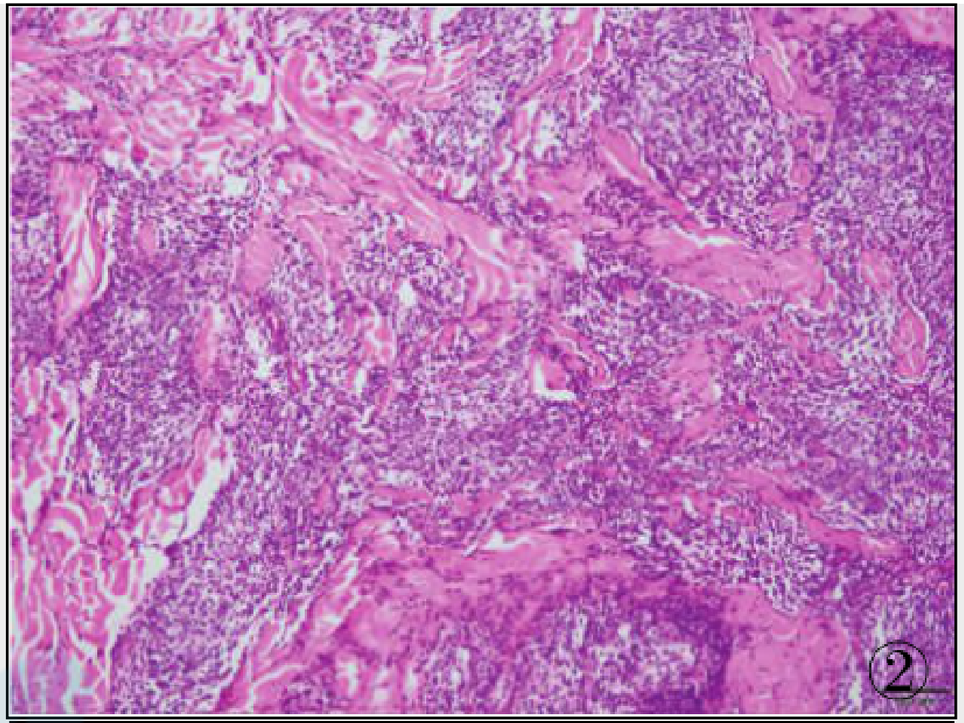
预后：临床多呈惰性过程，5年生存率超过90%，治疗上主要采取单纯切除，个别报道活检后病灶可自发消退。值得注意的是，当病变直径大于5cm、Ki-67增殖指数较高，以及出现全身系统性病变时，则提示患者预后较差。

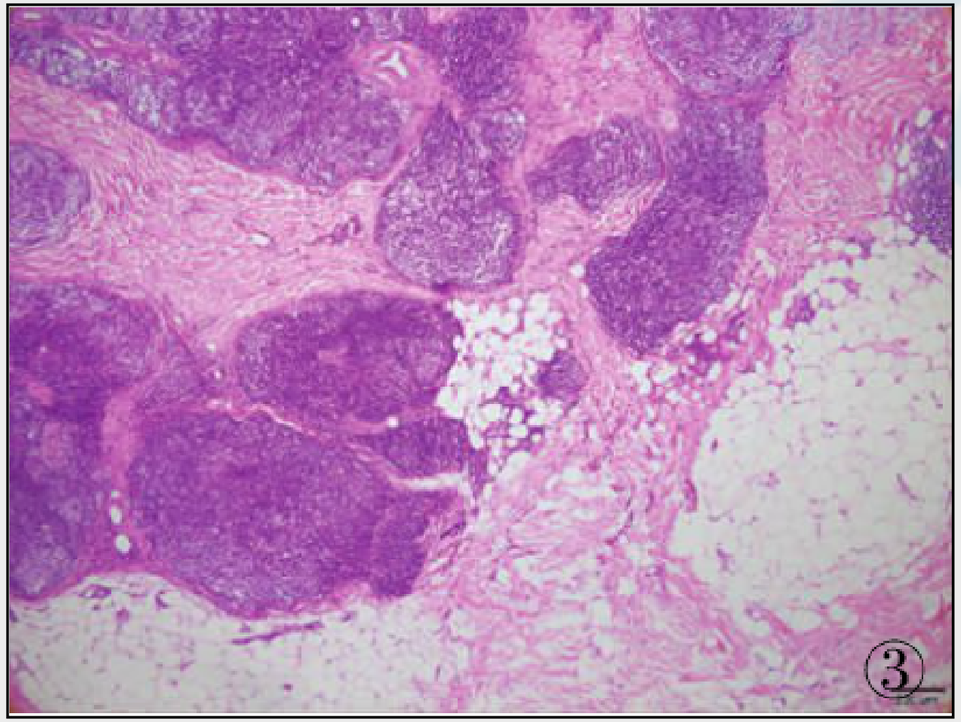
PCSMLPD

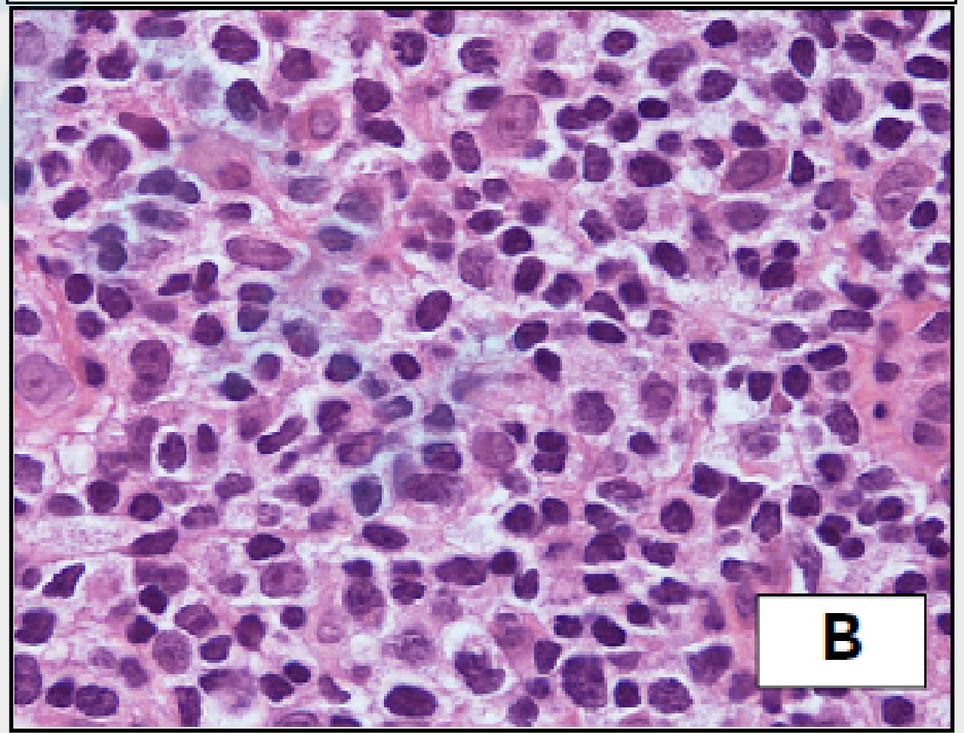
组织学改变：形态多样，典型表现为表皮基本正常，无亲表皮现象，少数情况可出现局灶表皮浸润；真皮内小到中等大多形性淋巴样细胞呈弥漫或结节状浸润，以血管及皮肤附属器周围浸润为主，可侵犯皮下脂肪层，有时出现多形性大细胞，但比例小于30%。可混杂CD8+T细胞、B细胞、浆细胞、组织细胞及嗜酸性粒细胞成分。

免疫表型：表达广谱T细胞标记，会出现个别抗原丢失，以CD5和CD7多见。抗原PD-1、BCL-6、CXCL-13有不同程度的表达。Ki-67增殖指数多为5%-40%，TCR重排单克隆阳性率高于60%。


①


②


③


B

材料 & 方法

入组人群：三所医院2011年-2016年经专家复核诊断为PCSMLPD共60例。

入组条件：诊断需满足以下条件（1）单发的皮肤病变，临床证实无皮肤外受累；（2）小到中等大多形性淋巴样细胞浸润（多形性大细胞比例＜30%）。（3）至少表达2个TFH标记： PD1、BCL6、ICOS、CXCL13 、CD10

方法：

（1）免疫组化： CD2, CD3, CD4, CD5,CD7, CD8, CD20, CD21, CD23, CD30, Ki67,CD10, CXCL13, ICOS, PD1, BCL6

（2）TCR、BCR重排

（3）统计学分析

TABLE 1. Clinical Features

Clinical features	N = 60, n/N (%)
Sex	
Male	27 (45.0)
Female	33 (55.0)
Age*	59.3 (23-95)
Type of lesion	
Papule	11 (18.3)
Nodule	27 (45.0)
Plaque	9 (15.0)
Tumor	13 (21.7)
Localization	
Trunk	17 (28.3)
Upper extremity	9 (15.0)
Lower extremity	4 (6.7)
Head and neck	30 (50.0)
Treatment	
Topical steroids	15 (25.0)
Surgical excision	24 (40.0)
Radiation	14 ((23.3)
None	11 (18.3)
Others	5 (8.3)
Spontaneous regression after biopsy	15 (25.0)
Partial	5 (8.3)
Complete	10 (16.7)
Evolution	
Complete remission	54/54 (100)
Local relapse, extracutaneous spreading	0

*Median age with extremes is given.

形态学改变（1）

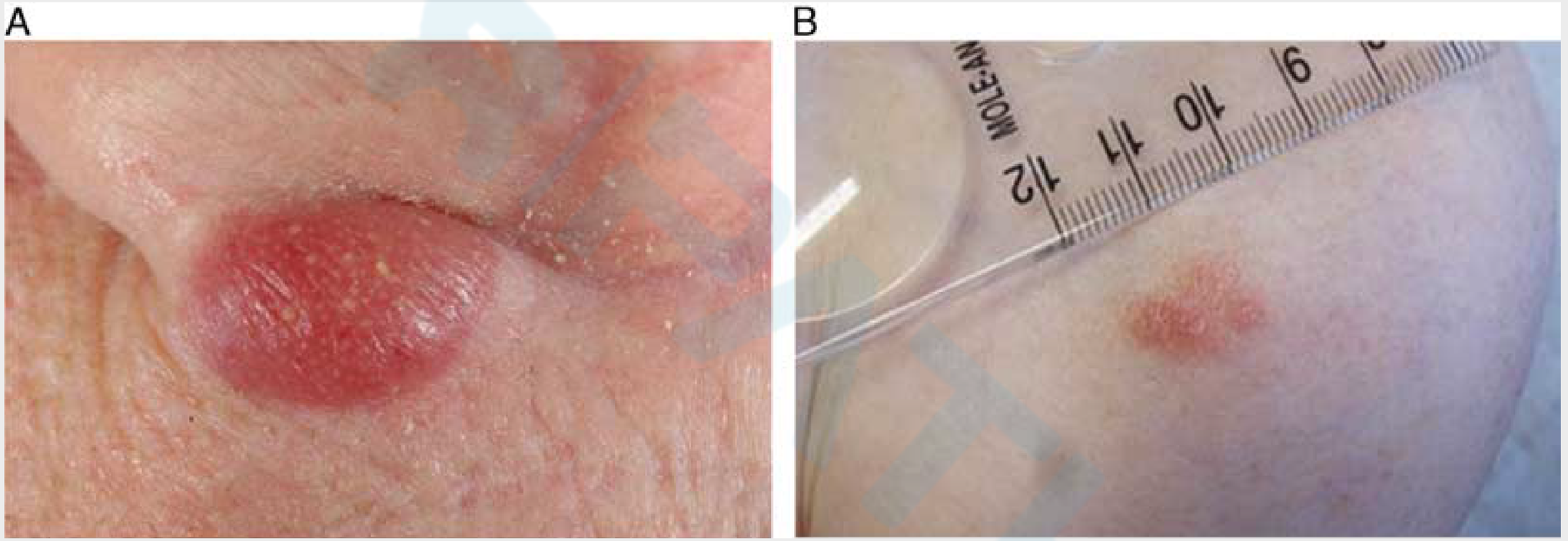


FIGURE 1. Clinical and morphologic spectrum of single cutaneous TFH lymphoproliferative disorders. Clinical presentation. A,Nodule. B, Plaque.

形态学改变（2）

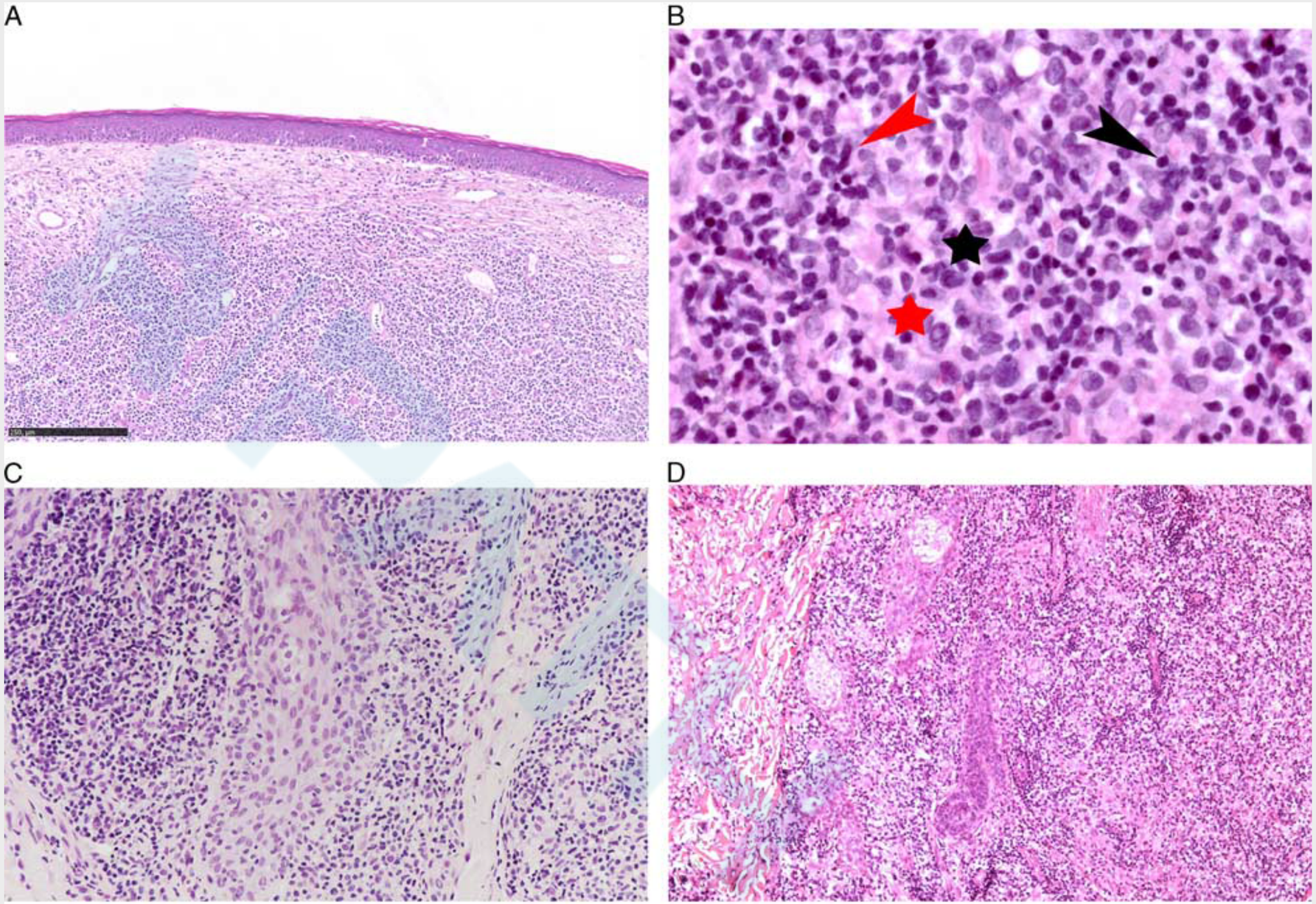


FIGURE 2. Morphologic aspects of single cutaneous lymphoproliferative disorders. A, Epidermotropism concerning isolated cells (HES). B, Admixture of small reactive lymphocytes (black arrow head), small atypical lymphocytes (red arrow head), medium-sized atypicallympho-cytes (black star), and large atypical lymphocytes (red star) (HES). C and D, Pilotropism and follicular dystrophy (HES).

形态学改变（3）

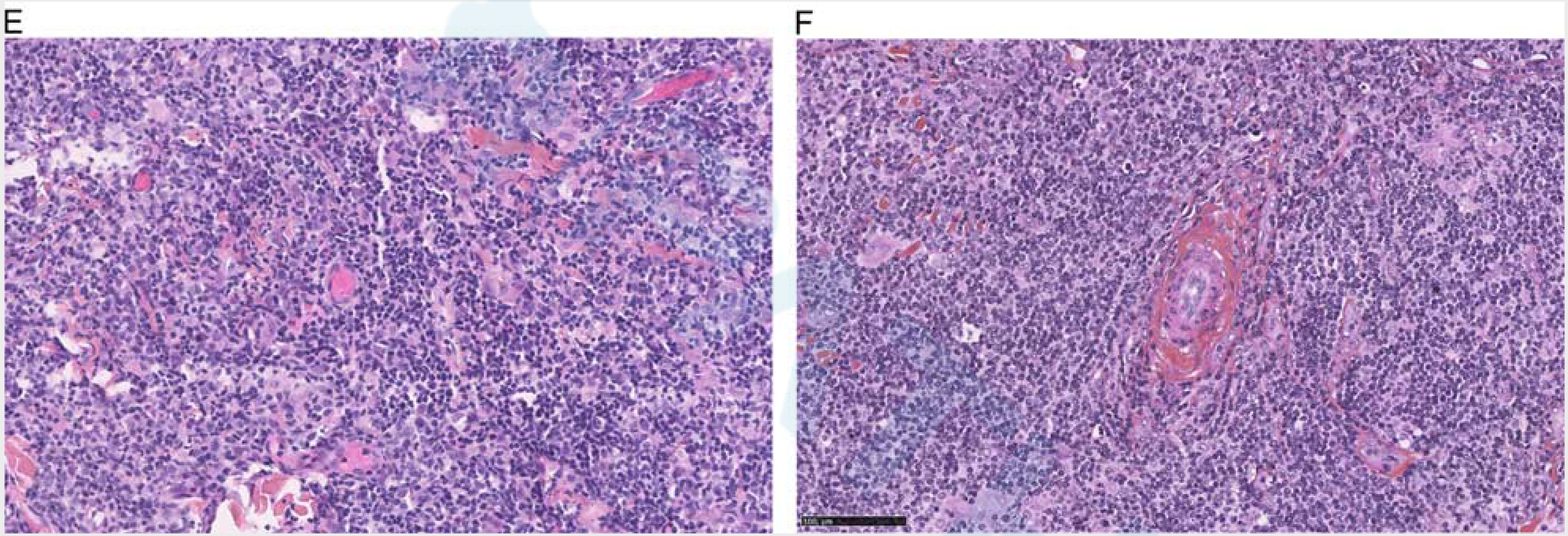
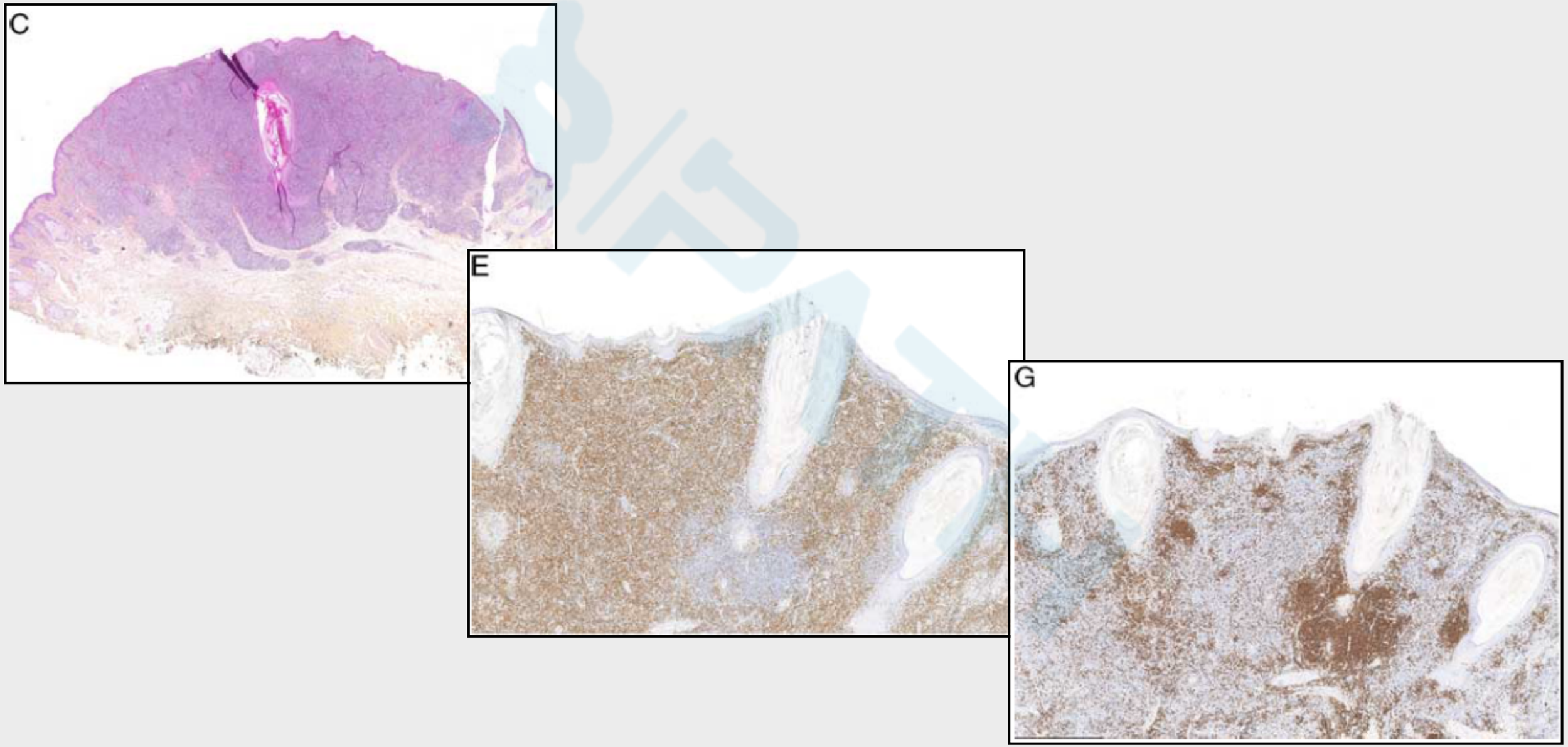


FIGURE 2. Vascular changes with vascular hyperplasia (E, HES) and angiocentrism (F, HES). HES indicates hematoxylin, eosin & saffron.

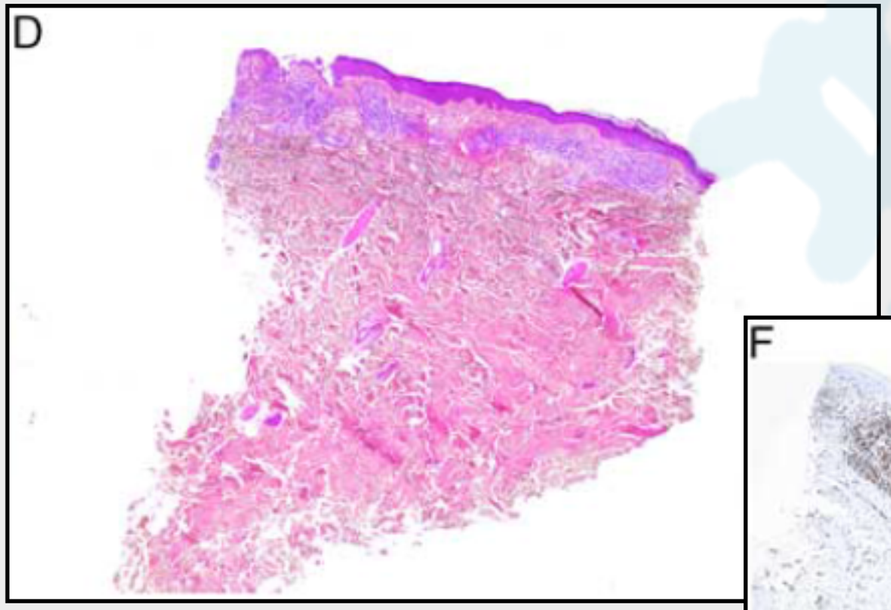
TABLE 2. Histopathologic Results

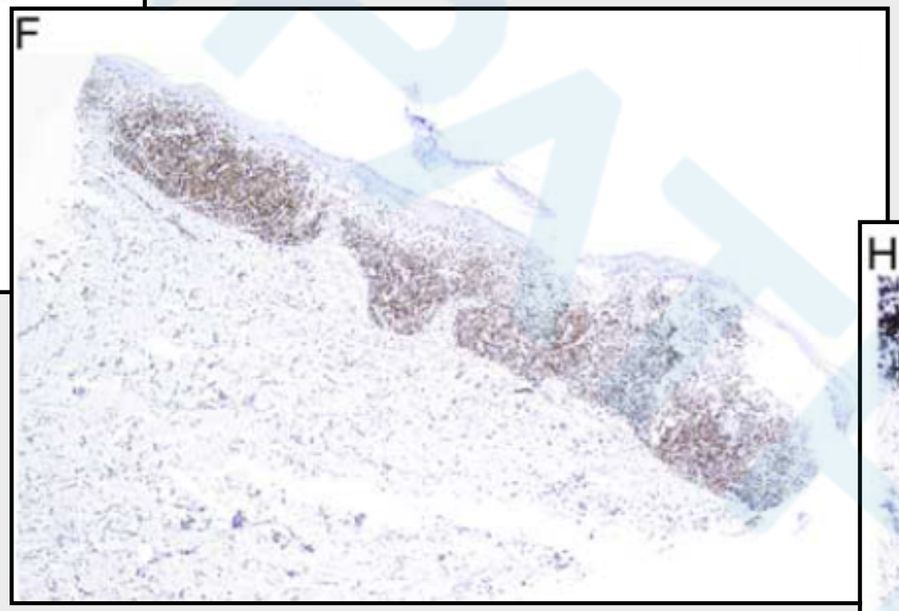
Lymphoproliferation Characteristics	Value, n (%)	Comments
Architecture (pattern)		
Pattern 1	47 (78.3)	Nodular/cell flow (n = 20) Nodular and diffuse (n = 10) Diffuse (n = 17)
Pattern 2	13 (21.7)	Net margin (n = 8) Periannexial cell flow (n = 5)
Infiltrate localization		
Superficial dermis	11 (18.3)	
Superficial and deep dermis	38 (63.3)	
Dermis and subcutis	11 (18.3)	
Epidermotropism	32 (53.3)	Pautrier abscesses (n = 9)
Mild	24 (40.0)	Single cell (n = 22)
Strong	8 (13.3)	Single file (n = 1)
Cytology (mean) (%)		
Small lymphocytes	64.9	
Medium/large lymphocytes	35.1	
Inflammatory cells		
Eosinophils	13 (22.8)	
Neutrophils	3 (5.3)	
Plasma cells	41 (71.9)	
Histiocytes	56 (98.3)	
Epidermal change	37 (61.7)	
Parakeratosis	5 (8.3)	
Atrophia	12 (20.0)	
Hyperplasia	5 (8.3)	
Spongiosis	15 (25.0)	
Keratinocyte necrosis	5 (8.3)	
Interface dermatitis	16 (26.7)	
Grenz zone	37 (64.9)	
Cutaneous appendage changes		
Pilotropism	44 (74.6)	
Follicular destruction	34 (57.6)	
Syringotropism	4 (6.7)	
Neurotropism	10 (16.7)	
Vascular changes		
Capillary hyperplasia	51 (85.0)	
Angiocentrism	25 (42.4)	
Angiotropism	23 (39.0)	

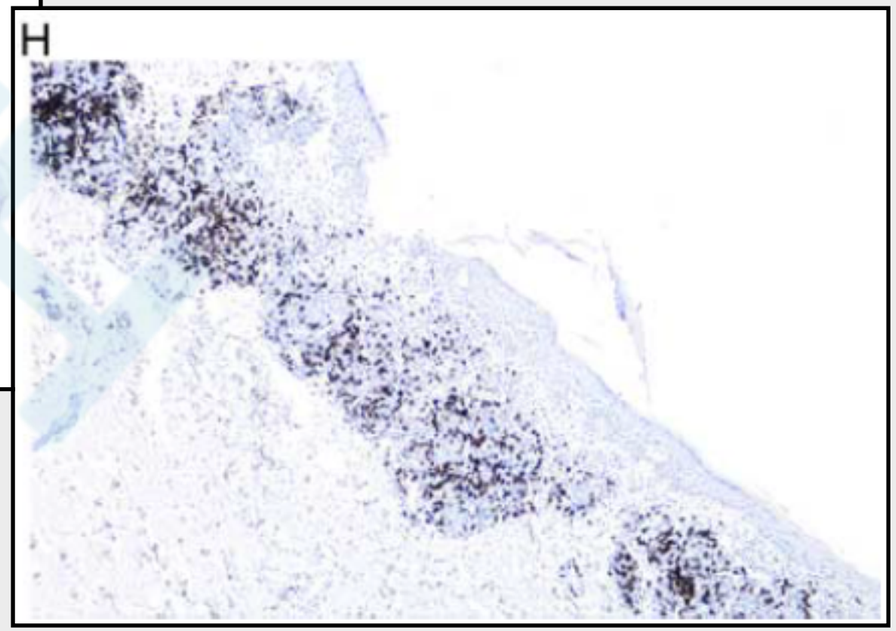
Pattern 1: 全部真皮层内淋巴组织呈结节状或弥漫性增生。



Pattern 2: 真皮浅层的条带状浸润，边界清楚。







	临床表现	组织学改变	病变部位
Pattern1	结节	血管改变（毛细血管增生、血管中心性生长、淋巴细胞浸润血管壁）	头颈部多见
Pattern2	丘疹	中等-大淋巴样细胞	上肢多见

免疫组化（1）

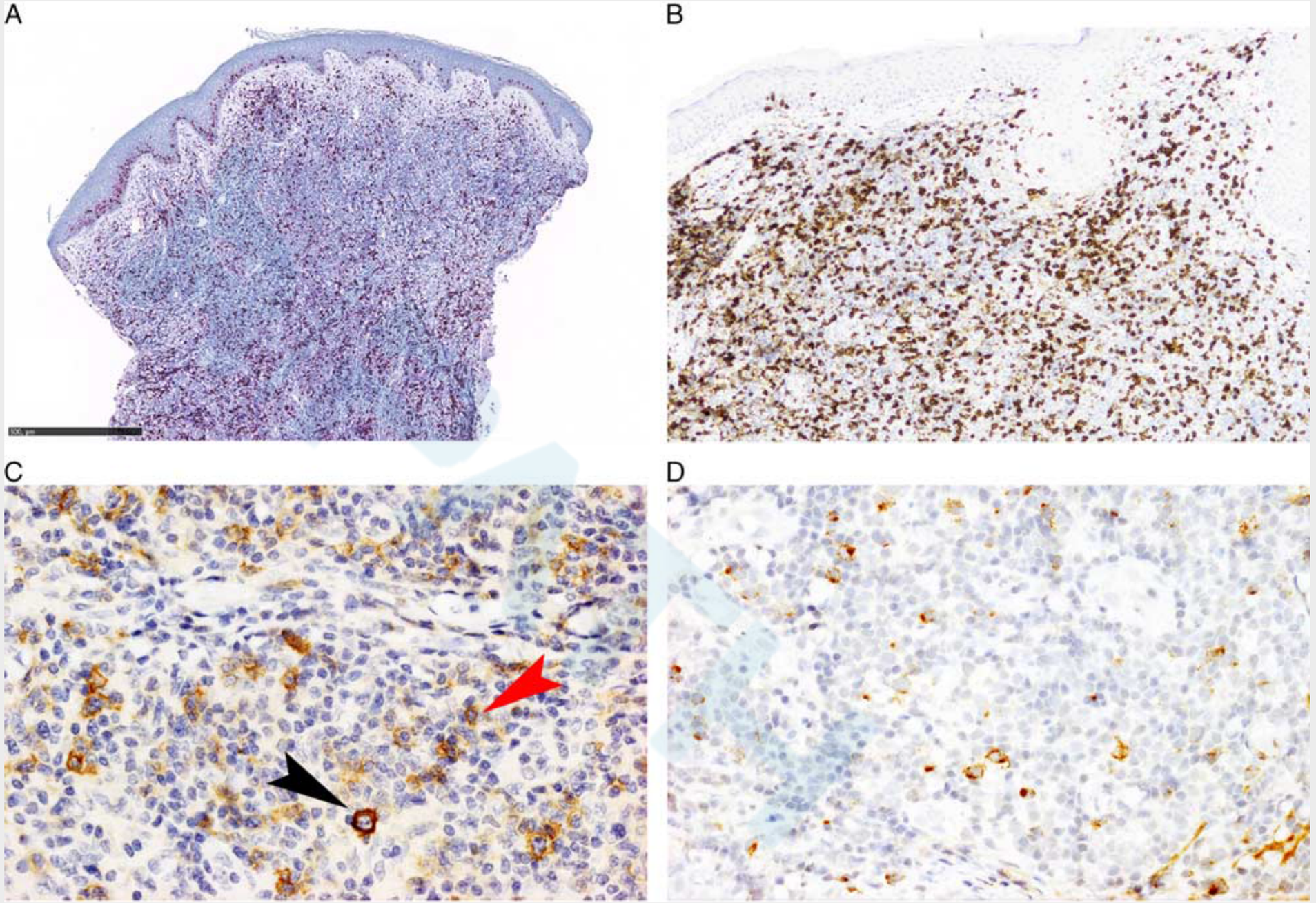


FIGURE 3. Immunophenotypical features of single cutaneous lymphoproliferative disorders. A, Low proliferation index (Ki67). B, Admixture with T-CD8+ lymphocytes. C, ICOS expression shows a double intensity of staining: strong on middle-to-large-sized cells(black arrow head) and mild o small atypical lymphocytes (red arrow head) (ICOS). D, Specific dot-like staining of CXCL13.

免疫组化（2）

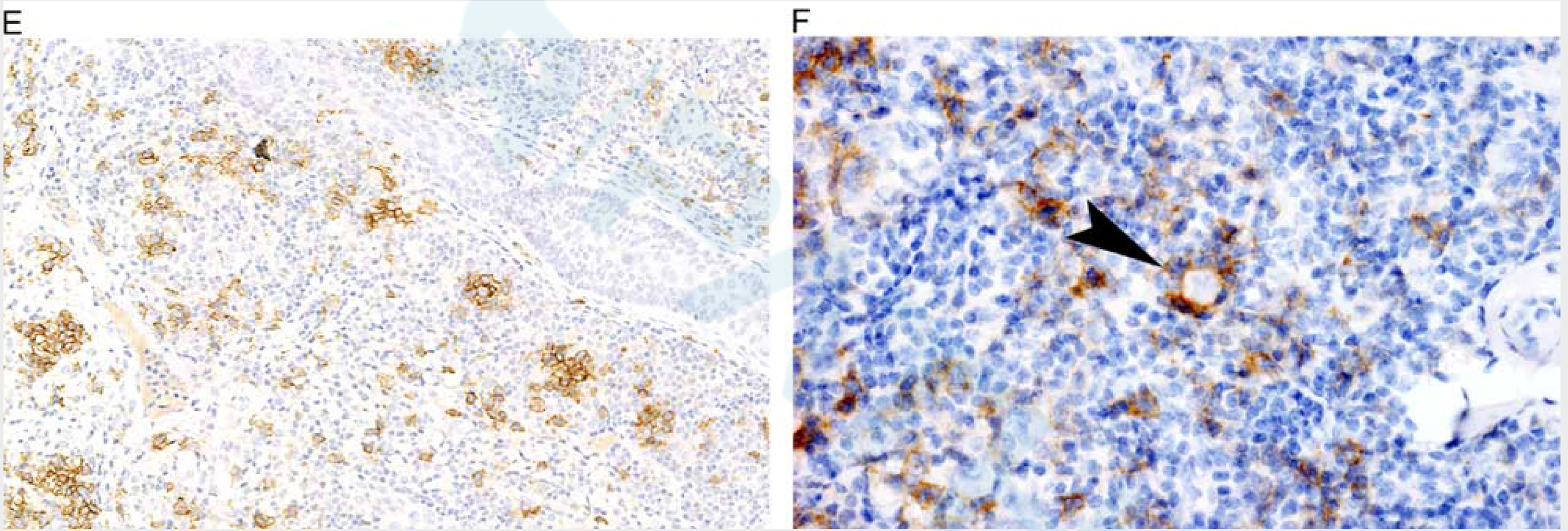


FIGURE 3. E (PD1) and F, Distribution of PD1+ cells in clusters or in a rosette around large cells (black arrow head) (PD1).

PCSMLPD

阳性：CD20、CD8、CD3、CD30、PD1、ICOS、CXCL13、BCL6、Ki-67 （平均增殖指数20%）。

阴性： CD10、CD5、CD7。

69%病例TCR基因重排阳性。

TABLE 3. Phenotypic Studies

Phenotypic Marker	n/N (%) All Cases	Pattern 1	Pattern 2	*P* (Pattern 1 vs. Pattern 2)
CD8	N = 58	N = 45	N = 13	
Median (p25-p75)	20 (10-30)	20 (10-30)	15 (10-20)	0.401
CD20	N = 58	N = 45	N = 13	
Median (p25-p75)	20 (20-30)	25 (20-30)	20 (10-30)	0.361
$CD20^+$ cells distribution				0.778
Sparse	32/56 (57.1)	24/43 (55.8)	8/13 (61.5)	
Clusters	21/56 (37.5)	17/43 (39.5)	4/13 (30.8)	
Nodules	3/56 (5.4)	2/43 (4.7)	1/13 (7.7)	
T-cell antigen loss	14/54 (25.9)	11/43 (25.8)	3/11 (27.3)	0.592
CD5	2/54 (3.7)	2/43 (4.7)	0	
CD7	13/54 (24.1)	11/43 (25.6)	2/11 (18.2)	
PD1				
Median (p25-p75)	20 (20-30)	20 (20-30)	25 (20-30)	0.324
< 5%	2/59 (3.4)	2/46 (4.4)	0	0.110
5%-50%	52/59 (88.1)	42/46 (91.3)	10/13 (76.9)	
> 50%	5/59 (8.5)	2/46 (4.2)	3/13 (23.1)	
$PD1^+$ cell distribution				0.176
Sparse	19/58 (32.8)	17/45 (37.8)	2/13 (15.4)	
Clusters	37/58 (63.8)	27/45 (60.0)	10/13 (76.9)	
Sheets	2/58 (3.5)	1/45 (2.2)	1/13 (7.7)	
ICOS				
Median (p25-p75)	30 (20-30)	27.5 (20-30)	30 (25-40)	0.230
< 5%	2/52 (3.9)	2/40 (5.0)	0	0.634
5%-50%	42/52 (80.8)	33/40 (82.5)	9/12 (75.0)	
> 50%	8/52 (15.4)	5/40 (12.5)	3/12 (25.0)	
$ICOS^+$ cell distribution				**0.034**
Sparse	43/50 (86.0)	36/39 (92.3)	7/11 (63.6)	
Clusters	7/50 (14.0)	3/39 (7.7)	4/11 (36.4)	

Pattern1中ICOS阳性细胞多散在分布，pattern2 ICOS阳性细胞多以束状出现。

CXCL13				
Median (p25-p75)	5 (1-10)	5 (1-5)	5 (2-20)	0.257
<20%	40/46 (87.0)	35/37 (94.6)	5/9 (55.6)	**0.009**
≥20%	6/46 (13.0)	2/37 (5.4)	4/9 (44.4)	
BCL6				
Median (p25-p75)	10 (10-20)	10 (10-20)	10 (5-10)	0.157
Ki67				
Median (p25-p75)	20 (15-30)	20 (15-30)	20 (10-20)	**0.039**
<25%	30/48 (62.5)	21/38 (55.3)	9/10 (90.0)	**0.044**
≥25%	18/48 (37.5)	17/38 (44.7)	1/10 (10.0)	
Cutaneous T-cell clone	36/53 (67.9)	31/43 (72.1)	5/10 (50)	0.165
Cutaneous B-cell clone	6/23 (26.1)	6/20 (30.0)	0/3 (0)	0.384

Bold values indicate statistical differences, $P < 0.05$.

CXCL13在pattern2中阳性细胞数较多；Ki-67在pattern1增殖指数较高。

PCSMLPD

TABLE 4. Key Features for Diagnosis

Major key features	
Clinical aspect	Erythematous nodule/tumor > > plaque/papule
	Head and neck > trunk > Lower and upper extremities
	Spontaneous regression after biopsy
Histopathology	Pattern 1: dense, nodular, and diffuse, in the entire dermis ± subcutis
	Pattern 2: subepidermal band-like ± periadnexal cell flow
	Pleomorphic atypical lymphocytes (30%-40% medium cells and <30% of large cells)
	Inflammatory cells: histiocytes > > plasmocytes > > eosinophils
	Vascular hyperplasia
Phenotype	$CD3^+$ $CD4^+$ atypical lymphocytes
	20% of B lymphocytes (mean) scattered throughout T lymphocytes
	20% of $CD8^+$ lymphocytes (mean), starry sky-like
	TFH markers:
	$PD1^{++}$: 25%, cluster and "rosette," medium/large cells
	$ICOS^{++}$: 25%-30%, sparse, small/medium/large cells
	$CXCL13^+$: 5%, sparse, medium-to-large cells
	$BCL6^+$: 10%, sparse, medium-to-large cells
	Cutaneous T-cell clone
Evolution	Complete remission
Minor key features	
Histopathology	Grenz zone (rare epidermotropism)
	Pilotropism/pilarisdystrophia
	Angiocentrism/angiotropism
Phenotype	Scattered $CD30^+$ large cells < 5%
	T-cell antigen loss (CD7 > CD5)
	Low proliferation index (median = 20%)

鉴别诊断

(1). 皮肤假淋巴瘤：好发于头颈部，皮损可表现为红斑、丘疹、结节等。组织学上真皮浅层及皮下见 淋巴细胞弥漫片状浸润，一般不侵犯皮肤附件，细胞大多数呈多克隆增生。

(2). 蕈样霉菌病：好发于躯干、下肢等非暴露部位，典型的临床过程分为3期：红斑期、斑块期和肿瘤期。组织学上病变通常为亲表皮性，表皮内可形成“Pautrier”微脓肿，肿瘤细胞具有脑回样核。

(3).血管免疫母细胞T细胞淋巴瘤：PD1、CXCL13以及BCL-6均有TFH细胞免疫特点，但AITL临床通常为系统性表现，EBER阳性及CD21“乱网”可有助于鉴别。

感 谢 观 看