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*Original Article*

# Discordant lymphoma consisting of mantle cell lymphoma and angioimmunoblastic T cell lymphoma: homology or heterogeneity?

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**Abstract:** Objects: To investigate the pathologic characteristic of discordant lymphoma with mantle cell lymphoma and angioimmunoblastic T cell lymphoma. Methods: The clinicopathologic data of cases of discordant lymphoma were organized and clinicopathologic features were analyzed by literature review. Results: A 49-year-old male was taken to the hospital due to the lymphandenopathy in January 2007 and mantle cell lymphoma was diagnosed in the pathology report. EBV-EBER staining was negative. Active chemotherapy was received and the patient achieved complete response. Seven years later since diagnosis, in 2014 scattered rashes were found. A skin biopsy was taken and the result was not mantle cell lymphoma but angioimmunoblastic T cell lymphoma. EBV-EBER positivity was detected. Clonal T cell receptor gamma locus gene rearrangements were detected while no clonal immunoglobin heavy locus gene rearrangement was detected in the skin sample. Conclusions: This is the first report on discordant lymphoma consisting of mantle cell lymphoma and angioimmunoblastic T cell lymphoma. There seems to be no relation these two different kinds of lymphoma, and EBV infection might prompt the development of angioimmunoblastic T cell lymphoma after transplantation. Rash is a common clinical manifestation when T cell lymphoma develops after treatment for MCL.

**Keywords:** Discordant lymphoma, mantle cell lymphoma, angioimmunoblastic T cell lymphoma

## Introduction

Composite lymphoma (CL) is defined as two or more kinds of lymphoma detected in the same sample while discordant lymphoma (DL) is recognized as different kinds of lymphoma occuring in different anatomic locations in the same patient [1]. CL/DL comprising B cells and T cells is rare and clinicopathologic features are unknown. Here we report an unusual DL case which was first diagnosed as cervical lymph node mantle cell lymphoma (MCL) and angioimmunoblastic T cell lymphoma (AITCL) in the skin and spleen seven years later.

## Materials and methods

### *Clinical data*

In this study, the case diagnosed as discordant lymphoma with MCL and AITCL was obtained from the Department of Pathology, Yantai Yuhuangding Hospital. All the clinical data including the process of diagnosis and treatment, and follow up information were obtained.

### *Sample process*

Tissue samples including lymph node, skin and spleen were fixed completely in 10% buffered formalin. Samples were dehydrated by gradient alcohol and embed by paraffin. Four μm sections were cut from tissue blocks prepared for hematoxylin and eosin (H&E) staining, immunohistochemical staining, and molecular detection.

### *Immunohistochemical staining*

The automatic immunostainer (Ventana, Roche Co.) was used to for immunohistochemical staining and DAB chromogen. Each 4 μm thick section was stained with positive control samples. Negative control was replacement of first

**Table 1.** Antibodies used in immunohistochemical staining

| Antibody | Clone | Dilution |
|---|---|---|
| CD2 | UMAB6 | Working fluid |
| CD3 | UMAB54 | Working fluid |
| CD4 | B486A1 | Working fluid |
| CD5 | UMAB9 | Working fluid |
| CD8 | SP16 | Working fluid |
| CD10 | UMAB235 | Working fluid |
| CD20 | OTI4B4 | Working fluid |
| Pax-5 | ZP007 | Working fluid |
| CyclinD1 | DCS-6 | 1:100 |
| CD23 | UMAB101 | Working fluid |
| Ki67 | MIB-1 | Working fluid |
| BCL-6 | LN22 | Working fluid |
| PD-1 | UMAB199 | 1:200 |
| CXCL13 | Sheep Polyclonal | 1:200 |
| Granzyme B | EP230 | Working fluid |

antibody by phosphate buffered saline. Information on all antibodies used in this study is shown in **Table 1**.

*In situ hybridization for EBV-EBER detection*

Tissue sections were dewaxed, dehydrated, and then digested in proteinase K under the situation of 37°C for 20 minutes. After the slices were immersed in absolute ethanol and dried, EBER probe hybridization solution (concentration: 100 ng/ml) was added and then incubated under the situation of 37°C for 30 minutes. Tissues were incubated with horseradish peroxidase-labeled digoxin for 30 minutes under 37°C. The slices were rinsed for three times with phosphate buffered saline buffer and two minutes for each time, and then rinsed under deionized water and 0.2 ml DAB to each slide for 15 min in the dark. Epstein Barr virus probe sequence was 5'-CTCCTCCCTACCAAAACCCTCACCACCCCC-3' purchased from Beijing Zhongshan Jinqiao Biological Company.

*Fluorescence in situ hybridization for IgH/CyclinD1 translocation*

After washing, sections were incubated with 200 μl of pepsinat under 37°C for 10 minutes, and then fixed with paraformaldehyde for 10 minutes. The slices were covered by 30 μl hybridization solution after ethanol gradient dehydration and heated for denaturing. Incubation was overnight at 37°C. After thorough rinsing, slides were counterstained with DAPI for 10 minutes and observed under fluorescence microscope.

*Cytogenetics*

The prepared slides from skin biopsy were baked in an oven under 65°C for 3 hours and immersed in trypsin solution for 20 seconds. The slides were removed and rinsed with distilled water, and then the trypsin solution was washed away. The Giemsa primary solution was diluted (1:10) with pH 6.7 phosphate buffer for 8 minutes. Dye solution was washed with distilled water and the slides were dried and analyzed under microscopy.

*Molecular detection for TCR-gamma fragment analysis*

Three pieces of paraffin sections of skin biopsy tissue were cut at 10 μm thick for each. The paraffin section sample was placed in a centrifuge tube and dewaxed. 1 ml xylene and 1 ml absolute ethanol were added successively to remove wax and xylene. DNA was extracted by the special kit and then DNA concentration and purity were measured. TCR-gamma fragment was amplified on the skin biopsy tissue by the Invivo scribe Gene Rearrangement Kit. PCR conditions: 95°C pre-denaturation for seven minutes and then 72°C for 90 seconds. There were 35 cycles in the total process. 1 μl PCR amplification product was mixed with 10 μl of formamide and 0.1 μl of GeneScan-500 LIZ (ABI Co. USA). PCR fragment analysis and interpretation were performed using ABI-3500 gene analyzer.

## Results

*Clinical data*

A 49-year-old male presented with a one-month history of lymphandenopathy in the bilateral neck and axilla and he was taken to the local hospital in January 2007. The patient had no any systematic symptom such as drenching night sweats, unexplained weight loss, or fever. No abnormal physical sign was found during medical examination except body surface palpation was positive for lymphadenopathy in the bilateral neck, axilla, and groin. Computed tomography scan revealed multiple lymph

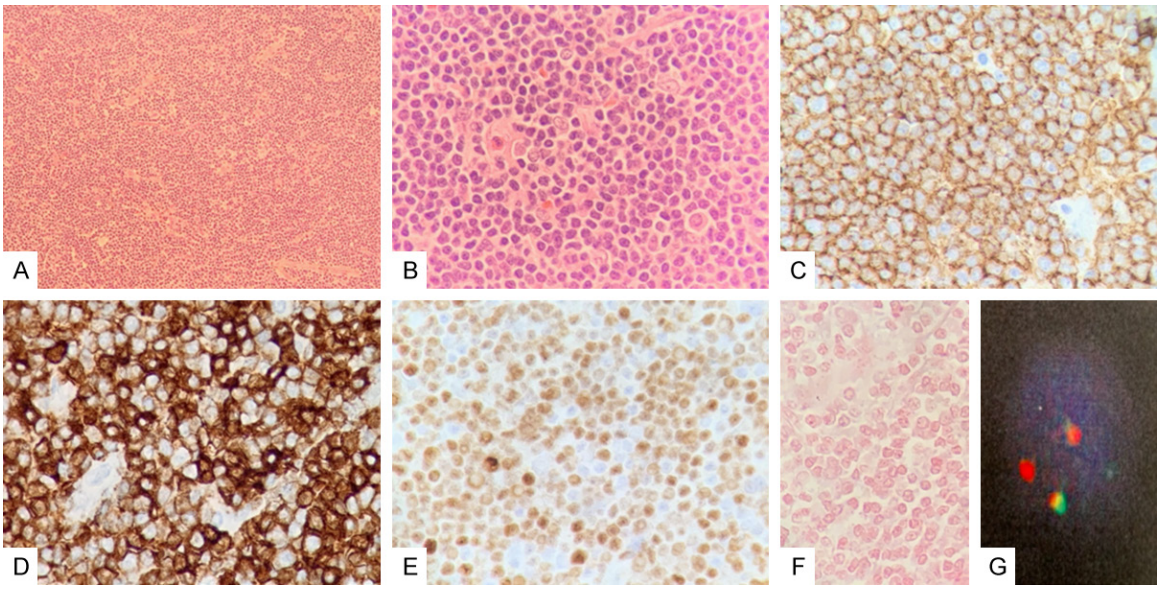


**Figure 1.** Histologic morphology and phenotype of tumor cells in lymph node excised in 2007. (A) Normal architecture of lymph node was not observed and it was replaced by neoplastic cells with a diffuse pattern. Hyaline degeneration of the interstitial vascular wall was obvious (H&E staining, 4 ×). (B) Neoplastic cells were small in size with an irregular nucleus and without conspicuous mitotic activity (H&E staining, 40 ×). The tumor cells were positive for (C) CD20, (D) CD5, and (E) CyclinD1 (EnVision, 40 ×). (F) EBV-EBER was negative (In situ hybridization, 40 ×). (G) Translocation between *IgH* and *CCND1* gene (Fluorescence in situ hybridization, 1000 ×).

nodes in the neck, axillary, groin and retroperitoneum. Hematological lab tests showed that White Blood Count was 8.5 × $10^3$ μl, neutrophil count 3.7 × $10^3$ μl, lymphocyte count 4.0 × $10^3$ μl, hemoglobin 13.8 g/dL and platelet count 325 K/c mm. Subsequently, the left cervical lymph node was excised for pathologic examination and MCL was diagnosed. Bone marrow biopsy confirmed that the bone marrow was involved by MCL and Ann Arbor Stage was IV. The patient received two courses of R-Hyper CVAD chemotherapy from February to April in 2007 and BEAM/peripheral blood autologous stem cell transplant was carried out in June 18, 2007. Rituxmab and Bortezomib were used as the maintenance treatment and the patient achieved complete response after the above therapy. Seven years later, scattered rash was found on the chest and back skin in April 2014. After skin biopsy, AITCL was diagnosed. Bone marrow biopsy also presented involvement simultaneously. The patient was then treated with two courses of R-CHOP regimen. The therapeutic regimen was changed to EPOCH. Although the patient got partial remission at that time, he died of pneumonia and secondary septic shock caused by progressive lymphoma in May 10, 2017.

*Histologic findings*

Gross examination showed the lymph node excised in 2007 was 8.5 gram in weight and 3.7 cm × 2.1 cm × 1.5 cm in size. Histology showed there was partial effacement of a large lymph node by neoplastic cells with a diffuse pattern. Significant hyaline degeneration of the interstitial vascular wall was observed (**Figure 1A**). The predominant cells were small, irregular lymphocytes without conspicuous mitotic activity (**Figure 1B**). The skin biopsy in 2014 showed that the structure was effaced (**Figure 2A**) and atypical lymphocytes infiltrated, composed of small to medium sized cells with irregular nuclear contours with a predominantly periadnexal and perivascular distribution on the background of a mixed population of eosinophils, neutrophils, and plasma cells (**Figure 2B**).

*Immunohistochemical and in situ hybridization staining*

The tumor cells in the lymph node were positive for CD20 (**Figure 1C**), CD5 (**Figure 1D**), and CyclinD1 (**Figure 1E**) but negative for CD3, CD10, and CD23. Ki67 index was about 5%. In situ hybridization stain for EBV-EBER was nega-

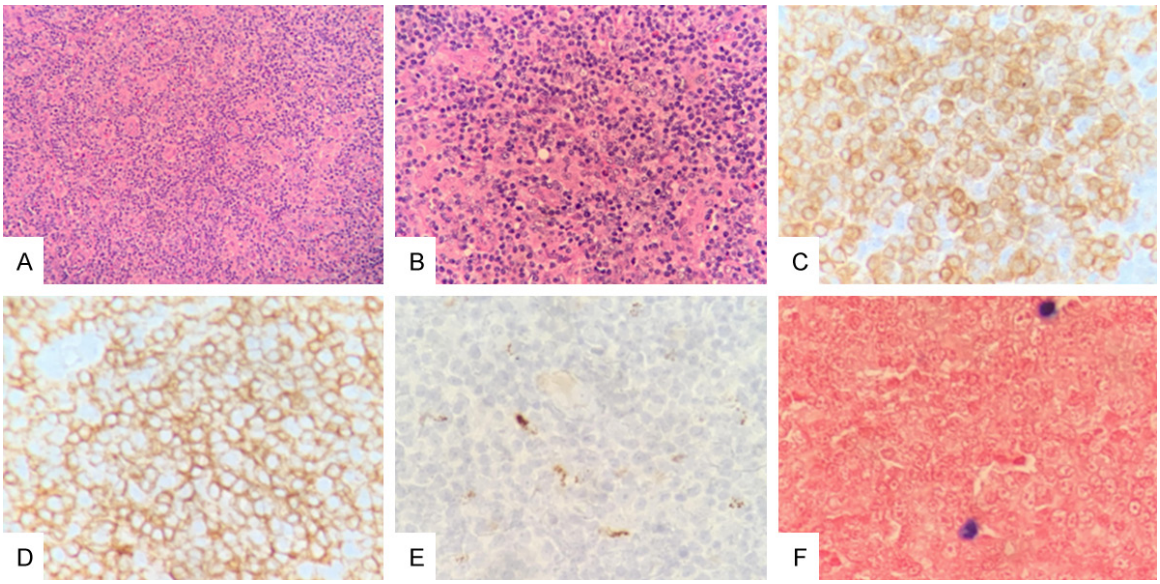


**Figure 2.** Histologic morphology and phenotype of tumor cells in skin excised in 2014. (A) The abnormal structure of skin was effaced (H&E staining, 4 ×). (B) Atypical lymphocytes composed of small to medium sized cells with irregular nuclear contours with a predominantly periadnexal and perivascular distribution in a background of a mixed population of eosinophils, neutrophils, and plasma cells (H&E staining, 20 ×). The tumor cells were positive for (C) CD3, (D) CD4, and (E) CXCL-13 (EnVision, 40 ×). (F) EBV-EBER was positive (In situ hybridization, 40 ×).

tive (**Figure 1F**). Immunostains on the skin sample shows that the atypical lymphoid cells were positive for CD2, CD3 (**Figure 2C**), CD4 (**Figure 2D**), CD10, BCL-6, PD-1, and CXCL13 (**Figure 2E**) but negative for Granzyme B, CD20, CD8, CyclinD1 and PAX5. CD23 staining showed the irregular follicular dendritic cell network. In situ hybridization stains for EBV-EBER showed scattered cells were positive (**Figure 2F**).

*Fluorescence in situ hybridization*

Fluorescence in situ hybridization results showed a translocation between *IgH* and *CCND1* genes, and the yellow signal represented a fusion made by red signal (IgH gene) and green signal (*CCND1* gene) (**Figure 1G**).

*Cytogenetics*

46,XY,der(1)t(1;7)(p11;q34)t(1;7)(q21;q34), der(7)t(1;7)(q21;q34)[12]/46,XY[8] was revealed by cytogenetic analysis which indicated the presence of an abnormal diploid clone characterized by a derivative 1 and 7 resulting from the translocation between 1p;7q and 1q;7q (**Figure 3**).

*Molecular detection*

Clonal T cell receptor gamma locus gene rearrangements were detected by DNA amplification in one-tube T-gamma assay using primers to the J gamma 1&2 and J gamma P 1&2 gene segments, while no clonal immunoglobin heavy locus gene rearrangement was detected using consensus primers to the heavy locus variable and joining regions in the skin sample (**Figure 4**).

## Discussion

To the best of our knowledge, there has been no report of composite lymphoma (CL) or discordant lymphoma (DL) consisting of mantle cell lymphoma (MCL) and AITCL, although MCL can be part of a composite with other B-cell non-Hodgkin lymphomas, such as Burkitt lymphoma, small lymphoid lymphoma, follicular lymphoma, plasma cell neoplasm, and even CHL simultaneously or sequentially [2, 3]. Reports of CL/DL including MCL with T cell lymphoma are exceedingly rare, and literature review yielded only five cases (**Table 2**) [4-7]. Some clinical characteristics of CL/DL composing MCL and T cell lymphoma may drawn as shown in the table: (1) The patient's age of onset is 45-87 years old with the median age 70 years; (2) The ratio of males to females is 5:1 which suggests that the odds of a combined T cell lymphoma for a man who suffers MCL are higher than for a woman due to the

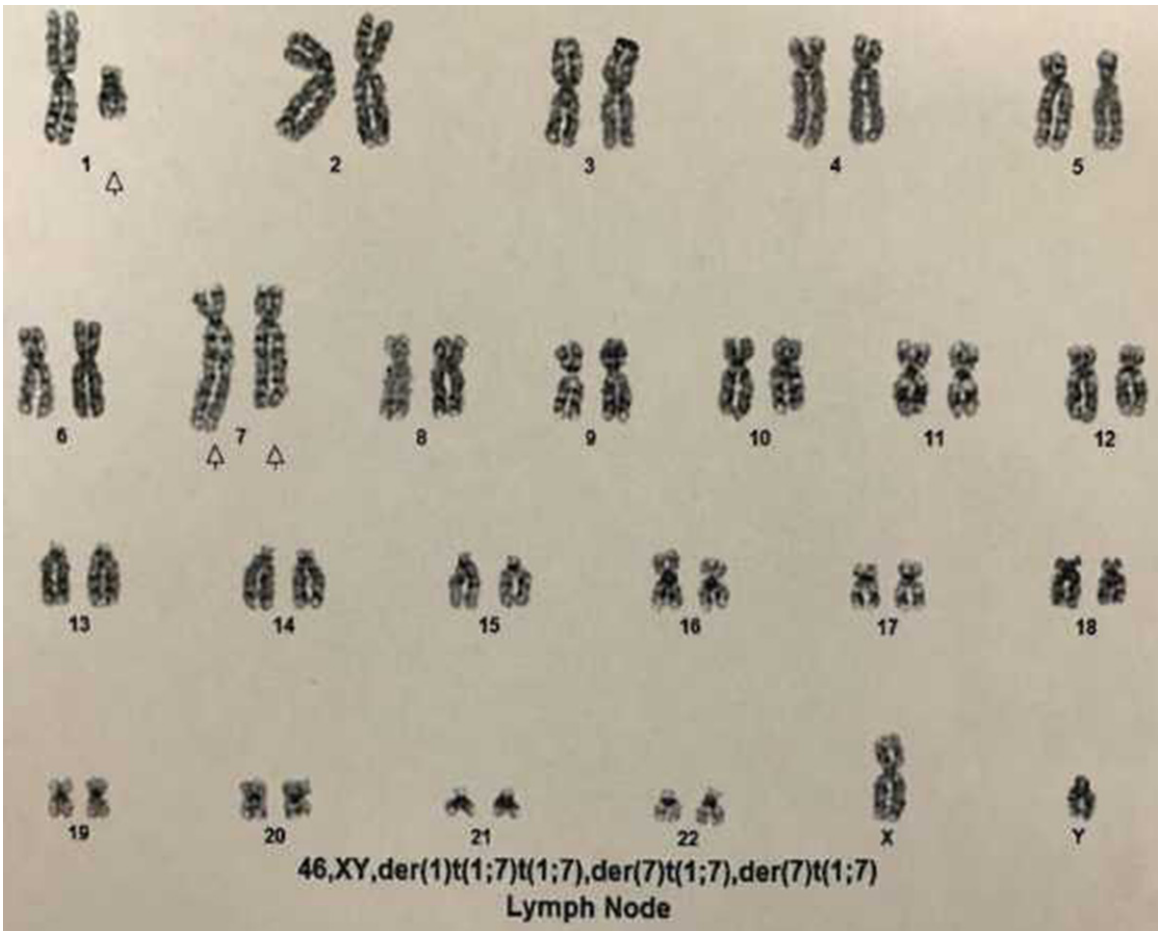


**Figure 3.** Cytogenetics result. Abnormal diploid clone characterized by a derivative 1 and 7 resulting from the translocation between 1p;7q and 1q;7q in the tumor cells of the skin sample.

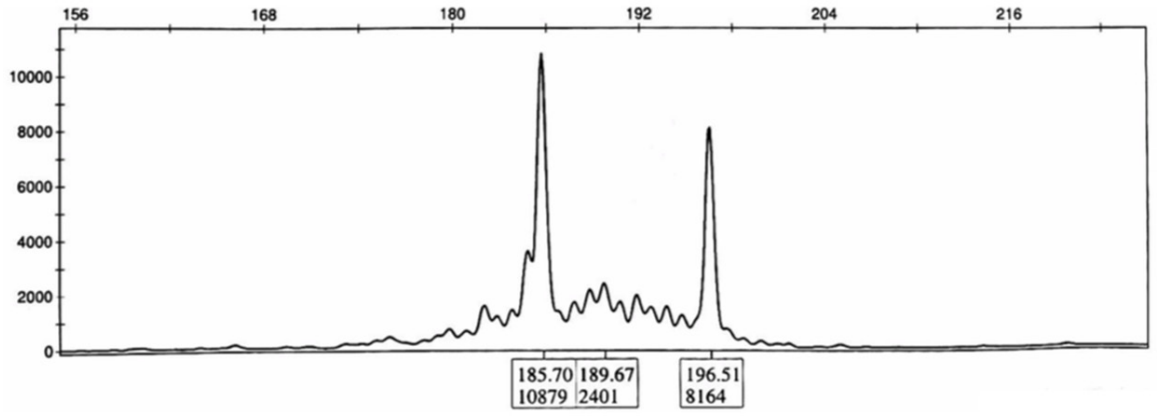


**Figure 4.** Clonal T cell receptor gamma locus gene rearrangements were detected by DNA amplification in tumor cells of the skin sample.

male predominance for MCL; (3) In terms of clinical manifestation, lymphadenopathy was present in five cases and sore throat in one patient, two cases showed splenomegaly, two cases had rash, and one case had anemia; (4) Considering Ann Arbor stage, three cases were in stage IV and one case in stage III among four patients with known clinical stage; (5) In this

**Table 2.** Clinical information of previously published cases involving MCL and T cell lymphoma

| No./Series | Age/ Sex | Clinical Presentation | Stage | Site of biopsy | Subtype of TCL/ Pattern of MCL | Time of tumor occurrence | B-IgH/ T-TCR | EBER | Initial TR | Follow-up Months | Status |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1/Endi Wang et al. 2014 [4] | 87/M | Generalized lymphadenopathy | III | Cervical LN | PTCL, NOS/Mantle zone | Simultaneous | +/+ | - | No | NA | NA |
| 2/Hiroki Katsushima et al. 2018 [5] | 81/M | Bilateral axillary and inguinal lymphadenopathy | NA | Inguinal LN | PTCL, NOS/Nodular | Simultaneous | +/+ | - | NA | NA | NA |
| 3/IGG. Marín et al. 2019 [6] | 64/F | Splenomegaly, lymphadenopathy | IV | Inguinal LN | PTCL, NOS/Nodular | Simultaneous | +/+ | - | R-CHOP and ASCT | NA | ANED |
| 4/IGG. Marín et al. 2019 [6] | 45/M | Persistent sore throat | IV | Tonsil | PTCL, NOS/Diffuse | Simultaneous | +/+ | NA | R-HyperCVAD and ASCT | 48 | ANED |
| 5/Charles Leduc et al. 2015 [7] | 76/M | Cervical lymphadenopathy, normocytic anemia (I); Pruritic maculopapular rash (S) | NA | Duodenum (B); Skin (L) | C-ALCL/Nodular | Successive; MCL (2 years before) | +/+ | - | R-CHOP | NA | NA |
| 6/Present case | 49/M | Cervical lymphadenopathy (I); Scattered rash and splenomegaly (S) | IV | Cervical LN (B); Skin (L) | AITCL/Nodular | Successive; MCL (7 years before) | +/+ | + | R-hyperCVAD and ASCT | 125 | DOL |

Abbreviations: LN, Lymph node; TR, Therapeutic regimen; PTCL, NOS, Peripheral T cell lymphoma, not other specified; ANED, Alive with no evidence of disease; DOL, Died of lymphoma; I, Initial disease; S, Secondary disease; NA, Not available; B, Before; L, Later.

group, four patients had the combination of MCL and T cell lymphoma simultaneously. Also, the subtype of T cell lymphoma in these patients that was combined with MCL was peripheral T cell lymphoma, NOS without exception. Among the four patients, the biopsy was taken from lymph node in three patients and the tonsil in one patient; (6) In another two patients, it was T cell lymphoma, not MCL, as the secondary disease, which included cutaneous anaplastic large cell lymphoma and AITCL. The important point is that the same clinical manifestation of the two patients was rash when T cell lymphomas occurred successively. Therefore, a biopsy should be done soon when rash happens after a long time of treatment for MCL to rule out the possibility of secondary T cell lymphoma; (7) Four cases show the nodular type of MCL in the histologic pattern while one case is diffuse type and one case is mantle zone type; (8) IgH rearrangement in MCL and TCR rearrangement in T cell lymphoma were confirmed by polymerase chain reaction in all cases, but there was no overlap for MCL and T cell lymphoma; (9) Only one case was positive for EBV infection in which the secondary lesion was AITCL in this group; (10) Patients who received R-CHOP or R-HyperCVAD accompanied by autologous stem cell transplantation seemed to have a favorable prognosis.

The relationship between B cell and T cell lymphoma in different anatomic sites of the same patient is still not clear, but there are three possibilities [8]: First, the two types of lymphocytes are derived from two unrelated clones and are two completely independent diseases. Second, both lymphomas are derived from the same precursor cell, which is typically a pluripotent tumor stem cell that differentiates into different clones. Third, the two lymphomas are clonally related diseases. Secondary lymphoma is transformed from the first diagnosed lymphoma and this could be much more common in the conversion of indolent lymphoma to aggressive lymphoma. As far as the present case is concerned, AITCL and MCL might be two unrelated diseases, and this point may be proven by TCR gene positive and IgH negative rearrangement in the secondary lymphoma. The development of AITCL seven years later after chemotherapy and autologous stem cell transplantation for MCL might be attributed to secondary EBV infection after transplantation which should be classified as post-transplant lymphoproliferative disorder, a T cell neoplasm (T-PTLD). As we all know, PTLD is commonly related with allogeneic stem cell transplantation and its occurrence after autologous stem cell transplant is unusual [9]. On the other hand, ATICL is still rare in T-PTLC, even if the incidence of EBV infection is enhanced after bone marrow transplantation; and its mechanism needs to be further explored [10].

## Conclusion

The present case is the first report on DL consisting of MCL and AITCL. There seems not to be a relationship between these two different kinds of lymphoma. and EBV infection might prompt the development of AITCL after transplantation. MCL appears with T cell lymphoma simultaneously, the subtype of which is peripheral T cell lymphoma, not otherwise specified consistently. Rash is a common clinical manifestation when T cell lymphoma occurs after treatment for MCL. The therapeutic regimen of R-CHOP or R-HyperCVAD with autologous stem cell transplantation may be a good choice for the patients.

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Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Disclosure of conflict of interest

None.

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## References

[1] Nishioka A, Ureshino H, Ando T, Kizuka H, Kusaba K, Sano H, Itamura H, Kubota Y, Kojima K, Ohshima K and Kimura S. Three coexisting

lymphomas in a single patient: composite lymphoma derived from a common germinal center B-cell precursor and unrelated discordant lymphoma. Int J Hematol 2018; 107: 703-708.
[2] Caleo A, Sánchez-Aguilera A, Rodríguez S, Dotor AM, Beltrán L, de Larrinoa AF, Menárguez FJ, Piris MA and García JF. Composite Hodgkin lymphoma and mantle cell lymphoma: two clonally unrelated tumors. Am J Surg Pathol 2003; 27: 1577-1580.
[3] Wang HY, Karandikar N, Payne D, Maleki A, Schultz BA, Collins R and McKenna RW. A 3-way collision tumor of the upper respiratory tract: a composite of 2 immunophenotypically distinct mantle cell lymphomas and a plasmacytoma. Hum Pathol 2008; 39: 781-787.
[4] Wang E, Papavassiliou P, Wang AR, Louissaint A Jr, Wang J, Hutchinson CB, Huang Q, Reddi D, Wei Q, Sebastian S, Rehder C, Brynes R and Siddiqi I. Composite lymphoid neoplasm of B-cell and T-cell origins: a pathologic study of 14 cases. Hum Pathol 2014; 45: 768-84.
[5] Hiroki K, Shinji N, Masanori T, Noriko F, Satoshi I, Yuko I, Hideo H and Ryo I. A composite lymphoma consisting of a mantle cell lymphoma and a peripheral T-cell lymphoma: a rare case with literature review. AJSP: Reviews & Reports 2018; 23: 255-261.
[6] González-Gascón Y Marín I, Menarguez J, Kwon M, Burdaspal A, Martínez-Laperche C, Castro Y, Infante MS, Díez-Martín JL and Hernández-Rivas JÁ. Composite lymphoma containing mantle cell and peripheral T-cell lymphoma, not otherwise specified: a report of 2 cases treated with up-front autologous stem cell transplantation. Appl Immunohistochem Mol Morphol 2019; [Epub ahead of print].
[7] Leduc C, Blandino II, Alhejaily A, Baetz T, Good DJ, Farmer PL, Squire JA and LeBrun DP. Composite mantle cell and primary cutaneous anaplastic large cell lymphoma: case report and review of the literature. Am J Dermatopathol 2015; 37: 232-326.
[8] Boyer DF, Lindeman NI, Harris NL and Ferry JA. Peripheral T-cell lymphomas with cytotoxic phenotype in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Am J Surg Pathol 2014; 38: 279-288.
[9] Komrokji RS, Oliva JL, Zand M, Felgar R and Abboud CN. Mini-BEAM and autologous hematopoietic stem-cell transplant for treatment of post-transplant lymphoproliferative disorders. Am J Hematol 2005; 79: 211-215.
[10] Ibrahim HA, Menasce LP, Pomplun S, Burke M, Bower M and Naresh KN. Presence of monoclonal T-cell populations in B-cell post-transplant lymphoproliferative disorders. Mod Pathol 2011; 24: 232-240.