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Class-switched Primary Cutaneous Marginal Zone Lymphomas Are Frequently IgG4-positive and Have Features Distinct From IgM-positive Cases

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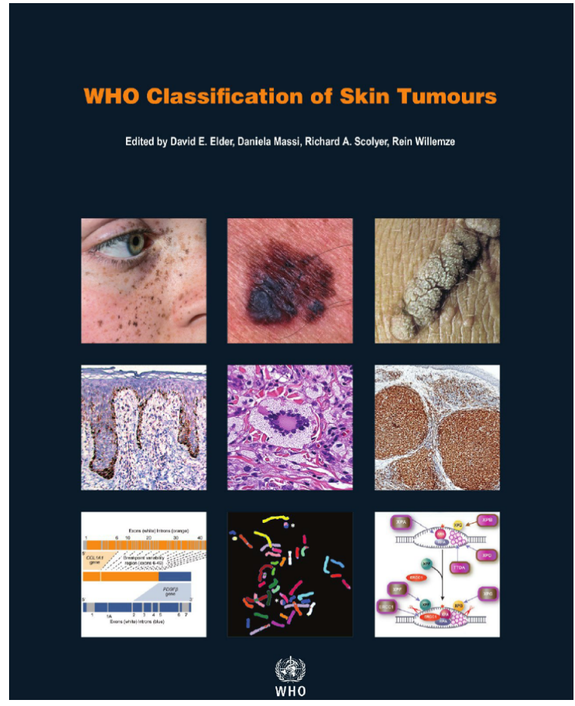


原发性皮肤边缘区淋巴瘤（PCMZL）

➢定义：PCMZ是由肿瘤性小B细胞、浆细胞和数量不定的反应性T细胞组成的一种惰性淋巴瘤。
在2017年WHO淋巴瘤分类的修订版中，PCMZL被包括在粘膜相关淋巴组织的结外边缘区淋巴瘤（MALT淋巴瘤）类别中。

➢ICD-O编码：9699/3

➢流行病学：占原发性皮肤B细胞淋巴瘤30-40%；
最常累及50-60岁的成人，男性多见；
是儿童和青少年最常见的皮肤B细胞淋巴瘤。

➢发病部位：主要位于躯干和上肢。

➢临床特点：通常表现为多灶性、有时呈孤立的红色或紫红色斑块或结节。

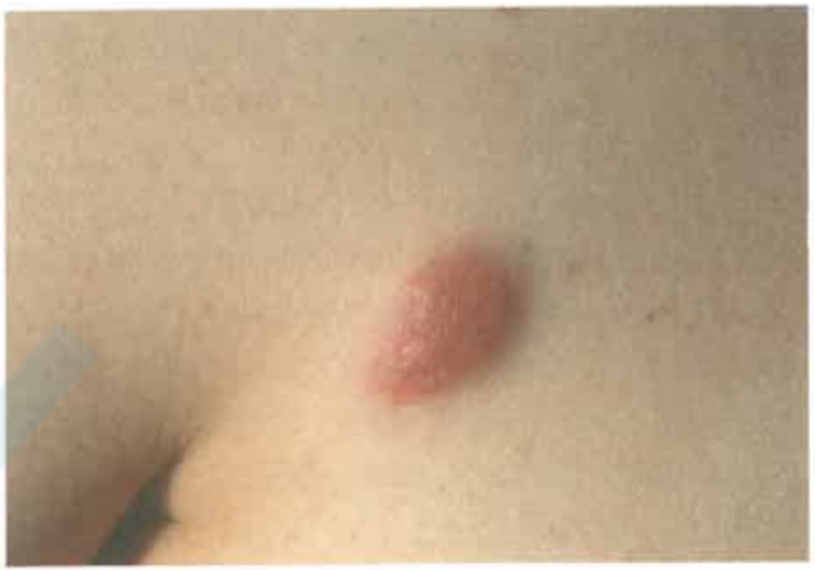


Fig. 4.73 Primary cutaneous marginal zone lymphoma. Erythematous nodule on the upper back.

2018 WHO Classification of Skin Tumors

- 组织病理学：

表现为小淋巴细胞、浆细胞和具有生发中心的反应性滤泡向致密的真皮组织的多结节浸润；

在大多数情况下，小B细胞具有淋巴浆细胞样形态，浆细胞通常位于浸润的周围。

- 免疫表型：

肿瘤性B细胞：CD19+、CD20+、CD79a+、bcl-2+；
CD5-、CD10-、bcl-6-、cyclin D1-

反应性生发中心： bcl-6+、 bcl-2-

- 预后：预后好，5年存活率>98%。
迁延性临床经过，复发常见。
皮肤外播散罕见（约4%）

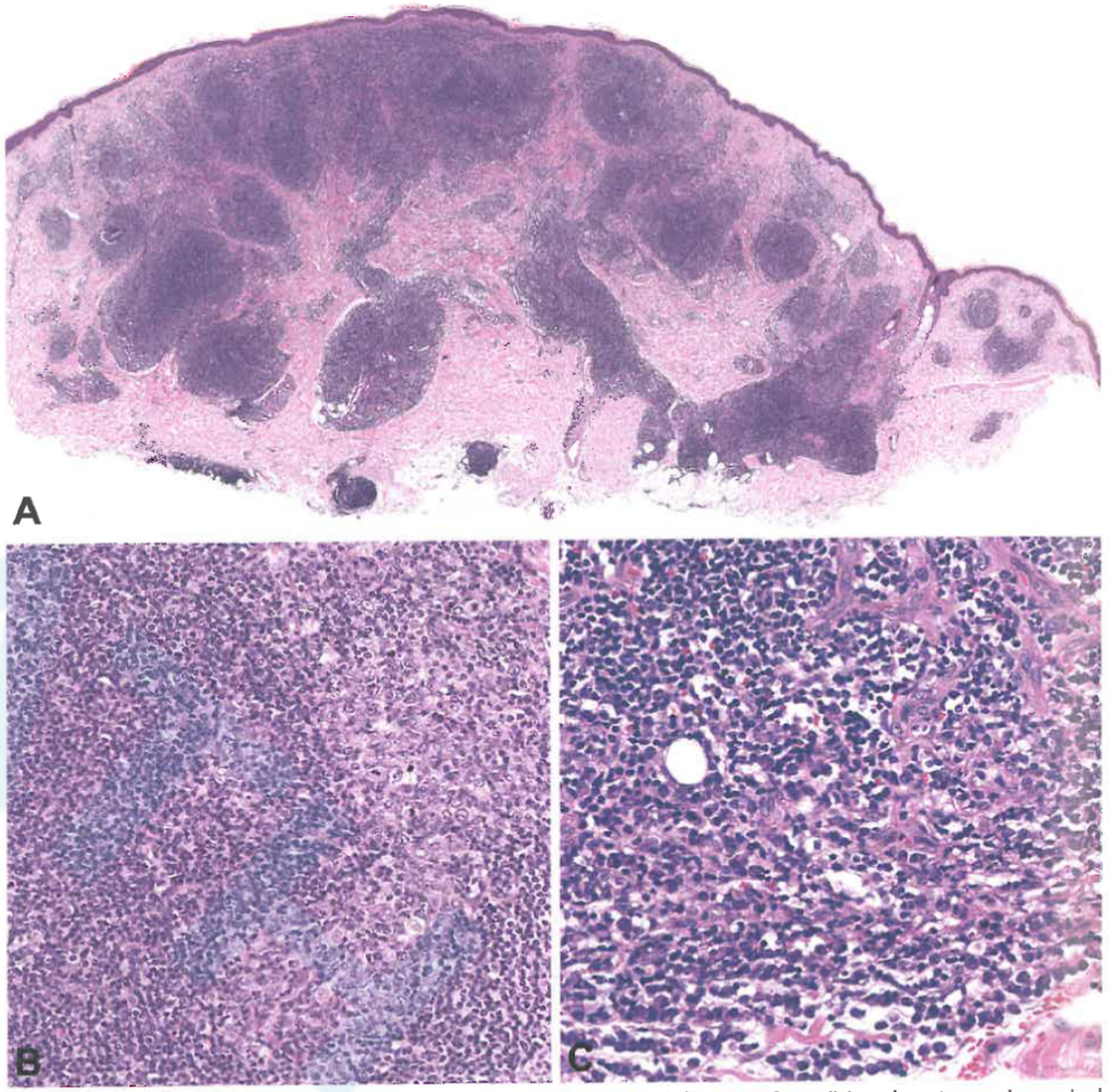


Fig. 4.74 Primary cutaneous marginal zone lymphoma. **A** Nodular infiltrates of small lymphocytes and germinal centres. **B** Infiltrate of small lymphocytes surrounding reactive germinal centres. **C** Plasma cells at the periphery of the infiltrates.

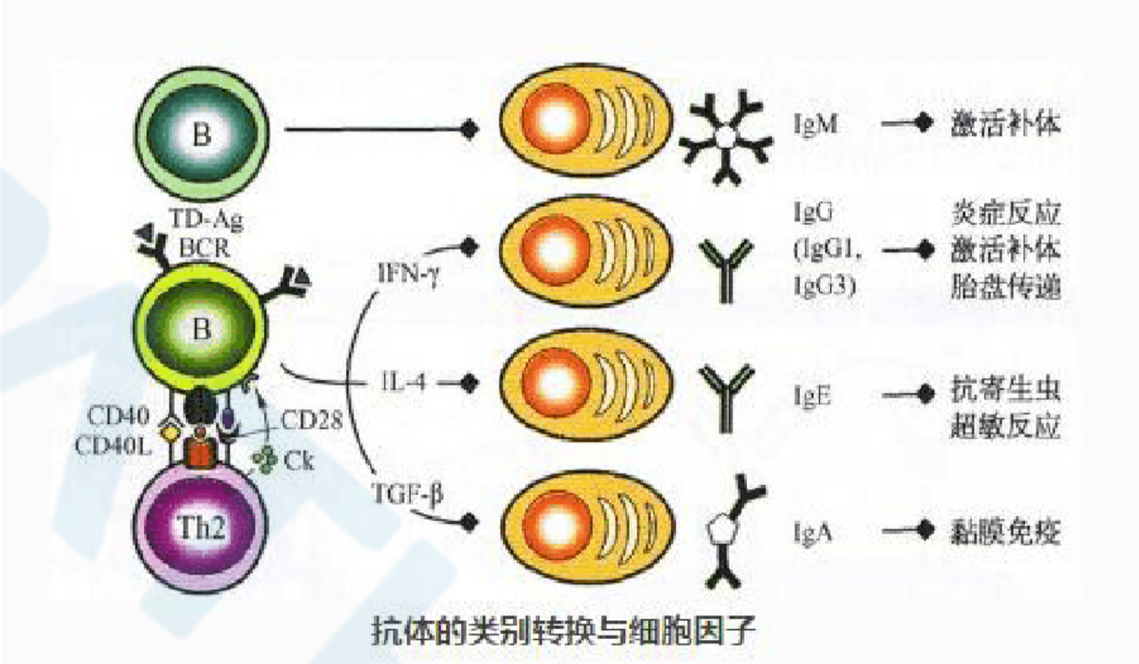
2018 WHO Classification of Skin Tumors

免疫球蛋白类别转换
（Ig class-switch）

- 免疫球蛋白的类别转换（class switch)是指Ig的可变区不变，即结合抗原的特异性相同，但其重链类型（恒定区）发生改变。

- 在免疫应答时首先合成IgM，然后转换产生IgG、IgA、IgE等。

- 类别转换依赖于T辅助细胞发送信号，尤其是需要T细胞上的CD40配体（CD154）和B细胞上的CD40结合。



抗体的类别转换与细胞因子

PCMZL Subtypes

Based on immunoglobulin (Ig) heavy chain expression, PCMZL can be subdivided into 2 subtypes

Heavy chain class-switched PCMZL	IgM-positive PCMZL
• more common subtype (85% of PCMZL) • IgG+, IgA+, IgE+, CXCR3- • predominantly Th2-driven • A high number of T cells • differs from many other MALT lymphomas	• less frequent subtype • IgM+, CXCR3+ • more Th1-driven process • Large sheets of B cells • similarities to MALT lymphomas at other sites

2018 WHO Classification of Skin Tumors

IgG4-positive PCMZL (40% of PCMZL)

Aim

- To further evaluate the proportion of IgG4-positive PCMZL
- To address whether IgG4-positive cases have any distinctive characteristics
- To assess whether additional features separating IgM-positive and class-switched cases could be identified

MATERIALS AND METHODS

➢ Case Selection

the Department of Pathology at UPMC; January 2001 to April 2017; skin or subcutaneous tissue biopsies

MZL or MALT lymphoma with plasmacytic differentiation; known extracutaneous MZL were excluded.

26 PCMZL obtained from 19 patients

clinical data: relevant clinical history, sites of disease, staging information, treatment, and follow-up

MATERIALS AND METHODS

➢ Histologic and Immunophenotypic Review:

Histologic assessment: diagnosis confirmation

Immunohistochemical stains: IgA, IgD, IgM, IgG, IgG4, kappa, lambda, CD20, CD3, CD4, CD8, CD279/PD1, GATA3, FOXP3, CD10 and BCL6

The dominant light chain and heavy chain in the plasma cells, the relative proportions of B cells, T cells, and T-cell subsets assessments

➢ MYD88 L265P Mutation Analysis:

All IgM-positive PCMZL; real-time PCR assay

➢ Statistics

MATERIALS AND METHODS

抗体	用途	判读标准
CD20，CD10，BCL6	肿瘤细胞表型	
IgA, IgD, IgM, IgG	是否有类别转换	IgG or IgA on >50% of plasma cells were considered class-switched
kappa, lambda	是否具有轻链限制性	
IgG4	是否为IgG4阳性病例	A case was considered positive for IgG4 when the IgG4:IgG ratio was ≥40%
CD3	反应性细胞是否T细胞为主	T细胞为主：>50% T cells
CD4, CD8	反应性T细胞的表型分类	CD4:CD8 ≥3:1 or <3:1
CD279/PD1, GATA3, FOXP3	残存的生发中心外浸润的T细胞的表型 CD279/PD1-positive TFH GATA3-positive Th2 cells FOXP3-positive Tregs	分三类： <5% , 5% to 10%， >10% positive cells

RESULTS 1

Clinical Features

- 19 patients: 11 females and 8 males; 25-80y (50y);
- Site: extremities, trunk, or head and neck
- Extracutaneous disease: None
- Treatment: 9 patients: local therapy; 5 patients: systemic multiagent chemotherapy; 4 patients: single-agent rituximab; 1 patient: excised the lesion
- Recurrence: 12 patients developed at least 1 recurrence (range: 1 to 7 recurrences)
- Follow-up: 15 patients were ANED; 3 were alive with persistent disease; 1 patient died of disease 35.5 months (range: 3.4 to 225.3 months)

TABLE 1. Clinical Features of 19 Patients With 26 PCMZL

Case No.	Age (y)	Sex	Dominant Plasma Cell Heavy Chain/ Light Chain	Sites of Disease at Initial Diagnosis	Extracutaneous Disease	Treatment	No. of Recurrences	Time to First Recurrence (mo)	Follow-Up Time (mo)	Status at Last Follow-Up
1	29	Female	IgG4/kappa	Extremities	No	RT, TS	0	NA	37.5	ANED
2a	50	Female	IgG4/lambda	Extremities, trunk	No	RT, R	1	24.5	150.6	ANED
2b			IgG/kappa							
3	47	Female	IgG4/lambda	Extremities	No	Excision	0	NA	95.4	ANED
4	49	Female	IgG4/kappa	Head/neck	Unknown*	RT	0	NA	3.4	ANED
5a	51	Female	IgG4/lambda	Trunk	No	RT, TS	2	22.1	87.6	ANED
5b			IgG/lambda							
6	43	Male	IgG4/kappa	Trunk	No	R	0	NA	12.5	ANED
7	62	Male	IgG4/lambda	Trunk	No	RT	0	NA	18.6	ANED
8	46	Male	IgG4/kappa	Extremities	No	RT, R	2	62.8	75.7	ANED
9	36	Male	IgG4/kappa	Extremities, trunk	No	TS	1	29.8	41.7	AWD
10a	50	Male	IgG/lambda	Extremities	No	CT, RT	2	69.7	225.3	ANED
10b			IgG/kappa							
11	25	Male	IgG/lambda	Extremities	No	R	1	86.3	133.9	ANED
12a	30	Male	IgG/kappa	Extremities	No	RT, TS	3	19.6	79.4	ANED
12b			IgG/lambda							
13a	67	Female	IgG/lambda	Extremities	No	CT, RT	1	45.6	46.1	AWD
13b			IgM/kappa							
14	45	Male	IgG/kappa	Extremities	No	TS	0	NA	30.6	ANED
15	63	Female	IgG/kappa	Extremities	No	RT	2	23.9	36.7	ANED
16a	64	Female	IgM and IgA/ kappa	Extremities, trunk	No	CT, RT	7	7.8	35.5	DOD†
16b			IgA/kappa							
16c			IgM/kappa							
17	69	Female	IgM/kappa	Extremities, head/neck	Unknown*	RT, TS	1	11.9	61.6	ANED
18	78	Female	IgM/kappa	Head/neck	No	CT	0	NA	84.8	ANED
19	80	Female	IgM/kappa‡	Extremities	No	CT, RT	2	159.1	187.8	AWD

*Results of radiologic imaging and bone marrow evaluations were not available; however, extracutaneous disease was not noted in routine clinical notes during follow-up.

†This patient died of disease 35.5 months after the initial diagnosis of PCMZL following multiple subcutaneous recurrences and eventual development of a diffuse large B-cell lymphoma involving the stomach and pleural fluid.

‡This case was characterized by diffuse IgM/kappa-positive lymphoid/plasmacytoid cells and more peripherally clustered IgG-positive, polytypic plasma cells.

ANED indicates alive with no evidence of disease; AWD, alive with disease; CT, chemotherapy with rituximab; NA, not applicable; R, rituximab; RT, radiation therapy; TS, topical/intralesional steroids.

RESULTS 2

Ig Expression and MYD88 L265P Mutation Analysis

- Ig Expression:
  22 of 26 (77%) PCMZL were heavy chain class-switched (19 IgG-positive, 1 IgA-positive), including 9 that were IgG4-positive (35%);
  5 of 26 (19%) PCMZL were IgM-positive

- MYD88 L265P mutation:
  None of them in all IgM-positive PCMZL

RESULTS 3

Correlation of Ig Heavy Chain Expression With Histologic and Other Immunophenotypic Features

- Location of infiltrate: 18 of 20(90%) class-switched PCMZL showed dermal based disease; 5 of 6 (83%) IgM-positive PCMZL exhibited primarily subcutaneous involvement
- Retained Follicles With GC: 22 of 26 (77%) PCMZL; No difference
- Follicular Colonization: only 1 of 20 (5%) class-switched PCMZL; all IgM-positive PCMZL
- Monocytoid B cells: 4 of 26 (15%) PCMZL, a feature more common in cases with a predominantly subcutaneous distribution of disease (3/4 cases)
- Distribution of Monotypic PC: All IgG4-positive and 10 of 11 (91%) class-switched PCMZL showed peripherally clustered monotypic; 4 of 6 (67%) IgM-positive PCMZL contained scattered monotypic PC
- Dutcher bodies and/or Mott cells: only 4 of 26 (15%) PCMZL
- CD3+ T cells: 17 of 20 (85%) class-switched PCMZL a predominance of T cells(>50%); all IgM-positive PCMZL had a predominance of B cells (≤ 50%)
- CD4:CD8 T cell ratios: 19 of 20 (95%) class-switched PCMZL≥3:1; 3 of 6 (50%) IgM-positive PCMZL<3:1
- CD279/PD1+、GATA3+、and FOXP3+ T cells: No difference

TABLE 2. Histologic and Immunophenotypic Features of 26 PCMZL

Case No.	Dominant PC HC	Location of Infiltrate	Retained Follicles With GC	Follicular Colonization	Monocytoid B Cells	Distribution of Monotypic PC	Dutcher Bodies or Mott Cells	% $CD3^+$ T Cells	CD4:CD8 Ratio	% $CD279/PD1^+$ T Cells	% $GATA3^+$ T Cells	% $FOXP3^+$ T Cells
1	IgG4	Dermis	No	No	No	Peripheral clusters	No	20-50	≥3:1	>10	>10	5-10
2a	IgG4	Dermis	Yes	No	Yes	Peripheral clusters	No	>50	≥3:1	>10	NA	5-10
2b	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
3	IgG4	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
4	IgG4	Dermis	No	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
5a	IgG4	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
5b	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
6	IgG4	Dermis	No	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
7	IgG4	Dermis	Yes	No	No	Peripheral clusters	Yes	>50	≥3:1	5-10	>10	<5
8	IgG4	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
9	IgG4	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
10a	IgG	Dermis	No	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
10b	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	5-10
11	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
12a	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	5-10	>10	5-10
12b	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
13a	IgG	Subcutis	Yes	No	Yes	Peripheral clusters	No	20-50	≥3:1	>10	>10	<5
13b	IgM	Subcutis	Yes	Yes*	Yes	Peripheral clusters	No	20-50	≥3:1	>10	>10	<5
14	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
15	IgG	Dermis	Yes	No	No	Peripheral clusters	No	>50	≥3:1	>10	>10	<5
16a	IgM and IgA	Subcutis	Yes	Yes*	No	Scattered	Yes	20-50	<3:1	>10	>10	<5
16b	IgA	Subcutis	Yes	Yes*	No	Scattered	Yes	<20	<3:1	>10	5-10	<5
16c	IgM	Subcutis	No	Yes*	No	Scattered	Yes	<20	<3:1	>10	5-10	5-10
17	IgM	Dermis	No	Yes†	No	Scattered	No	20-50	≥3:1	>10	>10	5-10
18	IgM	Subcutis	Yes	Yes†	No	Scattered	No	20-50	<3:1	>10	>10	5-10
19	IgM‡	Subcutis	Yes	Yes†	Yes	NA‡	No	20-50	≥3:1	>10	>10	<5

*Follicles mostly colonized by PCs.
†Follicles mostly colonized by lymphoid cells.
‡This case was characterized by diffuse IgM/kappa-positive lymphoid/plasmacytoid cells and many, more peripherally clustered, polytypic IgG-positive PCs, which obscured assessment of light chain expression by IgM-positive PCs.
GC indicates germinal centers; HC, heavy chain; NA, not available/applicable; PC, plasma cells.

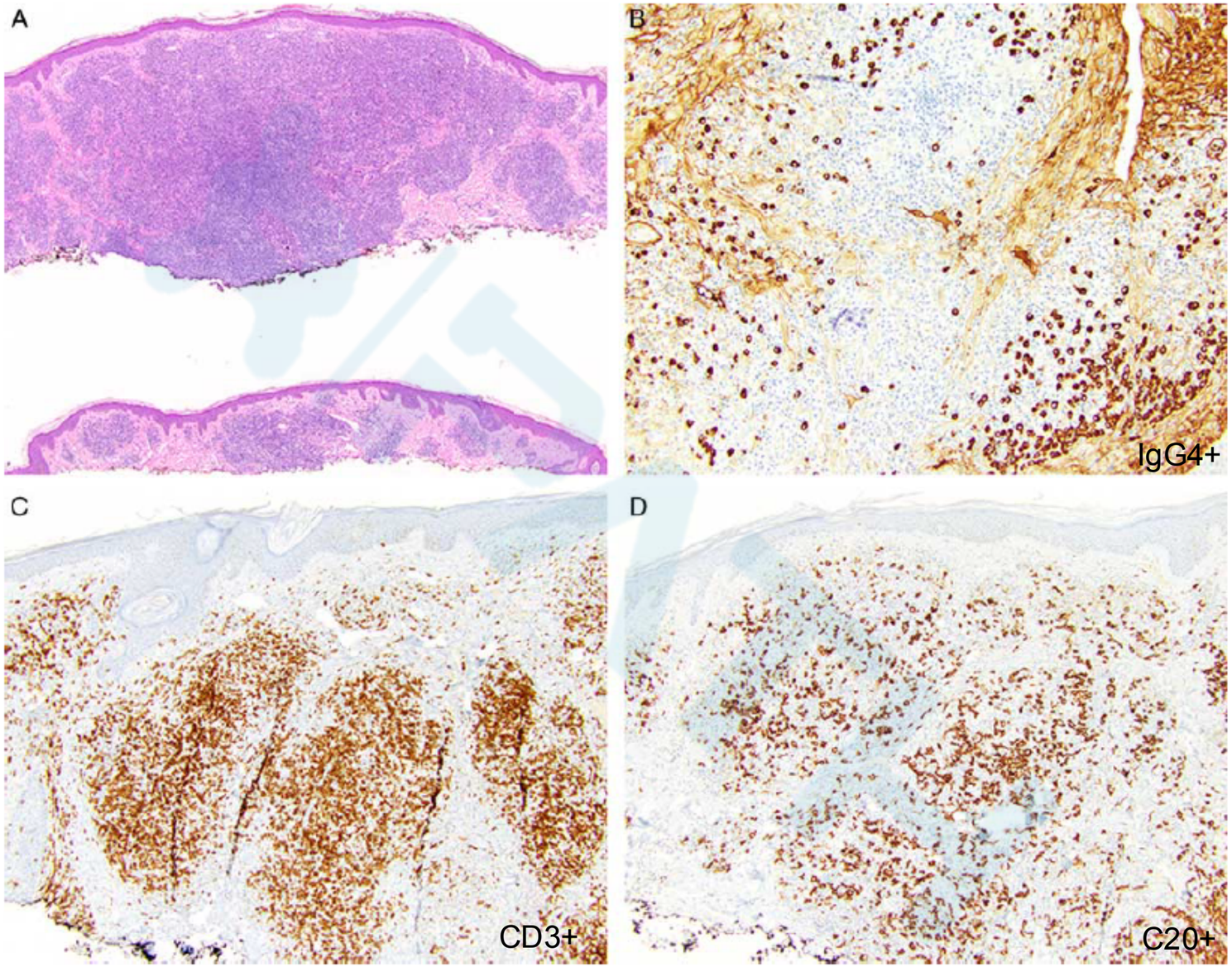


FIGURE 1. IgG4-positive PCMZL. This dermal-based PCMZL (A) contained peripherally clustered IgG4-positive, monotypic plasma cells (B). CD3-positive T cells (C) predominated over CD20-positive B cells (D). A, hematoxylin and eosin; B–D, immunohistochemical stain with hematoxylin counterstain.

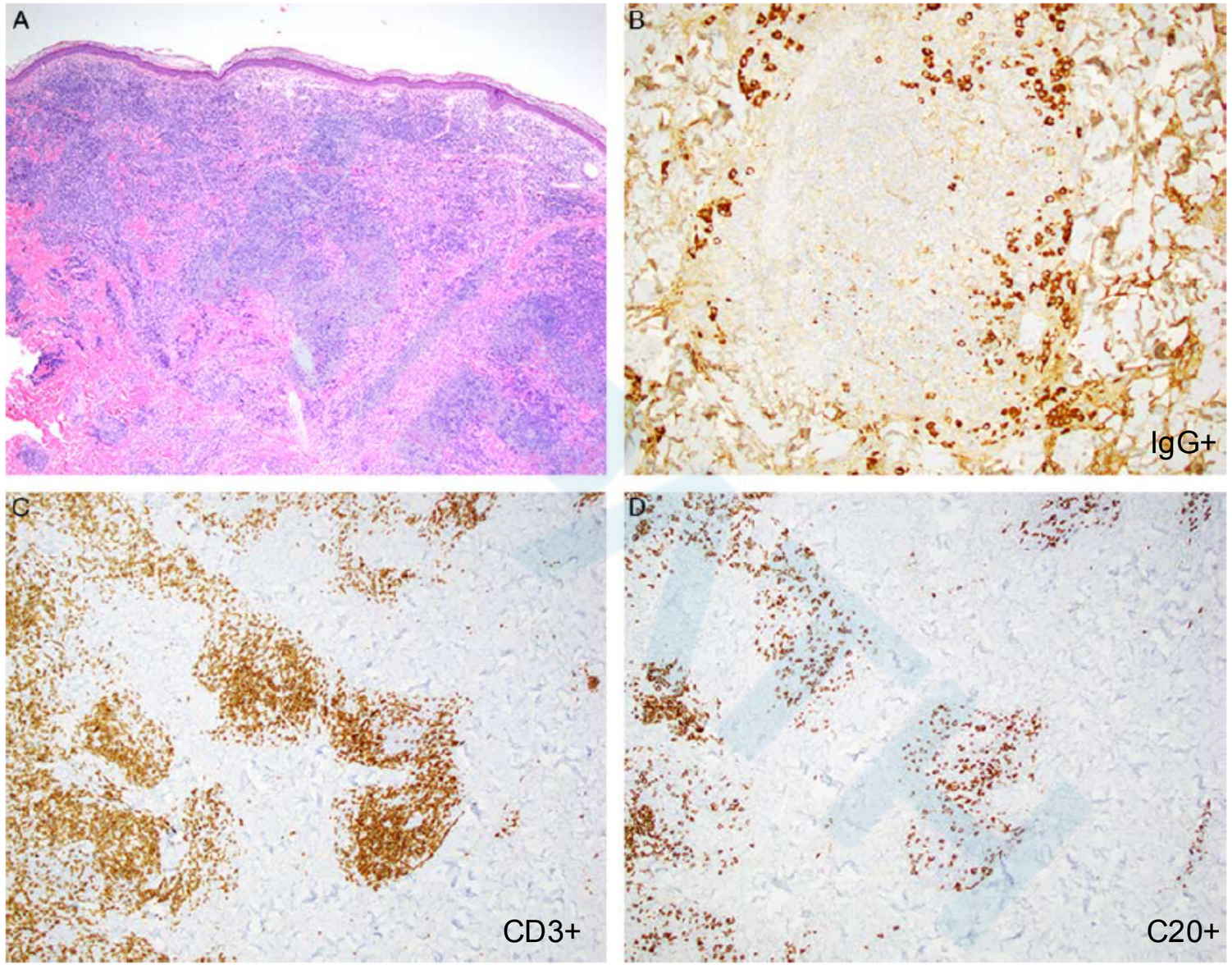


FIGURE 2. IgG4-negative/class-switched PCMZL. This IgG-positive (A) PCMZL was dermal-based and associated with peripherally clustered, monotypic plasma cells (B). Similar to the IgG4-positive cases, CD3-positive T cells (C) were more numerous than CD20-positive B cells (D). A, hematoxylin and eosin; B–D, immunohistochemical stain with hematoxylin counterstain.

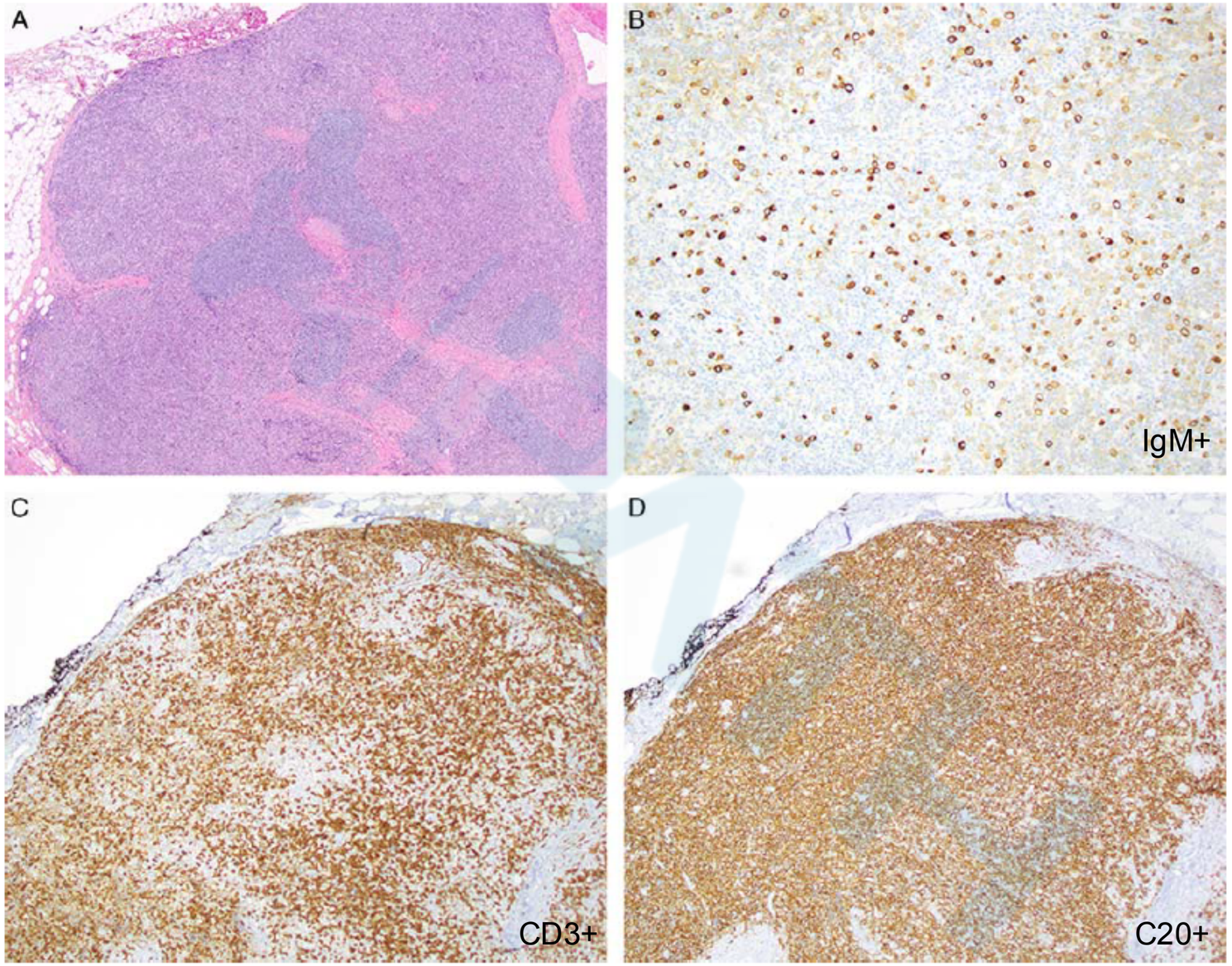


FIGURE 3. IgM-positive PCMZL. This subcutaneous PCMZL (A) contained scattered IgM-positive, monotypic plasma cells (B). In contrast to class-switched cases, CD3-positive T cells (C) were less numerous than CD20-positive B cells (D). A, hematoxylin and eosin; B–D, immunohistochemical stain with hematoxylin counterstain.

RESULTS 4

Correlation of Heavy Chain Expression With Clinical Features

- Ages: Patients with IgG4-positive and class-switched PCMZL were on average younger than patients with IgM-positive lymphomas (median: 46.5 vs. 69 y）.
- Disease recurrences and clinical outcome: No significant differences between IgG4-positive, IgG4-negative/class-switched, and IgM-positive cases.

DISCUSSION 1

PCMZL *v.s.* other MALT lymphomas

Common features	Different features	
	PCMZL	other MALT lymphomas
extranodal, extramedullary location indolent course CD5-, CD10- small B-cell phenotype frequent benign follicular structures	frequent heavy chain class-switching in PCMZL, usually with IgG expression IgM+ PCMZL share more features with other MALT lymphomas	MALT lymphomas are IgM+

DISCUSSION 2

Class-switched PCMZL *v.s.* CD4+ small/medium T-cell lymphoma

Class-switched PCMZL	Cutaneous T-cell lymphomas
PD1+ TFH cells（5% to 10%） BCR gene rearrangements are uncertain	PD1+ TFH cells（20% to 30%） Monoclonal TCR gene rearrangements are common

DISCUSSION 3

IG4+ PCMZL *v.s.* extracutaneous IgG4+ MALT

IgG4+ PCMZL	Extracutaneous IgG4+ MALT
(39%; 19/49 cases) were reported to be IgG4-positive	Only 1 extracutaneous MALT lymphoma from the ocular adnexa out of a total of 120 noncutaneous cases was IgG4-positive
absence of pre-existing IgG4-RD	Other groups have also reported a small number of extracutaneous IgG4-positive MALT lymphomas in the ocular adnexa, dura and salivary gland, which only sometimes have been associated with IgG4-RD

DISCUSSION 4

Th2 inflammatory background

- Th2 inflammatory background found in most class-switched PCMZL, whether or not they are IgG4-positive, is also a characteristic feature of IgG4-RD
- A modified Th2 immune response, in concert with Tregs, promotes B cells to produce IgG4
- No significant differences in the proportions of these T-cell subsets between IgG4-positive, IgG4-negative/class-switched or the relatively small number of IgM-positive cases
- It may be partially explained by the Th2-predominant microenvironment characteristic of most PCMZL, as this is distinct from the Th1 cytokine profile associated with most extracutaneous MALT lymphomas

CONCLUSIONS

- More than 1/3 of PCMZL with plasmacytic differentiation express IgG4, and IgG4-positive PCMZL had similar clinicopathologic features as other class-switched PCMZL.

- This study provides additional evidence, including previously undescribed differences in growth pattern and plasma cell distribution to demonstrate that the IgM-positive PCMZL had several features that were significantly different from heavy chain class-switched cases; PCMZL may be divided into 2 subsets.

- Emphasize the indolent nature of at least the class-switched PCMZL, which may warrant the concept that class-switched PCMZL might be better considered a clonal chronic lymphoproliferative disorder.

Thank You !