Human Pathology (2018) **79**, 86–92

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Clinicopathological analysis of immunohistochemical expression of retinoic acid–related orphan receptor-γt in peripheral T-cell lymphoma, not otherwise specified☆

Eriko Yanagida MD[a], Hiroaki Miyoshi MD, PhD[a,*], Keisuke Kawamoto MD, PhD[a], Kazutaka Nakashima MT[a], Kotaro Matsuda MD[a], Kyohei Yamada MD[a], Reiji Muto MD[a], Koji Nagafuji MD, PhD[b], Masao Seto MD, PhD[a], Koichi Ohshima MD, PhD[a]

[a]*Department of Pathology, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan*
[b]*Department of Hematology, Kurume University Hospital, Kurume, Fukuoka 830-0011, Japan*

Received 10 January 2018; revised 25 April 2018; accepted 2 May 2018

Keywords:
RORγt;
PTCL-NOS;
Pathology;
Prognosis

Summary Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is cytologically and phenotypically heterogeneous. Retinoic acid–related orphan receptor-γt (RORγt) is a transcription factor that regulates the differentiation of naïve $CD4^+$ helper T cells to Th17 cells. In the present study, we immunohistochemically confirmed the expression of RORγt in PTCL-NOS. Pathological and clinical investigations were performed for 170 cases of PTCL-NOS. RORγt-positive cases accounted for 17.6% (30/170) of the total cases, and they showed a significantly higher frequency of CD8 positivity ($P = .033$), lower counts of white blood cells ($P = .030$) and neutrophils ($P = .039$) in the peripheral blood, higher levels of hypergammaglobulinemia ($P = .031$), a higher frequency of a complete response ($P = .009$), and a tendency for a lower International Prognostic Index ($P = .061$) and better overall survival ($P = .0806$). These results suggest that RORγt-positive PTCL-NOS could be a subpopulation of PTCL-NOS. Further research associated with this genomic abnormality at the transcriptional level is needed to confirm the results of this study.

1. Introduction

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is a diverse, yet common subtype of peripheral T-cell lymphomas and natural killer/T-cell lymphomas, accounting for approximately 30% and 25% of all T-cell lymphomas in Western and Asian countries, respectively [1-3]. PTCL-NOS is cytologically and phenotypically heterogeneous and has a poor prognosis, with a 5-year overall survival (OS) of 32% [3].

☆ Disclosures: The authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

* Corresponding author at: Department of Pathology, School of Medicine, Kurume University, Asahimachi 67, Kurume-City, Fukuoka 830-0011, Japan.
E-mail address: miyoshi_hiroaki@med.kurume-u.ac.jp (H. Miyoshi).

https://doi.org/10.1016/j.humpath.2018.05.002
0046-8177/

Retinoic acid–related orphan receptor-γt (RORγt) is a nuclear transcription factor that regulates the differentiation of naive $CD4^+$ T helper cells to interleukin (IL)-17–secreting Th17 cells [4]. IL-17 is a proinflammatory cytokine and, like all members of the IL-17 family, plays an important role in inflammatory diseases [5]. The expression of RORγt has been studied in several cancers, including melanoma and colon cancer [6,7]. The association between RORγt expression and prognosis varies in different cancers. The expression of nuclear transcription factors, including RORγt, has been examined in a small number of PTCL-NOS cases; however, a study linking it to clinical information, including prognosis, has not been performed [8].

The differentiation of naive $CD4^+$ T helper cells into other effector T cells, such as Th1, Th2, Treg, and T follicular helper (Tfh) cells, is regulated by various transcription factors, such as T-Bet for Th1, GATA binding protein 3 (GATA3) for Th2, FoxP3 for Treg, and Bcl6 for Tfh cells [9]. Although angioimmunoblastic T-cell lymphomas (AITLs) originate from Tfh cells, adult T-cell lymphoma/leukemia cells are known to be derived from Treg cells [10,11]. Expression of T-bet and GATA3 has been reported in PTCL-NOS cells; an inferior prognosis is associated with the subtype overexpressing GATA3 [12,13].

Although RORγt expression in PTCL-NOS has only been studied in a small number of cases [8], its association with the clinicopathological characteristics of PTCL-NOS has never been investigated. In the present study, we examined the clinicopathological characteristics of RORγt-positive PTCL-NOS.

2. Materials and methods

2.1. Patients

We reviewed 170 cases of PTCL-NOS, including 62 cases from the International Peripheral T-cell and Natural Killer/T-cell Lymphoma Study [3], with a tissue microarray, and 108 cases diagnosed at Kurume University between 2005 and 2013. Some of these cases were included in our previous study [14]. All cases were reviewed by experienced hematopathologists (O. K., M. H., and Y. E.) according to the World Health Organization classification [2]. Clinical information was collected in 75 cases by reviewing the patients' medical charts. The study was approved by the Research Ethics Committee of Kurume University and was conducted in accordance with the Declaration of Helsinki.

2.2. Morphologic and immunohistochemical analysis

Each sample was investigated for its morphologic characteristics according to our previous study [15]. Neoplastic T cells were detected by assessing morphologic findings including cell size and nuclear atypia. Nuclear atypia was evaluated by some characteristics including pleomorphic nuclei of varying sizes, large nucleoli, and hyperchromatism with coarse and irregular distribution.

Immunohistochemical staining of formalin-fixed, paraffin-embedded tissue sections was performed using an anti-RORγt mouse monoclonal antibody (clone 6F3.1MABF81; Merck Millipore, Darmstadt, Germany). We also used antibodies to CD3 (clone LN10; Leica Biosystems, Newcastle, UK), CD4 (4B12; MBL, Nagoya, Japan), CD8 (4B11; Leica Biosystems), CD30 (Ber-H2; Dako, Glostrup, Denmark), TIA1 (2G9A10F5; Beckman Coulter, Brea, CA), Granzyme B (GrB-7; Chemicon, Temecula, CA), GATA3 (D13C9; Cell Signaling Technology, Tokyo, Japan), and T-bet/Tbx21 (4B10; Abcam, Tokyo, Japan). Tumor cells with more than 30% staining were considered positive, and a case positive for TIA1 and/or Granzyme B was considered cytotoxic molecule positive. Cases with follicular helper T-cell phenotype (Tfh markers) were defined if at least 2 antibodies against

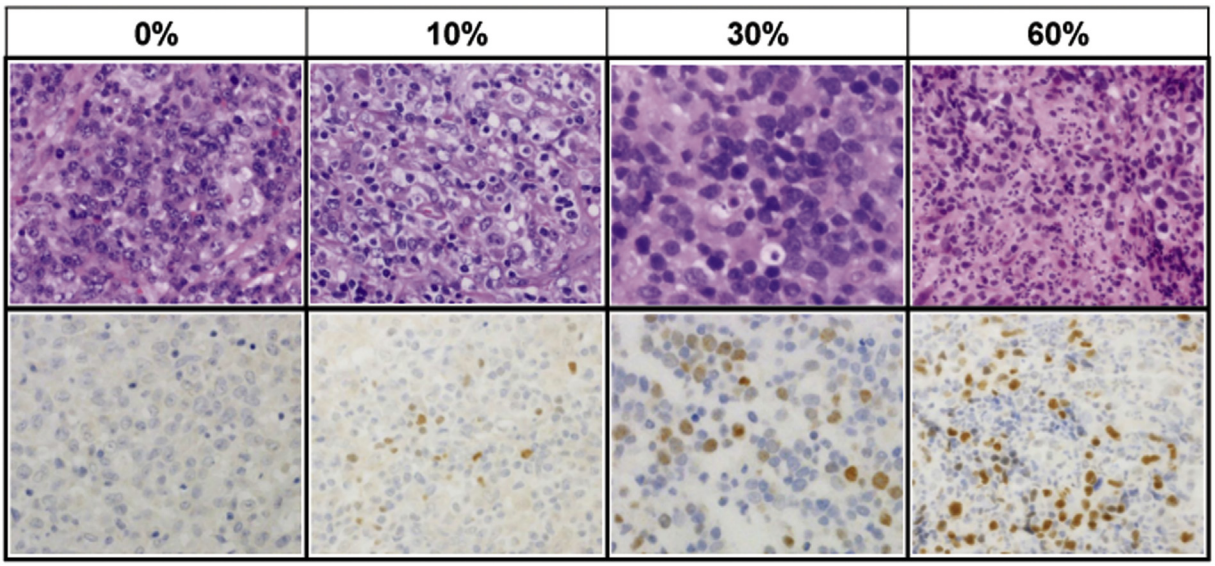

Fig. 1 Representative hematoxylin and eosin and immunohistochemical staining of RORγt in PTCL-NOS (original magnification ×400). Cases with 0%, 10%, 30%, and 60% RORγt expression are shown.

Tfh markers, including programmed death-1 (PD-1), CXCL13, CD10, and BCL6, were positive.

2.3. In situ hybridization for Epstein-Barr virus–encoded RNA

Epstein-Barr virus (EBV) was detected using in situ hybridization with a fluorescein-conjugated EBV peptide nucleic acid probe kit (DakoCytomatin, Glostrup, Denmark), as described previously [16].

2.4. Cutoff value determination for RORγt

The optimal cutoff value for RORγt expression was defined on the basis of the receiver operating characteristic curve and the Youden index [17], as well as previous studies [18]. In the present study, the International Prognostic Index (IPI) score, which has been recognized as a prognostic predictor [19,20], was applied as a dichotomous variable, and RORγt expression as a continuous variable. The Youden index revealed an optimal cutoff value as 5% RORγt expression, and cases with higher than 5% expression were defined as RORγt positive (Fig. 1).

2.5. Statistical analysis

The clinical and pathological findings were compared using the {chi}^{2} test, the Fisher exact test, or the Mann-Whitney *U* test. The Kaplan-Meier method was used to estimate OS. A log-rank test was used to compare the survival curves. A Cox proportional hazards model was used to assess the prognostic value of each factor. *P* values calculated in this study were all based on 2-sided tests, and those less than .05 were considered statistically significant. Statistical analysis in this study was carried out using JMP, version 12 (SAS Institute, Tokyo, Japan).

3. Results

3.1. The proportion of neoplastic cells with RORγt expression in PTCL-NOS

As for the proportion of RORγt expression, less than 5% neoplastic cells expressed RORγt in almost cases of PTCL-NOS (Supplementary Fig. 1).

3.2. Pathological features

Table 1 shows a comparison of the pathological features of 170 RORγt-positive and RORγt-negative cases. There were 17.6% (30/170) RORγt-positive cases and 82.4% (140/170) RORγt-negative cases. The RORγt-positive group showed significantly higher CD8 positivity ($P = .033$), although the other pathological characteristics did not show a significant difference.

3.3. Clinical features

Table 2 summarizes the characteristics of the 75 patients with clinical information. Compared with the RORγt-negative cases, the RORγt-positive cases showed significantly lower counts of white blood cells (WBCs)

Table 1 Comparison of pathological features between RORγt-positive PTCL-NOS and RORγt-negative PTCL-NOS

Characteristics	Total (n = 170)	RORγt (+) (n = 30)	RORγt (−) (n = 140)	*P*
Neoplastic cells				
Clear cell, >30%	38.8% (66/170)	46.7% (14/30)	37.1% (52/140)	.335
Cell size, large	54.1% (92/170)	46.7% (14/30)	55.7% (78/140)	.368
CD4 positive, >30%	69.2% (117/169)	70.0% (21/30)	69.1% (96/139)	.920
CD8 positive, >30%	21.4% (36/168)	36.7% (11/30)	18.1% (25/138)	.033
TIA-1 and/or Granzyme B, >30%	40.0% (66/165)	50.0% (15/30)	37.8% (51/135)	.220
CD30, >30%	20.5% (24/117)	27.3% (6/22)	19.0% (18/95)	.396
EBV positive, >30%	8.7% (14/161)	3.5% (1/29)	9.9% (13/132)	.468 [a]
T-bet positive	20.0% (34/170)	23.3% (7/30)	19.3% (27/140)	.620
GATA3 positive	81.2% (138/170)	90.0% (27/30)	79.3% (111/140)	.207 [a]
Tfh marker positive				
>2 markers positive	3.2% (2/62)	0% (0/12)	4.0% (2/50)	1.000 [a]
Only 1 marker positive	21.0% (13/62)	25.0% (3/12)	20.0% (10/50)	.703 [a]
Microenvironment				
Infiltration of neutrophils, average/median [range] (counts/HPF)	1.2/0 [0-46.4]	2.8/0 [0-46.4]	0.8/0 [0-30.2]	.262
Infiltration of eosinophils, average/median [range] (counts/HPF)	5.5/0.4 [0-211]	2.5/0.4 [0-39.7]	6.2/0.4 [0-211]	.952
Infiltration of plasma cells, average/median [range] (counts/HPF)	3.9/0.3 [0-87]	7.1/0.6 [0-50.3]	3.2/0.3 [0-87]	.403
Proliferation of HEV, average/median [range] (counts/HPF)	2.2/1.6 [0-11.6]	2.1/1.7 [0.3-5.9]	2.3/1.6 [0-11.6]	1.000
EBV (+) nonneoplastic cells, average/median [range] (counts/HPF)	1.4/0 [0-51.4]	1.3/0 [0-16.9]	1.4/0 [0-51.4]	.429

Abbreviations: HPF, high-power field; HEV, high endothelial venules.
[a] Fisher exact test.

($P = .030$) and neutrophils ($P = .039$), a higher incidence of hypergammaglobulinemia ($P = .031$) and a better complete response (CR) rate to the initial treatment ($P = .009$), and a tendency for lower IPI scores ($P = .061$). The other clinical factors did not show a significant difference between the 2 groups.

3.4. OS in PTCL-NOS patients based on RORγt expression

Although not significant, RORγt-positive PTCL-NOS showed a trend toward better OS compared with RORγt-negative cases ($P = .0806$; Fig. 2).

Univariate analyses identified the following variables as prognostic factors (Table 3): a high IPI score (hazard ratio [HR], 3.132; 95% confidence interval [CI], 1.626-6.174; $P = .0007$), Ann Arbor stage III/IV (HR, 1.950; 95% CI, 1.024-3.867; $P = .0421$), performance status (PS; HR, 6.896; 95% CI, 3.412-14.468; $P < .001$), and B-symptoms (HR, 2.221; 95% CI, 1.170-4.325; $P = .0147$). However, RORγt positivity did not attain statistical significance (HR, 0.441; 95% CI, 0.150-1.036; $P = .0612$).

We conducted a multivariate analysis to evaluate the association of RORγt positivity with B-symptoms and constituents of IPI, including age, Ann Arbor stage, PS, lactate dehydrogenase (LDH), and extranodal site (multivariate analysis 1). The expression of RORγt was a significant prognostic factor (HR, 0.2969; 95% CI, 0.091-0.808; $P = .0161$). In contrast, when we conducted multivariate analysis for RORγt positivity, B-symptom, and IPI score (multivariate analysis 2), RORγt expression failed to reach statistical significance (HR, 0.420; 95% CI, 0.132-1.125; $P = .0867$).

4. Discussion

In the present study, RORγt-positive PTCL-NOS cases showed significantly a higher CR rate, hypergammaglobulinemia, lower WBC and neutrophil counts, and a tendency for lower IPI scores and a good prognosis. Consistent with

Table 2 Comparison of clinical features between RORγt-positive and RORγt-negative PTCL-NOS cases

	Total (n = 75)	RORγt (+) (n = 13)	RORγt (–) (n = 62)	*P*
Characteristics				
Sex, male/female	41/34	8/5	33/29	.761 [a]
Age (y), average/median [range]	62.9/68 [6-87]	59.8/63.0 [6-79]	63.5/68.5 [12-87]	.506
Clinical findings				
B-symptoms	45.3% (34/75)	46.2% (6/13)	45.2% (28/62)	.948
Raised rash	9.3% (7/75)	7.7% (1/13)	9.7% (6/62)	1.000 [a]
Hepatomegaly	5.3% (4/75)	0% (0/13)	6.5% (4/62)	1.000 [a]
Splenomegaly	13.3% (10/75)	0% (0/13)	16.1% (10/62)	.194 [a]
Skin infiltration	13.3% (10/75)	15.4% (2/13)	12.9% (8/62)	1.000 [a]
Hemophagocytic syndrome	14.3% (9/63)	18.2% (2/11)	13.5% (7/52)	.650 [a]
Bone marrow involvement	16.2% (11/68)	0% (0/11)	19.3% (11/57)	.190 [a]
Extranodal involvement	53.3% (40/75)	46.2% (6/13)	54.8% (34/62)	.569
Ann Arbor stage, III or IV	53.3% (40/75)	38.5% (5/13)	56.5% (35/62)	.360 [a]
PS (2-4)	33.3% (25/75)	23.1% (3/13)	35.5% (22/62)	.524 [a]
IPI, high-risk group (3-5)	41.3% (31/75)	15.4% (2/13)	46.8% (29/62)	.061 [a]
PIT, high-risk group (3-4)	23.9% (16/67)	9.1% (1/11)	26.8% (15/56)	.275 [a]
Blood examination data				
WBC, average/median [range] ($\times 10^3$ counts/μL)	6.5/5.7 [1-29.3]	4.7/3.7 [2.0-12.1]	6.9/5.9 [1-29.3]	.030
Neutrophil, average/median [range] ($\times 10^3$ counts/μL)	4.4/3.2 [1-15.8]	2.3/2.3 [1.9-3.1]	4.9/3.8 [1-15.8]	.039
Hemoglobin, average/median [range] (mg/dL)	12.0/12.1 [6.8-16.4]	11.9/12.1 [8.7-14.4]	12.0/12.3 [6.8-16.4]	.916
Platelets, average/median [range] ($\times 10^3$ counts/μL)	213.8/204 [31-548]	192.0/190.0 [56-323]	218.4/218.5 [31-548]	.437
Hemolytic anemia	2.8% (2/71)	0% (0/12)	3.4% (2/59)	1.000 [a]
Elevated LDH	49.3% (37/75)	46.2% (6/13)	50.0% (31/62)	.801
Hypergammaglobulinemia	18.0% (11/61)	41.7% (5/12)	12.2% (6/49)	.031 [a]
Elevated CRP	61.6% (45/73)	46.2% (6/13)	65.0% (39/60)	.211
Treatment				
Treatment	94.7% (71/75)	100% (13/13)	93.6% (58/62)	1.000 [a]
CHOP/CHOP like	79.2% (57/72)	69.2% (9/13)	81.4% (48/59)	.450 [a]
Initial radiotherapy	26.1% (6/23)	40.0% (2/5)	22.2% (4/18)	.576 [a]
Transplantation	6.7% (5/75)	7.7% (1/13)	6.5% (4/62)	1.000 [a]
Recurrence	55.6% (35/63)	58.3% (7/12)	54.9% (28/51)	1.000 [a]
Response to initial treatment, CR or CR(u)	40.3% (25/62)	75.0% (9/12)	32.0% (16/50)	.009 [a]

Abbreviations: PIT, Prognostic Index for T-cell lymphoma; CRP, C-reactive protein; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response/remission; CR(u), uncertain complete response/remission.

[a] Fisher exact test.

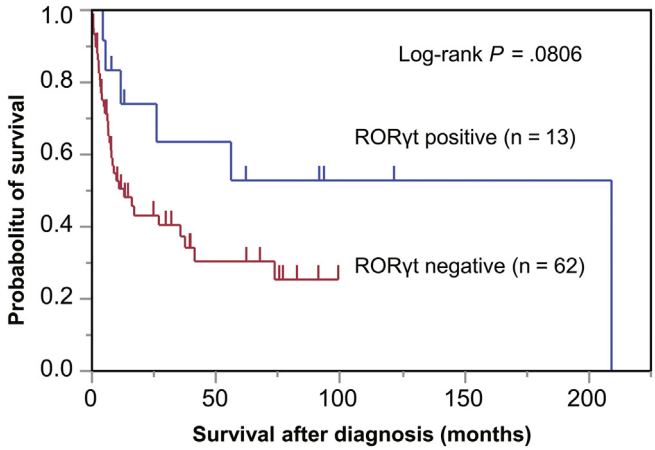

Fig. 2 Kaplan-Meier curves for OS for PTCL-NOS cases according to RORγt expression. OS of cases with at least 5% RORγt expression was better than of cases with less than 5% RORγt expression ($P = .0806$).

Table 3 Prognostic factors affecting the OS of patients with PTCL-NOS

Characteristics	Univariate analysis		Multivariate analysis 1 [a]		Multivariate analysis 2 [b]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
RORγt, positive (*vs* RORγt, negative)	0.441 (0.150-1.036)	.0612	0.2969 (0.091-0.808)	.0161	0.420 (0.132-1.125)	.0867
PS, 2-4 (*vs* 0 or 1)	6.896 (3.412-14.468)	<.001	7.364 (3.263-17.558)	<.001		
Age, >60 y (*vs* <60 y)	1.140 (0.596-2.290)	.6981	0.590 (0.271-1.310)	.1908		
Ann Arbor stage, III/IV (*vs* I/II)	1.950 (1.024-3.867)	.0421	1.264 (0.563-2.897)	.5710		
Extranodal sites ≥2 (*vs* <2)	1.997 (0.972-3.871)	.0475	0.998 (0.410-2.331)	.9972		
LDH, elevated (*vs* normal)	1.352 (0.717-2.576)	.3508	0.981 (0.491-1.968)	.9563		
B-symptom present (*vs* absent)	2.221 (1.170-4.325)	.0147	2.376 (1.149-5.014)	.0196	2.809 (1.424-5.737)	.0028
Cytotoxic molecule positive (*vs* negative)	1.754 (0.931-3.338)	.0816	1.864 (0.906-3.874)	.0904	2.130 (1.077-4.272)	.0299
IPI, high (*vs* low)	3.132 (1.626-6.174)	.0007			2.727 (1.367-5.625)	.0043

[a] The variables included in multivariate analysis 1 for OS were age, Ann arbor stage, PS, LDH, B-symptom, cytotoxic molecule, and the expression of RORγt.

[b] The variables included in the second multivariate analysis 2 for OS were IPI, cytotoxic molecules, and the expression of RORγt.

previous reports [19,20], our study indicates that a tendency for low IPI score is a good prognostic factor for PTCL-NOS, which also indicates that our cohort is devoid of any selection bias. The RORγt-positive PTCL-NOS group, characterized by a high CR rate in response to the initial treatment, hypergammaglobulinemia, low counts of WBC and neutrophils, and tendency for lower IPI scores and a good prognosis, may therefore comprise a new subtype.

So far, several studies have reported an association between prognosis and RORγt expression in neoplastic cells or tumor-infiltrating lymphocytes (TILs). RORγt can act as key transcription factor for the development of Th17 cells also in mouse [3]. The analysis of RORγt-knockout mice disclosed that these mice develop the T-cell lymphoma, although the underlying mechanism remains unclear [21]. On the other hand, it has been reported that high expression of RORγt in TILs is a risk factor for lymph node metastasis and is an independent poor prognostic factor for OS in colon cancer [7]. Th17 cells that are regulated by RORγt, as well as cytokines such as interleukin-6 (IL-6) and transforming growth factor β, induce the production of proinflammatory cytokines IL-17, IL-22, and tumor necrosis factor α. Chronic and recurrent inflammation induced by these cytokines can lead to carcinogenesis by inducing genome instability and increasing the potential for tumor cell growth and angiogenesis [7]. Unlike in TILs, RORγt expression has been reported to be associated with a good prognosis in malignant melanoma [22], although the underlying mechanism is not clear. In this study of PTCL-NOS, the RORγt expression observed in the tumor cells was associated with a better prognosis than that seen in malignant melanoma, whereas low expression of RORγt was seen in TILs (data not shown). Studies to understand the mechanisms are required in the future.

The RORγt-positive group had significantly higher levels of hypergammaglobulinemia and low counts of WBCs and neutrophils. Studies have shown that naïve helper $CD4^+$ T cells differentiate into the Th17 lineage under the regulation of RORγt, with simultaneous stimulation from IL-6 and transforming growth factor β [4]. Th17 cells produce not only IL-17 but also IL-6 [4]. Stimulation by IL-6 induces the differentiation of antibody-producing plasma cells, which may result in hypergammaglobulinemia [4,23,24]. Studies with transgenic

mice have shown that RORγt overexpression causes an elevation in IL-6 levels, leading to polyclonal plasmacytosis, and an increased antibody production, resulting in hypergammaglobulinemia [25,26]. These reports suggest a potential role of Th17 cells in the hypergammaglobulinemia observed in RORγt-positive PTCL NOS.

RORγt-positive PTCL-NOS cases showed clear cells in half of the cases as well as hypergammaglobulinemia, which are characteristics of AITL. We compared RORγt-positive PTCL-NOS with AITL (Supplementary Table 1) clinicopathologically, using data from our previous studies [16]. Statistical differences, based on clinicopathological findings between RORγt-positive PTCL-NOS and AITL, have been shown, although no significant difference in prognosis was observed. These differences suggested that RORγt-positive PTCL-NOS and AITL might be another disease entity.

In this study, patients with RORγt-positive PTCL-NOS showed a significantly higher proportion of CD8-positive cells, although no association among the expression of RORγt, CD4, CD8, and cytotoxic molecules was detected (data not shown). Double staining of RORγt and CD8 (Supplementary Fig. 2) showed that some neoplastic cells had only CD8 expression and some had only ROR-γt, whereas the rest had both RORγt and CD8 expression. Neoplastic cells actually showed various expression patterns of RORγt and CD8. Patients with RORγt-positive PTCL-NOS showed a significantly higher proportion of CD8-positive cells compared with those with RORγt-negative PTCL-NOS. However, CD4 expression was also observed in most of the cases (70%) in both RORγt-negative and RORγt-positive groups, regardless of CD8 expression. Whether the expression of CD4 or CD8 in RORγt-positive neoplastic cells corresponds to the nature of neoplastic cell origin is yet to be clarified. In addition, the significance of CD8 expression in RORγt-positive PTCL-NOS remains unknown and should be explored in the future.

On the other hand, RORγt is considered a major transcription factor for Th17 cells. The RORγt is necessary for the differentiation of naïve $CD4^+$ helper T cells into Th17 cells [4]. This study suggests the possibility that Th17 might be the derived cells of RORγt-positive PTCL-NOS, because RORγt is a transcription factor for Th17 cells and RORγt-positive PTCL-NOS expressed CD4 in most of the cases, although it is difficult to confirm derived cells based on RORγt expression only.

Solt et al [27] have reported a synthetic RORγt ligand that inhibits the differentiation of Th17 and has been used in the treatment of autoimmune diseases. Huh et al [28] reported that derivatives of digoxin can be used as therapeutic agents to target RORγt and attenuate inflammatory lymphocyte functions in autoimmune diseases. Targeting the RORγt might be an effective treatment for RORγt-positive PTCL-NOS.

In conclusion, PTCL-NOS patients with and without RORγt expression showed different clinicopathological traits, suggesting that RORγt-positive PTCL-NOS could be a subtype of PTCL-NOS. Larger cohort studies are needed to confirm the results of this study.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2018.05.002.

Acknowledgments

The authors thank Mayumi Miura, Kanoko Miyazaki, Yuki Morotomi, Chie Kuroki, and Kaoruko Nagatomo for their technical assistance.

References

[1] Pileri SA, Weisenburger DD, Sng I, et al. Peripheral T-cell lymphoma, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, et al, editors. World Health Organisation classification of tumors of haematopoietic and lymphoid tissues, 4th ed. Lyon: IARC Press; 2017. p. 403-7.
[2] Pileri SA, Weisenburger DD, Sng I, et al. Peripheral T-cell lymphoma, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, et al, editors. World Health Organisation classification of tumors of haematopoietic and lymphoid tissues, 4th ed. Lyon: IARC Press; 2008. p. 306-8.
[3] Vose J, Armitage J, Weisenburger D. International T-cell lymphoma project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26:4124-30.
[4] Ivanov II, McKenzie BS, Zhou L, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 2004;126:1121-33.
[5] Kolls JK, Lindén A. Interleukin-17 family members and inflammation. Immunity 2004;21:467-76.
[6] Brożyna AA, Jozwicki W, Skobowiat C, Jetten A, Slominski AT. RORα and RORγ expression inversely correlates with human melanoma progression. Oncotarget 2016;7:63261-82.
[7] Yoshida N, Kinugasa T, Miyoshi H, et al. A high RORγT/CD3 ratio is a strong prognostic factor for postoperative survival in advanced colorectal cancer: analysis of helper T cell lymphocytes (Th1, Th2, Th17 and regulatory T cells). Ann Surg Oncol 2016;23:919-27.
[8] Matsumoto Y, Horiike S, Ohshiro M, et al. Expression of master regulators of helper T-cell differentiation in peripheral T-cell lymphoma, not otherwise specified, by immunohistochemical analysis. Am J Clin Pathol 2010;133:281-90.
[9] Inghirami G, Chan WC, Pileri S. Peripheral T-cell and NK cell lymphoproliferative disorders: cell of origin, clinical and pathological implications. Immunol Rev 2015;263:124-59.
[10] Zhan HQ, Li XQ, Zhu XZ, Lu HF, Zhou XY, Chen Y. Expression of follicular helper T cell markers in nodal peripheral T cell lymphomas: a tissue microarray analysis of 162 cases. J Clin Pathol 2011;64:319-24.
[11] Karube K, Aoki R, Sugita Y, et al. The relationship of FOXP3 expression and clinicopathological characteristics in adult T-cell leukemia/lymphoma. Mod Pathol 2008;21:617-25.
[12] Iqbal J, Wright G, Wang C, et al. Lymphoma leukemia molecular profiling project and the international peripheral T-cell lymphoma project. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. Blood 2014;123:2915-23.
[13] Wang T, Feldman AL, Wada DA, et al. GATA-3 expression identifies a high-risk subset of PTCL-NOS with distinct molecular and clinical features. Blood 2014;123:3007-15.

[14] Kawamoto K, Miyoshi H, Yanagida E, et al. Comparison of clinicopathological characteristics between T-cell prolymphocytic leukemia and peripheral T-cell lymphoma, not otherwise specified. Eur J Haematol 2017; 98:459-66.
[15] Kato T, Miyoshi H, Kobayashi S, et al. Clinicopathological analysis in PTCL-NOS with CADM1 expression. Virchows Arch 2017;471: 659-66.
[16] Miyoshi H, Sato K, Niino D, et al. Clinicopathologic analysis of peripheral T-cell lymphoma, follicular variant, and comparison with angioimmunoblastic T-cell lymphoma: Bcl-6 expression might affect progression between these disorders. Am J Clin Pathol 2012;137: 879-89.
[17] Akobeng AK. Understanding diagnostic tests 3: receiver operating characteristic curves. Acta Paediatr 2007;96:644-7.
[18] Yokoyama S, Miyoshi H, Nakashima K, et al. Prognostic value of programmed death ligand 1 and programmed death 1 expression in thymic carcinoma. Clin Cancer Res 2016;22:4727-34.
[19] Gallamini A, Stelitano C, Calvi R, et al. Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004;103:2474-9.
[20] Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol 2004;15:1467-75.
[21] Ueda E, Kurebayashi S, Sakaue M, Backlund M, Koller B, Jetten AM. High incidence of T-cell lymphomas in mice deficient in the retinoid-related orphan receptor RORgamma. Cancer Res 2002;62:901-9.
[22] Slominski AT, Kim TK, Takeda Y, et al. RORα and RORγ are expressed in human skin and serve as receptors for endogenously produced noncalcemic 20-hydroxy- and 20,23-dihydroxyvitamin D. FASEB J 2014;28: 2775-89.
[23] Kishimoto T. Interleukin-6: from basic science to medicine-40 years in immunology. Ann Rev Immunol 2005;23:1-21.
[24] Zhou L, Ivanov II, Spolski R, et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol 2007;8:967-74.
[25] Yoh K, Morito N, Ojima M, et al. Overexpression of RORγt under control of the CD2 promoter induces polyclonal plasmacytosis and autoantibody production in transgenic mice. Eur J Immunol 2012;42:1999-2009.
[26] Anderson P, Nagler-Anderson C, O'Brien C, et al. A monoclonal antibody reactive with a 15-kDa cytoplasmic granule-associated protein defines a subpopulation of CD8+ T lymphocytes. J Immunol 1990;144: 574-82.
[27] Solt LA, Kumar N, Nuhant P, et al. Suppression of TH17 differentiation and autoimmunity by a synthetic ROR ligand. Nature 2011;472:491-4.
[28] Huh JR, Leung MW, Huang P, et al. Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing RORγt activity. Nature 2011; 472:486-90.