Identification of CD5/Cyclin D1 Double-negative Pleomorphic Mantle Cell Lymphoma

A Clinicopathologic, Genetic, and Gene Expression Study

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汇报人：颜临丽

Mantle Cell Lymphoma

- MCL is a mature B-cell neoplasm usually composed of small to medium-sized lymphoid cells.
- More than 95% of MCL cases have a translocation involving CCND1, most commonly an IGH-CCND1 translocation, which results in overexpression of cyclin D1 and a derangement in cell cycle control.
- MCL is generally an aggressive tumor with a median survival of 3 to 5 years,
- The vast majority of patients cannot be cured despite initial response to chemotherapy or immunochemotherapy

Table 13.21 Morphological variants of mantle cell lymphoma

Aggressive variants	**Blastoid:** Cells resemble lymphoblasts with dispersed chromatin and a high mitotic rate (usually ≥20–30 mitoses per 10 high-power fields).
Pleomorphic mantle cell lymphoma (PMCL)	**Pleomorphic:** Cells are pleomorphic, but many are large with oval to irregular nuclear contours, generally pale cytoplasm, and often prominent nucleoli in at least some of the cells.
Other variants	**Small-cell:** Cells are small round lymphocytes with more clumped chromatin, either admixed or predominant, mimicking a small lymphocytic lymphoma. **Marginal zone–like:** There are prominent foci of cells with abundant pale cytoplasm resembling marginal zone or monocytoid B cells, mimicking a marginal zone lymphoma; sometimes these paler foci also resemble proliferation centres of chronic lymphocytic leukaemia / small lymphocytic lymphoma.

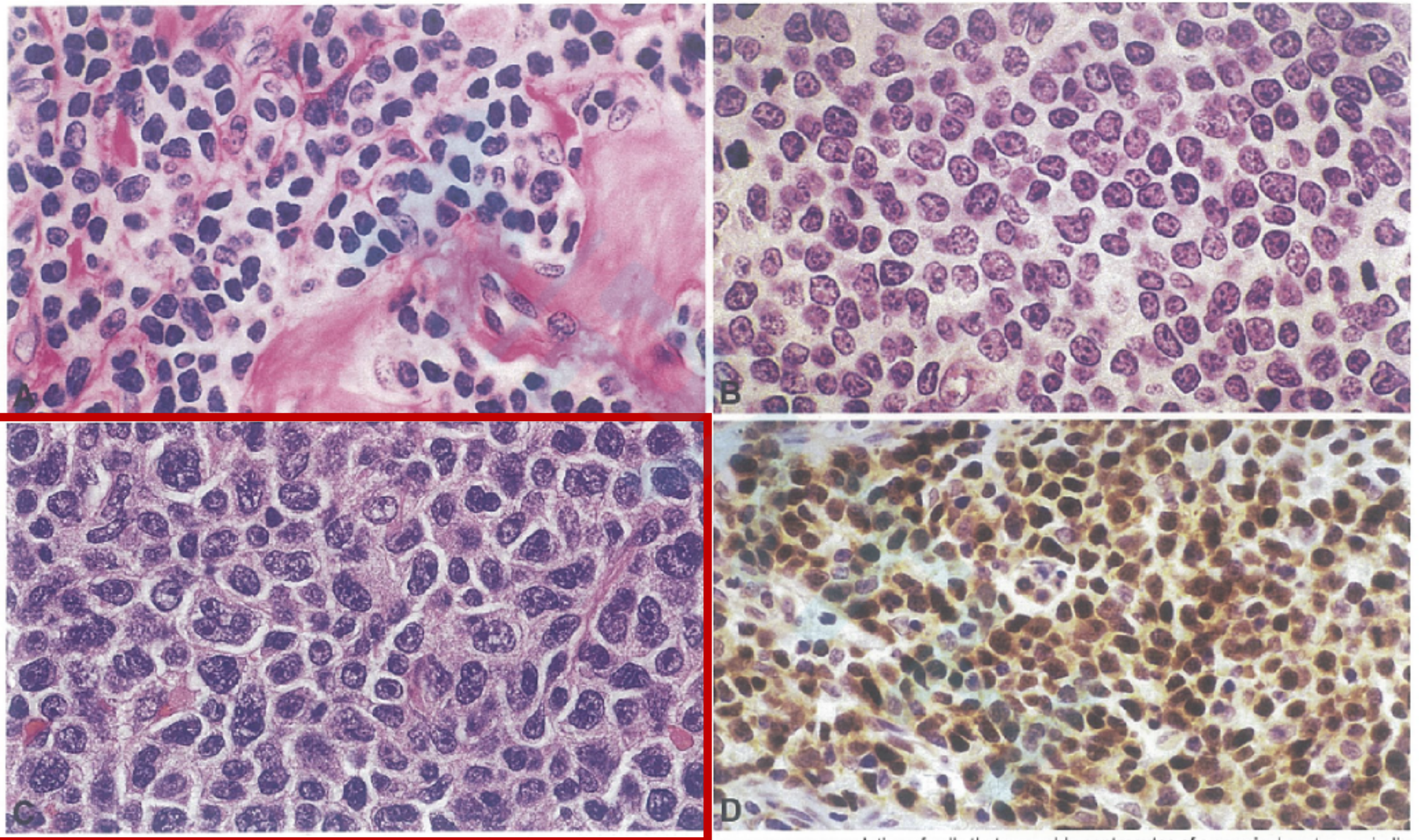
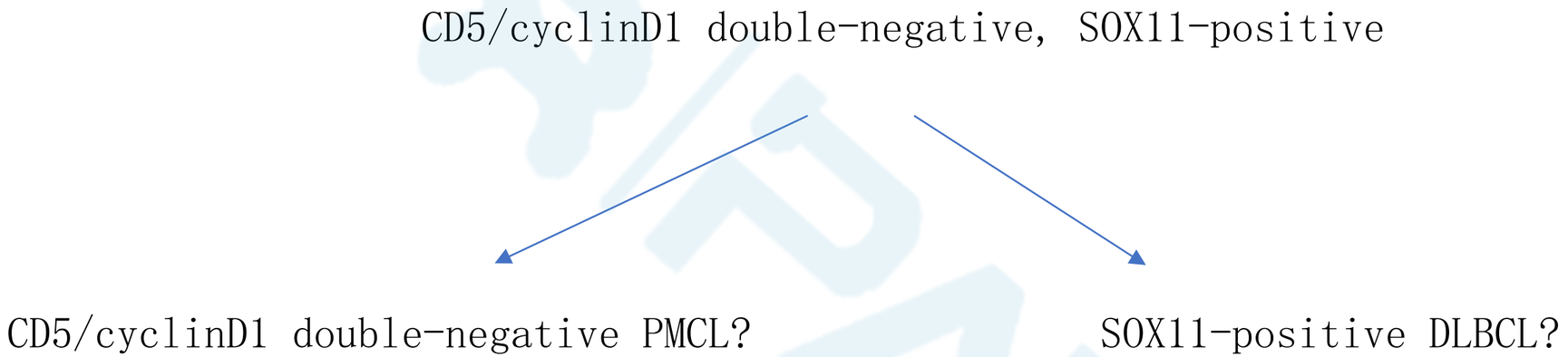


Fig. 13.98 Mantle cell lymphoma. **A** This typical mantle cell lymphoma demonstrates a homogeneous population of cells that resemble centrocytes of a germinal centre, periodic acid–Schiff (PAS) stain. **B** The cells in the blastoid variant resemble lymphoblasts and have a high mitotic rate. **C** Note the large and pleomorphic cells, including cells with prominent nucleoli, in the pleomorphic variant. **D** Cyclin D1 immunostaining shows nuclear positivity.

PMCL *vs* DLBCL

- PMCL can closely mimic diffuse large B-cell lymphoma (DLBCL) morphologically. And its diagnosis can be established by the expression of both CD5 and cyclin D1.
- About 10% of MCL cases are negative for CD5, a phenomenon also observed in PMCL
- Rarely, MCL could lack the cyclin D1 positivity and CCND1 translocation
- SOX11 is a highly specific marker for MCL, and positivity can be used to identify rare cases of cyclinD1-negative MCL, including PMCL morphologically mimicking DLBCL.
- To date, no cases of CD5/cyclinD1 double-negative MCL (whether pleomorphic or not) have been reported.



The differential diagnosis is very important clinically, as PMCL and DLBCL have different biological nature, clinical features and treatment strategies.

MATERIALS AND METHODS

- 4 cases CD5(−) cyclin D1(−) SOX11(+)

500 cases of CD5(−) cyclinD1(−)DLBCL → SOX11(+) → 2 cases

2 more previously identified cases

-a reported case(reported as SOX11-positive DLBCL)

-an unreported case

- 4 cases(GCB) DLBCL
- 4 cases(ABC)DLBCL
- 4 cases cyclin D1-positive PMCL [CD5(+)and SOX11(+)]
- 4 cases cyclin D1-negative PMCL [CD5(+) andSOX11(+)]

- Immunohistochemistry
- EBER In Situ Hybridization
- Fluorescence In Situ Hybridization
- Genome-wide Copy Number Analysis
- Gene Expression Analysis

RESULTS

TABLE 1. Clinical Features of CD5/Cyclin D1 Double-negative PMCL Patients

Case	Case 1	Case 2	Case 3*	Case 4
SOX11 IHC intensity/ percentage	Strong/95	Strong/95	Intermediate/95	Weak/65
Age (y)/sex	82/male	39/male	77/male	66/male
Stage	IIA	IVB	IVB	IA
Biopsy site	Tonsil	LN	Colon	LN
Extranodal involvement	Tonsil	Pharynx, kidney, liver, spleen, ascites, pleural effusion, BM	Colon	No
LDH	Normal	High	High	Normal
IPI (risk)	2 (low-I)	2 (low-I)	3 (high-I)	1 (low)
Therapy	Oral CS	R-CHOP	R-COP	R-CHOP
Response	PD	PR	PR	CR
PFS (mo)	1	5	7	73
OS (mo)	6	8	8	85

*This case has been reported in a previous article.[4]

BM indicates bone marrow; C, cyclophosphamide; CR, complete remission; H, doxorubicin; I, intermediate; IHC, immunohistochemistry; IPI, international prognostic index; LDH, lactate dehydrogenase; LN, lymph node; O, vincristine; OS, overall survival; P, prednisolone; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, rituximab; S, steroid.

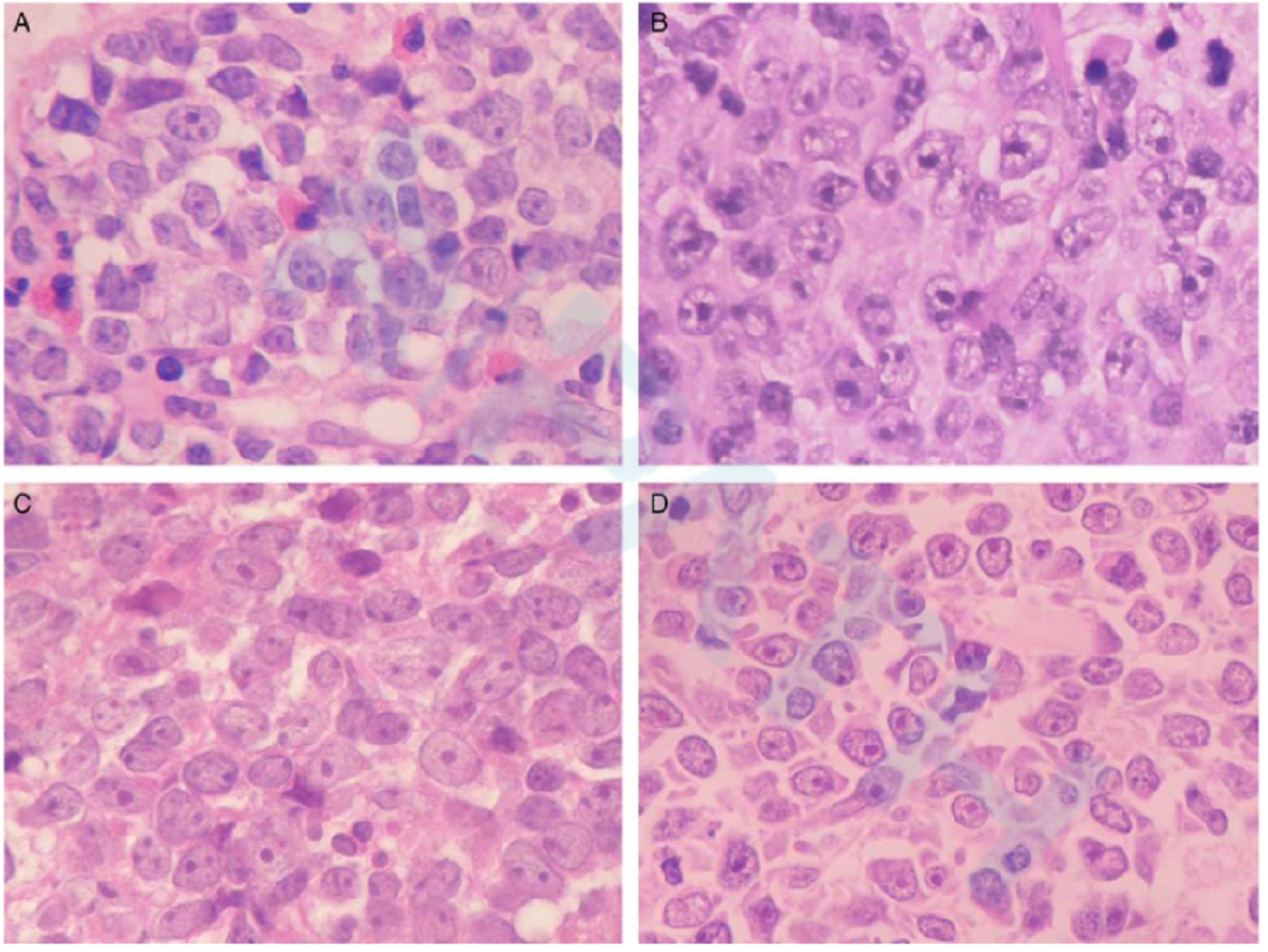


FIGURE 1. Microscopic pictures (hematoxylin and eosin stain) of our CD5/cyclin D1 double-negative PMCL cases (A: case 1; B: case 2; C: case 3; D: case 4).

TABLE 2. Results of Immunohistochemistry

Case	Case 1	Case 2	Case 3*	Case 4
SOX11 IHC intensity/ percentage	Strong/95	Strong/95	Intermediate/95	Weak/65
CD20	+	+	+	+
CD5	−	−	−	−
Cyclin D1	−	−	−	−
TdT	−	−	−	−
CD10 ≥ 30%	−	−	+	−
BCL6 ≥ 30%	+	+	+	+
MUM1 ≥ 30%	+	+	+	+
MYC ≥ 40%	−	+	−	+
BCL2 ≥ 50%	+	+	+	+
Ki-67 (%)	85	95	95	70

*This case has been reported in a previous article.[4]

IHC indicates immunohistochemistry; TdT, terminal deoxynucleotidyl transferase.

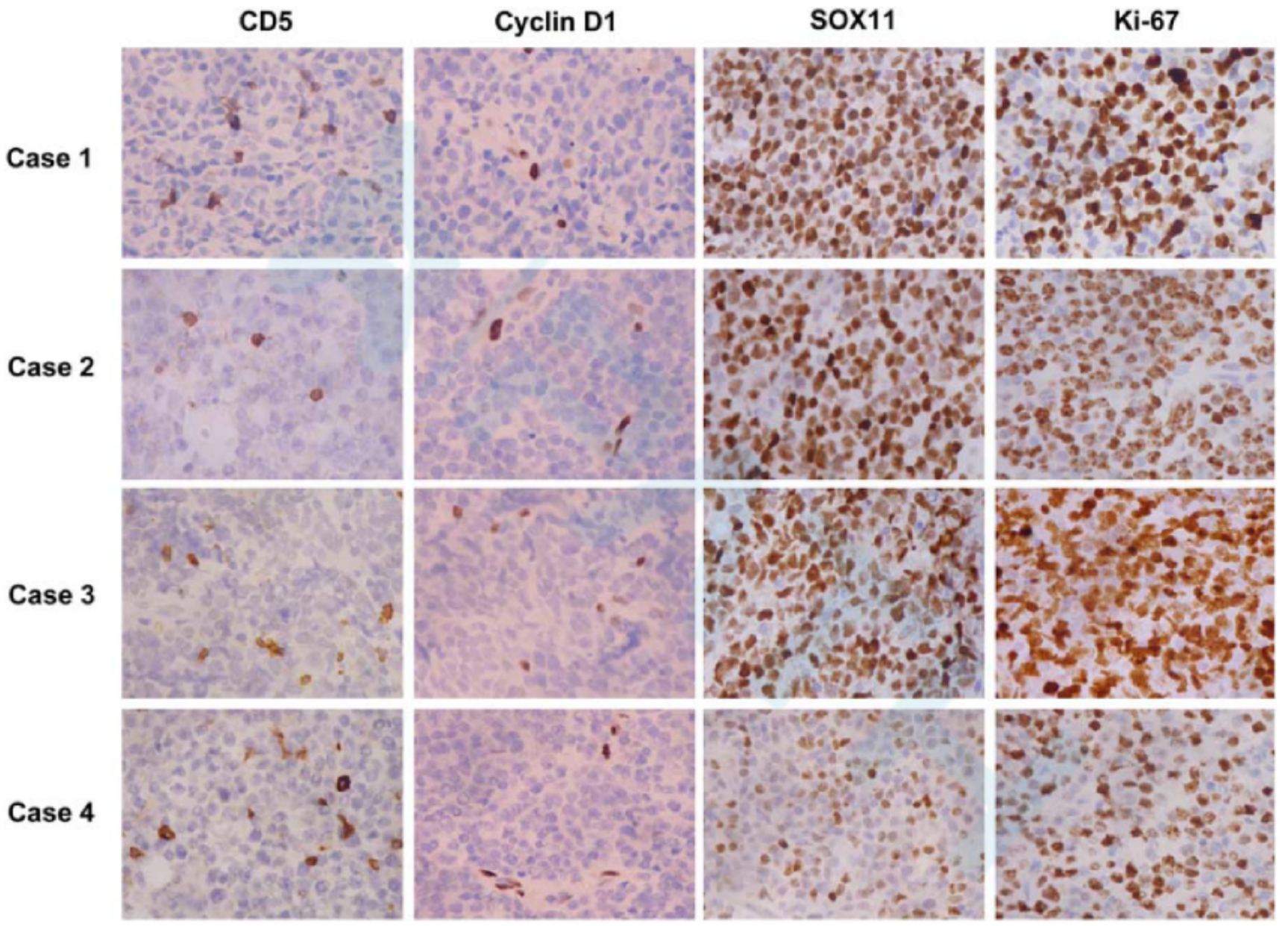
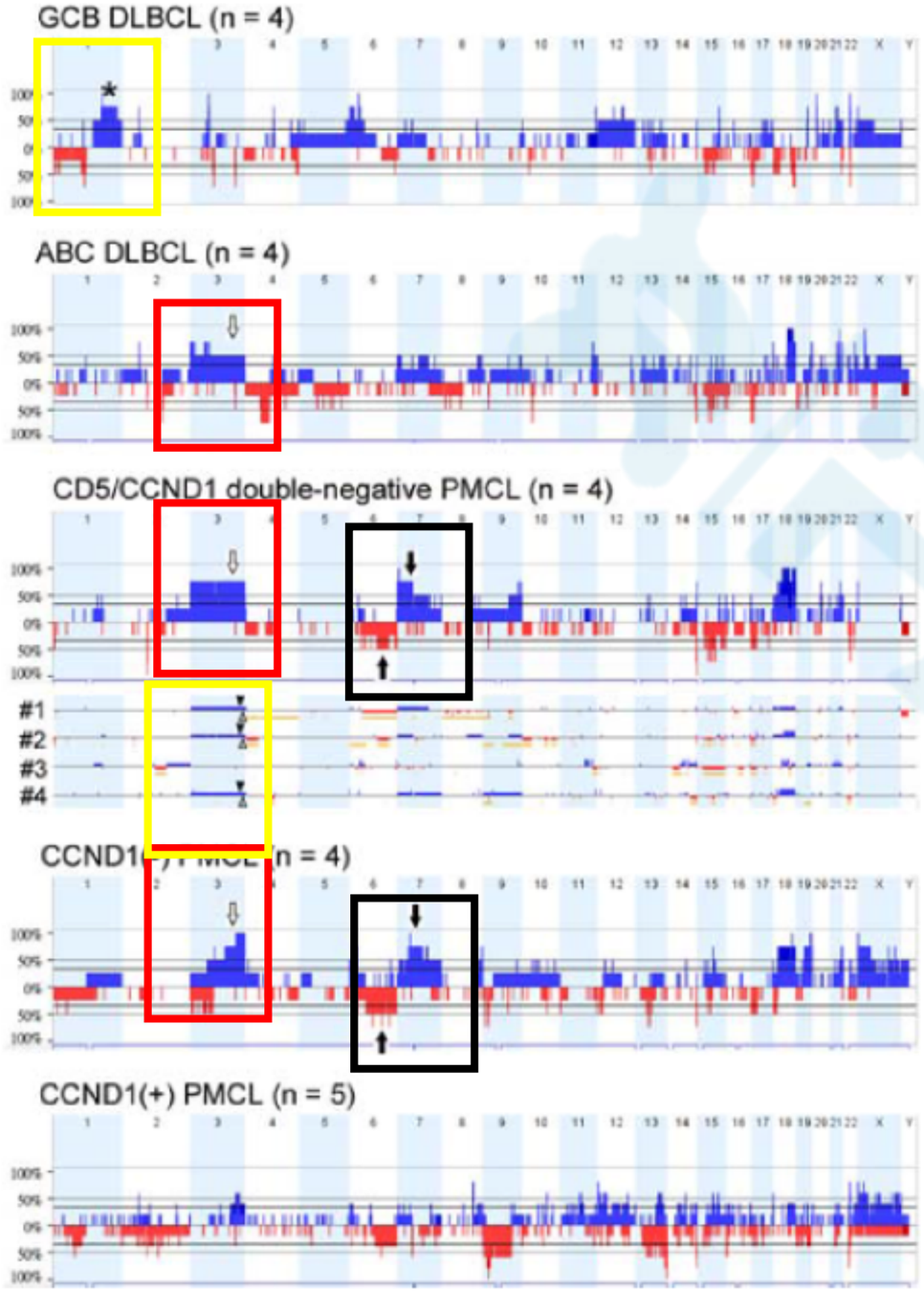


FIGURE 2. Microscopic pictures of immunohistochemistry for CD5, cyclin D1, SOX11, and Ki-67. The internal controls for CD5 and cyclin D1 were well stained.

- EBER In Situ Hybridization: All 4 cases were negative for EBER.

- Fluorescence In Situ Hybridization: None of our 4 cases had detectable rearrangement of IGH-CCND1, CCND2, CCND3, CCNE1, CCNE2, MYC, BCL2, or BCL6.



Genome-wide Copy Number Analysis

1、The profile of double-negative PMCL was similar to cyclin D1-negative PMCL.
2、Losses at 6q and gains at 7p (black arrows) were common in both double-negative and cyclin D1-negative PMCL.
3、Large segmental gains at 3q (white arrows) were common in double negative PMCL, cyclin D1-negatitve PMCL and ABC DLBCL.
4、Large segmental gains at 1q (asterisk) were common in GCB DLBCL, but uncommon in other types of lymphoma.
5. Note the gains of PIK3CA (black arrowhead) and CCDC50 (white arrowhead) at 3q in 3 cases of CD5/cyclin D1 double-negative PMCL.
The results of case 3, cyclin D1-negative PMCL and cyclin
D1-positive PMCL have been reported in a previous article

Gene Expression Analysis

- We studied the expression of SOX11, CCND1, CCND2, CCND3, CCNE1, and CCNE2.
- Twenty genes differentially expressed in MCL,GCB DLBCL, and ABC DLBCL, including WNT3,CHL1, ALOX5, CCDC50, BANK1, CD1D, MARCKS,FCRL2, CEACAM1, RNGTT, MMP11, EPHB6, LY86, MFHAS1, LIMD1, PIM2, CYB5R2, MME, ASB13, andMYBL1, were selected according to previously published data.
- Three housekeeping genes, including GUSB, UBXN4, and TRIM62

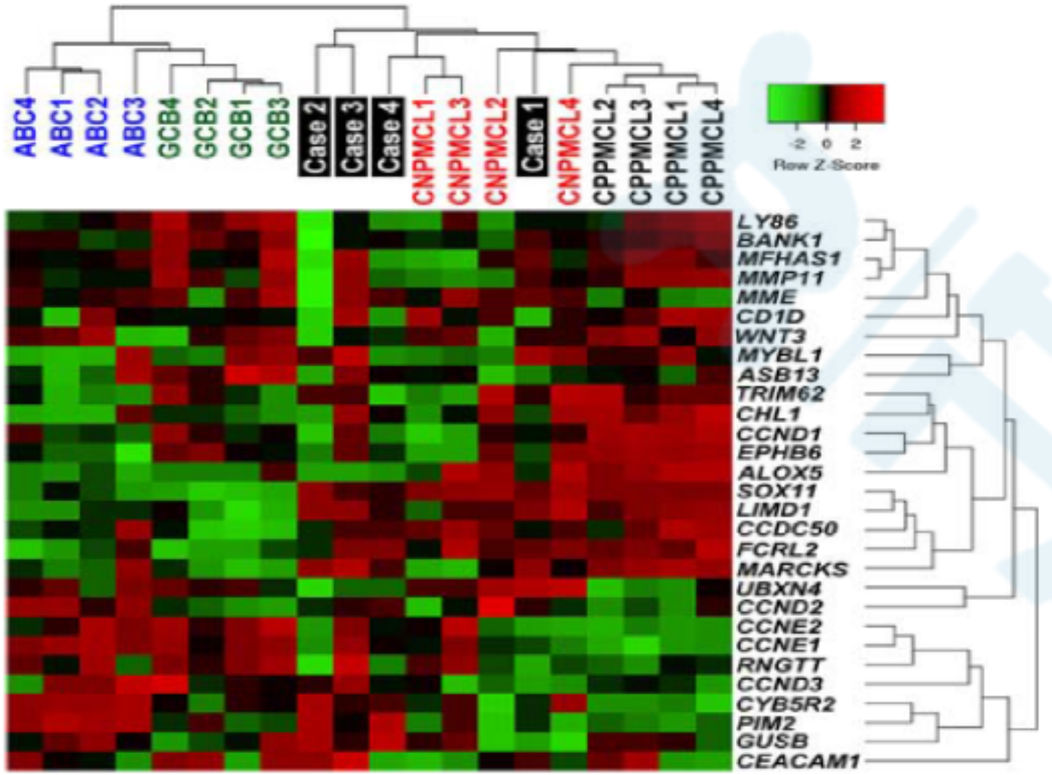


FIGURE 6. The gene expression patterns of CD5/cyclin D1 double-negative PMCL (cases 1 to 4), with comparison to GCB DLBCL (GCB), ABC DLBCL (ABC), cyclin D1-positive PMCL (CPPMCL), and cyclin D1-negative PMCL (CNPMCL). Unsupervised hierarchical clustering successfully separated 2 main groups of PMCL and DLBCL. The gene expression patterns of CD5/cyclin D1 double-negative PMCL were similar to those of CNPMCL.

1.Unsupervised hierarchical clustering successfully separated 2 main groups of PMCL and DLBCL.
2. The gene expression patterns of CD5/cyclin D1 double-negative PMCL were similar to those of CNPMCL.

DISCUSSION

Clinical Feature

- male individuals,
- age at diagnosis being 39, 62, 77, and 82 years, respectively.
- Two patients presented with an advanced stage IV disease, and 3 patients died within a year.
- The predominance of elderly male individuals and the aggressive clinical course were compatible with PMCL.

- The gene expression patterns of CD5/cyclin D1 double-negative PMCL were similar to those of CNPMCL.
- the genome-wide copy number profiles and gene expression patterns of our 4 cases were similar to those of cyclin D1-negative PMCL
- supporting that these cases were truly CD5/cyclin D1 double-negative PMCL.

SOX11

- Interestingly, the only patient who achieved complete remission and died of disease after 7 years had a tumor weakly positive for SOX11, whereas other 3 tumors were strongly or intermediately positive for SOX11.
- Future studies on more cases are needed to clarify the clinical significance of SOX11 intensity in such rare tumors.

SOX11

- MCL
- lymphoblastic lymphoma (small to medium-sized lymphoid cells with fine chromatin and small nucleoli, expression of TdT)
- Burkitt lymphoma (monotonous medium-sized lymphoid cells, starry-sky pattern, and presence of an MYC translocation)
- hairy cell leukemia (composed of small to medium-sized lymphoid cells with oval nuclei and abundant pale cytoplasm,and the tumor cells rarely involve sites other than spleen, bone marrow and peripheral blood)

- In conclusion, here we demonstrate for the first time that PMCL could lose both CD5 and cyclin D1 expression and have morphologic features indistinguishable from DLBCL.
- Immunostaining for SOX11 can be used to identify such rare cases of CD5/cyclin D1 double-negative PMCL.
- Further genetic and gene expression studies would be helpful to confirm the diagnosis.