学 位 論 文 の 要 旨

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論 文 内 容 の 要 旨

INTRODUCTION

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) is the most common subtype of PTCL, accounting for approximately 25% of all PTCLs. Previous studies revealed that PTCL-NOS is classified into two biologically distinct major subtypes. PTCL-TBX21 and PTCL-GATA3 based on cellular origin, such as Th1 and Th2. Gene profiling analysis has reported prognostic differences and genetic abnormalities between the two subtypes PTCL-TBX21 and PTCL-GATA3.The same group showed that the immunohistochemical (IHC) algorithm using T-bet/TBX21, GATA3, CXCR3, and CCR4 classified into the two subtypes; PTCL-TBX21 and PTCL-GATA3. However, clinical or pathological features of the two subtypes remain unknown.

We compared the clinicopathological features by IHC algorithm, and tumor-immunological gene expressions by nCounter analysis system between PTCL-TBX21 and PTCL-GATA3 in a Japanese Cohort.

MATERIALS AND METHODS

The study cohort comprised 100 patients newly diagnosed with PTCL-NOS at the Department of Pathology, Kurume University School of Medicine.

In this study, the IHC algorithm reported in previous studies was used to classify PTCL-NOS subtypes; the four antibodies used in the IHC algorithm were T-bet, CXCR3, GATA3 and CCR4, and if tumor cells were positive for T-bet or CXCR3 more than 20%, those cases were classified as PTCL-TBX21. If tumor cells were positive for GATA3 or CCR4 more than 50%, those cases were classified as PTCL-GATA3. The cases not classified as PTCL-TBX21 or PTCL-GATA3 were determined as PTCL-unclassified. Gene expression analysis was performed using nCounter with the PanCancer immune-profiling panel. Twenty-eight patients for gene expression analysis included 13 PTCL-TBX21, 5 PTCL-GATA3 and 10 PTCL-unclassified cases. The use of the patient sample was approved by Research Ethics Committee of Kurume University, and the research was conducted in accordance with the guidelines of the Declaration of Helsinki. The Research Ethics Committee approved an opt-out method for informed consent.

RESULTS AND DISCUSSION

100 PTCL-NOS patients were classified as PTCL-TBX21 in 55 cases, PTCL-GATA3 in 24 cases and PTCL-unclassified in 21 cases using the IHC algorithm.

PTCL-GATA3 tended to have higher proportions of Complete response (CR) rate at initial treatment than PTCL-TBX21 ($P = 0.088$). Pathological studies showed that CD4 expression was significantly lower in PTCL-TBX21 than in PTCL-GATA3 ($P = 0.047$). When evaluating the tumor microenvironment, the number of high endothelial venous was predominantly lower in PTCL-TBX21 than in PTCL-GATA3 ($P = 0.032$).

In the volcano plot comparing gene expression in PTCL-TBX21 and PTCL-GATA3, 34 genes were up-regulated in PTCL-TBX21 and two genes in PTCL-GATA3. The up-regulated genes in PTCL-TBX21 included Th1-related genes such as CXCR3, CD38, INFG, CXCL9, CXCL11 and IL27, and genes related to tumor immunity such as *CD274 (PD-L1)*, *LAG3* and *IDO1*. Consistent with the IHC algorithm, *TBX21* and *CXCR3* were highly expressed in PTCL-TBX21, and *GATA3* and *CCR4* were highly expressed in PTCL-GATA3.

PTCL-unclassified had significantly lower age ($P = 0.049$), lower elevated LDH levels ($P = 0.035$), lower CD8 expression ($P = 0.008$) and smaller large cells size ($P = 0.003$) compared to PTCL-TBX21. In the analysis of PFS, PTCL-unclassified showed that PTCL-unclassified had a better prognosis than PTCL-GATA3 ($P = 0.031$).

PTCL-GATA3 showed significantly worse overall survival (OS) ($P = 0.047$) and a trend towards worse progression-free survival (PFS) ($P = 0.074$) compared to PTCL-TBX21. In univariate analysis for OS, PTCL-GATA3 was a significant prognostic factor (HR: 2.02; 95% CI, 1.09-3.77; $P = 0.027$), but was not significant in multivariate analysis (HR: 2.09; 95% CI, 0.89-4.88; $P = 0.090$). PTCL-GATA3 was an independent prognostic factor by univariate and multivariate analyses of PFS. (univariate HR: 1.96; 95% CI, 1.08-3.56; $P = 0.027$, multivariate

analysis HR: 2.91; 95% CI, 1.24-6.84; $P = 0.014$)

The present study showed that Japanese patients with PTCL-NOS were classified into PTCL-TBX21, PTCL-GATA3 and PTCL-unclassified using the IHC algorithm. PTCL-GATA3 had worse prognosis in OS and PFS than PTCL-TBX21. We confirmed that PTCL-GATA3 as an independent poor prognostic factor for PFS.

The difference between our study and previous study (Amador et al. *Blood.* 2019; 134:2159-2170) was the immunostaining of six follicular helper T cell (TFH) markers, including CD10, PD-1, BCL6, ICOS, CXCL13 and CXCR5, which strictly excluded TFH-type PTCL. PTCL-NOS diagnosed in this study is a population that has been pathologically reviewed and diagnosed as PTCL-NOS.

The results of protein expression by IHC algorithm ware consistent with the results of genetic profiling (GEP) by nCounter in this study. These results are considered to reflect the reproducibility of the IHC algorithm as an alternative method for GEP analysis. There are a small of number of studies on the IHC algorithm. Further investigation will be able to construct more appropriate IHC algorithm form clinicopathological viewpoints by evaluating cutoff value of each protein expression and adopting more specific markers for Th1 and Th2 segregation.

In this study, the higher expression of tumor suppressor genes including *IDO1*, *CD274 (PD-L1)* and *LAG3* was observed in PTCL-TBX21. Our previous studies (Sugio et al. *Blood Adv.* 2018; 2:2242-2252) showed that *PD-L1* and *IDO1* were highly expressed in tumor-infiltrating macrophages in some PTCL-NOS patients. These genes are associated with escape mechanisms from tumor immunity, which may play an important role in the pathogenesis of PTCL-TBX21. The immune checkpoints targeting PD-1, PD-L1, IDO1 and LAG3 may improve prognosis in PTCL-TBX21 patients.

CONCLUSION

The classification of PTCL-TBX21 and PTCL-GATA3 using the IHC algorithm for Japanese patients of PTCL-NOS showed different clinicopathological features and gene expression patterns, including tumor immune suppressor genes. These results suggest that PTCL-NOS subtyping may be useful in predicting prognosis of Japanese patients and in stratifying tumor immune checkpoint inhibitor use in clinical practice.