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■ ORIGINAL ARTICLE ■

Expression of HAT1 and HDAC1, 2, 3 in Diffuse Large B-Cell Lymphomas, Peripheral T-Cell Lymphomas, and NK/T-Cell Lymphomas

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Background: It has generally been proven that histone acetylation and deacetylation are involved in the malignant transformation. To date, however, this has rarely been studied in cases of malignant lymphoma. **Methods:** We studied nine cases of reactive lymphoid hyperplasia, 78 cases of diffuse large B-cell lymphoma (DLBCL), 13 cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and 13 cases of extranodal NK/T-cell lymphoma, nasal type (NKTCL). Thus, we attempted to elucidate the associations of the degree of the expression of histone acetyltransferase 1 (HAT1), histone deacetylase (HDAC) 1, HDAC2, and HDAC3 with the clinical behaviors of above malignant lymphomas using the immunohistochemistry and a western blot analysis. **Results:** The degree of the expression of HAT1 was higher in cases of DLBCL, PTCL-NOS or NKTCL as compared with reactive lymphoid hyperplasia ($p<0.05$). The degree of the expression of HAT1 was correlated with that of HDAC1 in cases of DLBCL or NKTCL ($p<0.05$). The degree of the expression of HAT1 and HDAC1 was correlated with a poor survival in cases of DLBCL or PTCL-NOS ($p>0.05$). **Conclusions:** HAT1, HDAC1, and HDAC2 play a critical role in the development of malignant lymphomas. Both HAT1 and HDAC1 might be indicators for a poor prognosis in cases of DLBCL as cooperating factors.

Key Words: Acetylation; Deacetylation; Histone deacetylase inhibitors; Lymphoma

Histone proteins bind to the DNA backbone to package the DNA into chromatin. Normal histone tails are positively charged because of amine groups that are present on their lysine and arginine residues, and bind to the DNA backbone with phosphate groups that were negatively charged. Histone-related proteins (histone acetyltransferases [HATs] and histone deacetylases [HDACs]) can influence the DNA transcription through the balance between the histone acetylation and deacetylation. Histone acetylation induces loose chromatin by HATs that cause the lysine residue to lose the positive charge. This process is related to the promotion of the DNA transcription. By contrast, histone deacetylation induces condensed chromatin by HDACs that play a role in recovering the positive charge, which is associated with the gene repression.

To date, it has been known that mutations, overexpression and improper recruitment of HATs and HDACs develop malignant tumors. Mutations in HATs could lead to increase of histone acetylation.[1] Histone acetylation may play an important role in the pathogenesis of lymphoma with the up-regulation of the recombination of the T-cell receptor gene segments.[2] But histone hypoacetylation is also involved in the development of tumors through mutations, chromosomal translocations, or the increased activity of HDACs.[3] Furthermore, the decrease in histone acetylation is also involved in tumor invasion and metastasis.[4]

HDACs normally function together with cofactors that recruit HDACs to target genes.[5] Their activity is associated with the development of several cancers in human, where more than

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one mechanism is involved. The transcriptional repression of tumor suppressor-genes by the overexpression and improper recruitment of HDACs to their promoter region could be a common phenomenon in the development and progression of tumors.[3] For example, chromosomal translocation is associated with the production of fusion proteins that recruit the HDAC repressor complex with a high affinity to a specific promoter. After that, these multi-protein complexes are involved in the development of the hematological malignancy by the repression of genes that regulate normal differentiation and proliferation of hematopoietic cells.[6-8] The aberrant recruitment of HDACs to the E-cadherin promoter may also have an important role in the invasion and metastasis of tumor.[9,10] HDAC inhibitors are currently intriguing many researchers who are trying to discover better anticancer agents. Suberoylanilide hydroxamic acid (vorinostat) has been approved by the US Food and Drug Administration (US FDA) for its indication in treating cutaneous T-cell lymphoma (CTCL).

To date, however, few studies have examined the expressions of HATs and HDACs in association with malignant lymphoma. Given the above background, we studied the expression of HAT1 and class 1 HDACs including HDAC1, HDAC2, and HDAC3 in reactive lymphoid hyperplasia (RLH), diffuse large B-cell lymphomas (DLBCL), peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS) and extranodal NK/T-cell lymphomas, nasal type (NKTCL) to identify the correlation between the histone acetylation/deacetylation and clinical behavior of the tumor.

MATERIALS AND METHODS

Materials

This study was approved by the Institutional Ethics Committee of our medical institution. We selected nine cases of RLH, 78 cases of DLBCL, 13 cases of PTCL-NOS, and 13 cases of NKTCL based on the criteria that the paraffin blocks were well preserved with a sufficient amount of tissue for evaluation. The clinical data, pathology reports and pathology slides were reviewed. In addition, 3-mm tissue microarrays were made.

Immunohistochemical (IHC) stains

IHC reactions were performed on paraffin tissue sections using an automated IHC stainer (Ventana BenchMark XT, Ventana Medical Systems Inc., Tucson, AZ, USA) according to the manufacturer's protocol. Detection was done using the Ventana i VEIW DAB detection kit (Ventana Medical Systems Inc.). Briefly, IHC staining was performed as follows: 4-μm-tissue sections were deparaffinized using EZ Prep solution. CC1 standard (pH 8.4 buffer containing Tris/Borate/ethylenediaminetetraacetic acid) was used for antigen retrieval at 99°C for 60 minutes. i VIEW inhibitor (3% H_2O_2, endogenous peroxidase) was blocked at 37°C for four minutes. Slides were incubated with primary antibodies (Table 1) at 42°C for 32 minutes and secondary antibody to i VIEW biotinylated Ig at 37°C for 8 minutes. Slides were incubated in i VIEW streptavidin HRP at 37°C for 8 minutes and then DAB + H_2O_2 substrate for 8 minutes, which was followed by counterstaining with hematoxylin and bluing reagent at 37°C. Reaction buffer (pH 7.6 Tris buffer) was used as a washing solution.

Interpretation of IHCs

Antibodies to HAT1, HDAC1, HDAC2, HDAC3, and Ki-67 stained the nuclei. The IHCs associated with histone-related proteins (HAT1, HDAC1, HDAC2, and HDAC3) were interpreted based on the intensity: 0, 1+, 2+, and 3+, where 0 is negative, but Ki-67 based on the proportion (< 26%, 26-50%, 51-75%, and > 75%). In HAT1 and HDAC1 with an intensity of 1+, the intensity of nearby endothelial cells was served as the control one. In HAT1 and HDAC1 with an intensity of 3+, however, the intensity of germinal center cells was served as the control one. Besides, in HDAC2 and HDAC3 with an intensity of 1+, the intensity of endothelial cells was served as the control one. In HDAC2 and HDAC3 with an intensity of 3+, however, the intensity of nearby histiocytes was served as the control one. Furthermore, 2+ was considered the moderate intensity between 1+ and 3+ (Figs. 1, 2). Finally, the intensity and proportion of histone-related proteins were compared using a Kaplan-Meier survival and a Spearman correlation coefficient.

Table 1. Antibodies used for this study

Antibodies	Dilution ratio	Companies	City, State, Nation
IHCs			
HAT1 polyclonal	1 : 200	Proteintech	Chicago, IL, USA
HDAC1 monoclonal	1 : 4,000	Abnova	Taipei, Taiwan
HDAC2 polyclonal	1 : 2,000	Abnova	Taipei, Taiwan
HDAC3 polyclonal	1 : 200	Abnova	Taipei, Taiwan
Ki-67 monoclonal	1 : 500	Lab vision	Fremont, CA, USA
Western blot			
HAT1 polyclonal	1 : 5,000	Proteintech	Chicago, IL, USA
HDAC1 monoclonal	1 : 5,000	Abnova	Taipei, Taiwan
β-actin monoclonal	1 : 10,000	Sigma-Aldrich	St. Louis, MO, USA

IHCs, immunohistochemical staining; HAT1, histone acetyltransferase 1; HDAC, histone deacetylase.

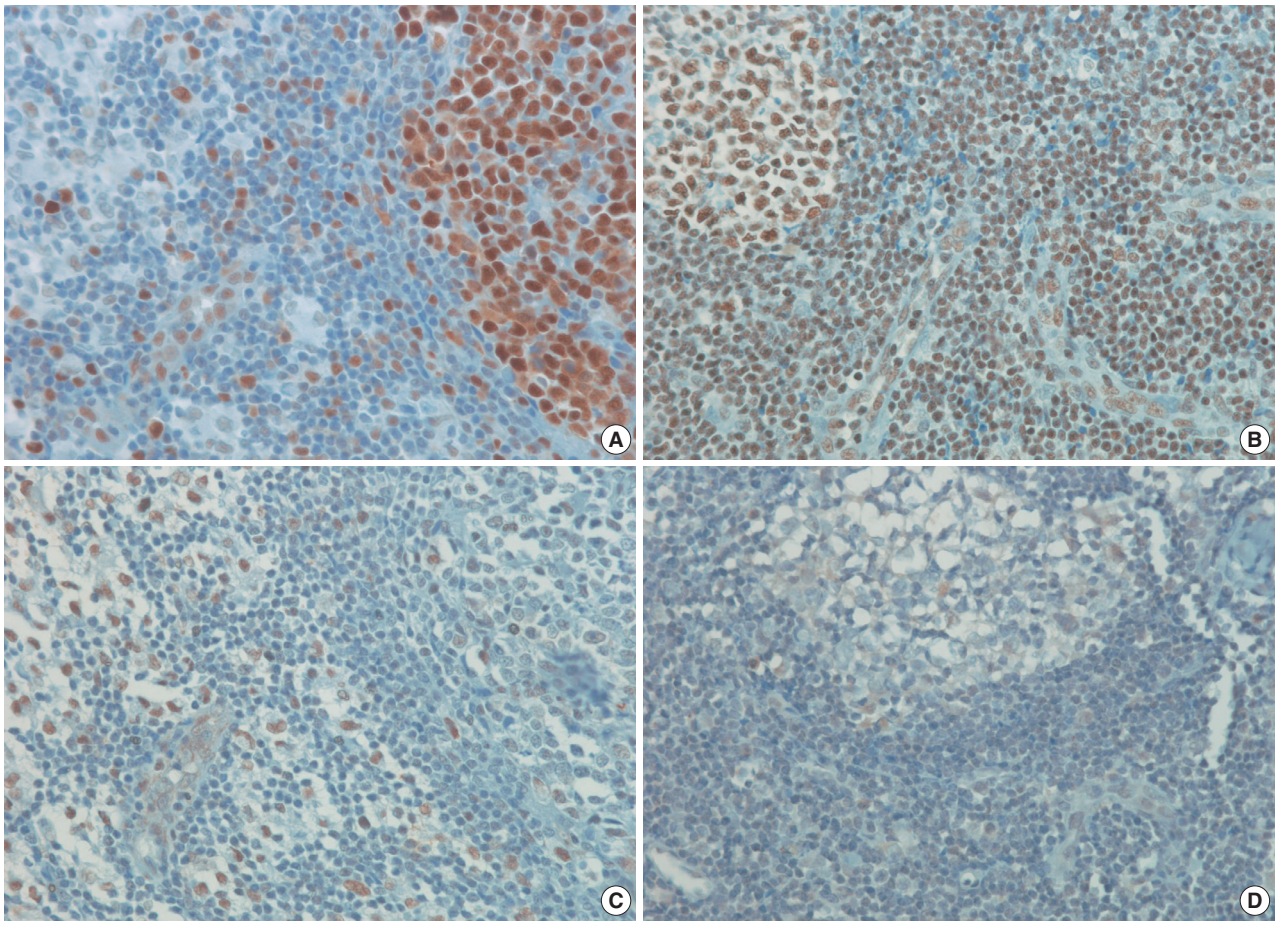

Fig. 1. Immunohistochemical (IHC) stains for histone acetyltransferase 1 (A) and histone deacetylase (HDAC) 1 (B) show strong positive cells in the reactive germinal centers and are weak positive on the endothelial cells. IHC stains for HDAC2 (C) and HDAC3 (D) show more strong positive reaction for the histiocytes than for the endothelial cells.

Western blot

Western blot analysis was available only for three cases of RLH, four cases of DLBCL and three cases of PTCL-NOS. Protein extraction was performed with the modified methods of Azimzadeh *et al*.[11] Briefly, western blot analysis was performed as follows: paraffin sections were prepared from the samples of RLH and malignant lymphomas by the microdissection. This was followed by processing for western blot analysis. Then, the paraffin sections were subjected to deparaffinization after incubated twice with xylene at room temperature for ten minutes. Following the dehydration in a graded series of ethanol (100%, 90%, and 70% EtOH) for ten min each, the sections were washed with a 0.5% octylglucoside (Sigma-Aldrich, St. Louis, MO, USA). The deparaffinized sections were resuspended in an extraction buffer (20 mM Tris-HCl, pH 8.8, 2% sodium dodecyl sulfate [SDS], 1% octylglucoside, 200 mM dithiothreitol, 200 mM glycine; Sigma-Aldrich) and then sonicated three times at 24℃ for 30 seconds in Brasonic 8510R-DTH sonicator (Brason, Danbury, CT, USA). This was followed by a 10-minute boiling at 100℃ and a centrifugation at 15,000 ×g at 4℃ for 10 minutes. Then the protein in the supernatant was separated by the SDS-polyacrylamide gel electrophoresis and then transferred onto a Hybond-N nitrocellulose membrane (GE Healthcare, Pittsburgh, PA, USA). Monoclonal anti-actin antibodies were served as loading controls. In addition, rabbit polyclonal anti-HAT1 antibodies and monoclonal anti-HDAC1 ones were used to detect HAT1 and HDAC1 (Table 1).

Interpretation of western blot

The intensity of anti-actin band and anti-HAT1/HDAC1 one was semi-automatically measured using the "wander tools" and "histogram" functions in the Adobe Photoshop (Adobe, San Jose, CA, USA) as previously described by Park *et al*.[12] Then, the intensity was compared using one-way analysis of

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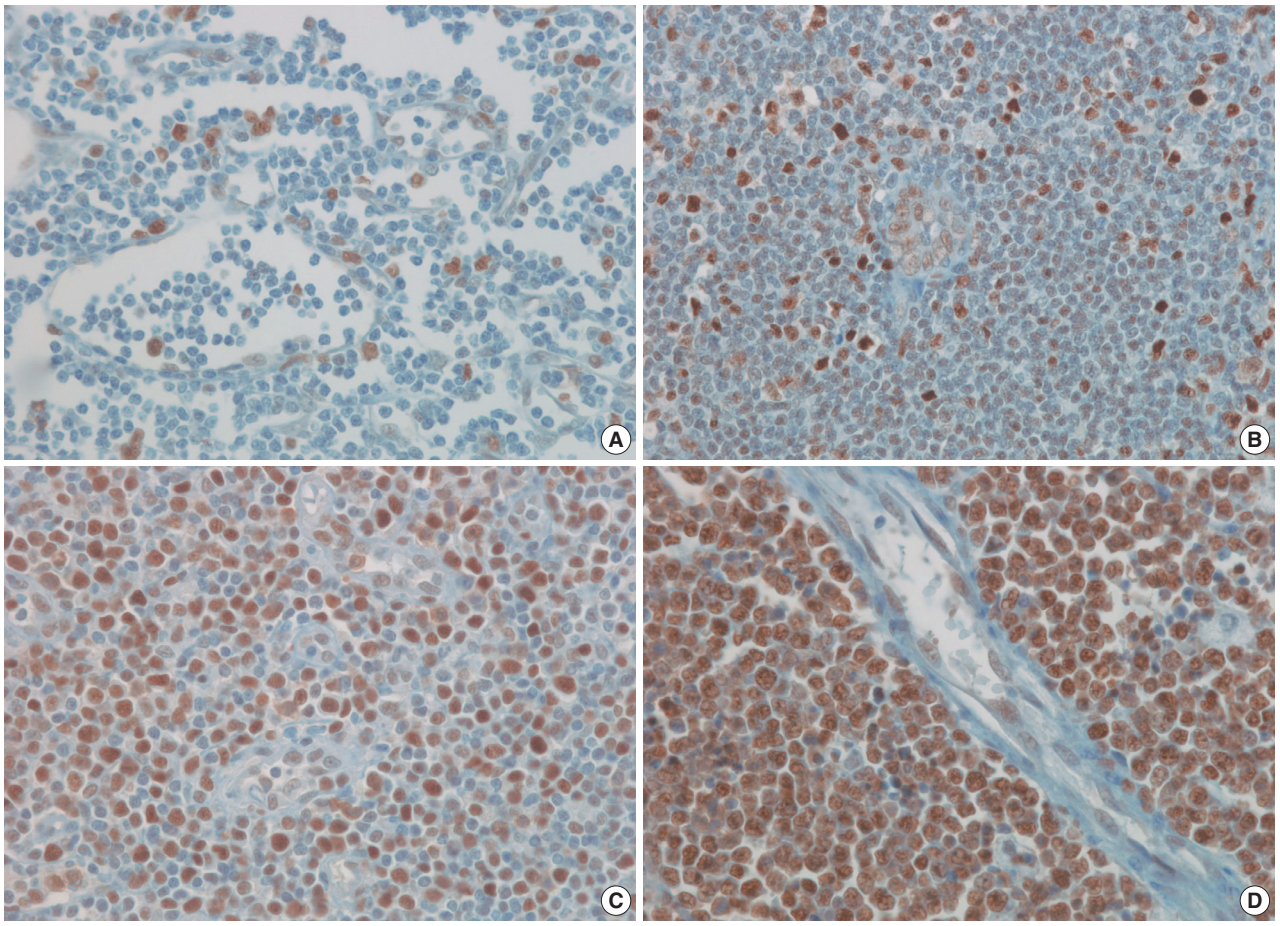

Fig. 2. Immunohistochemical (IHC) stain for histone deacetylase 1 (HDAC1) is negative (A). Immunohistochemistry for HDAC1 shows the same intensity (1+) on the lymphoma cells and the endothelial cells (B). IHC stains for HDAC1 are 2+ (C) and 3+ (D) on the lymphoma cells that are stronger than on the nearby endothelial cells.

variance (ANOVA) with the Duncan's test in the SAS program (SAS Institute, Cary, NC, USA).

RESULTS

The mean age of patients was 61 years old in 78 cases of DLBCL, 50 years old in 13 cases of PTCL-NOS and 58 years old in 13 cases of NKTCL. No male predilection or female one was observed in our series of clinical cases. The mean follow-up periods were 31, 18, and 15.8 months in cases of DLBCL, PTCL-NOS, and NKTCL, respectively (range, 1 to 162 months). Of the three types of lymphoma, the PTCL-NOS showed the poorest prognosis based on the death rate (Table 2).

Table 2. Summary of data of clinical cases of malignant lymphoma

	DLBCL (n=78)	PTCL-NOS (n=13)	NKTCL (n=13)
Age (yr)[a]	61 (15-96)	50 (25-81)	58 (32-92)
Sex (M : F)	41 : 37	8 : 5	7 : 6
Follow-up (mo)[a]	31 (1-162)	18 (2-64)	15.8 (3-68)
Death (mo)[a]	19.6 (1-71, n=34)	10.3 (2-64, n=11)	7 (3-15, n=7)
Death rate (%)	43.6	84.6	53.8

DLBCL, diffuse large B-cell lymphomas; PTCL-NOS, peripheral T-cell lymphomas, not otherwise specified; NKTCL, NK/T-cell lymphomas, nasal type; M, male; F, female.
[a]Values are presented as mean (range).

IHC studies

The frequency of Ki-67 staining was the highest in the area of >26% and <50% and the lowest in that of >75% in all the three types of lymphoma. In cases of RLH, the intensity was mostly 2+ for HAT1, HDAC1 and HDAC2 but 0 and 1+ for HDAC3. Besides, in cases of DLBCL, PTCL-NOS, and NKTCL, it was mostly 3+ for HAT1, HDAC1, and HDAC2 but 0 and 1+ for HDAC3. The degree of the expression of HAT1 was significantly higher in cases of DLBCL, PTCL-NOS or NKTCL compared with RLH ($p<0.05$). The degree of the expression of

HDAC1 was significantly higher in cases of DLBCL as compared with RLH ($p < 0.05$). Besides, the degree of the expression of HDAC2 was significantly higher in cases of PTCL-NOS and NKTCL as compared with RLH ($p < 0.05$) (Fig. 3). The proliferation index (Ki-67) was significantly correlated with the degree of the expression of HAT1 and HDAC1 in cases of DLBCL and that of HDAC2 in cases of NKTCL ($p < 0.05$). In addition, it was also significantly correlated with the degree of the expression of HAT1 and that of HDAC1 in cases of DLBCL and NKTCL ($p < 0.05$). Furthermore, there were significant correlations between the degree of the expression of HDAC1 and that of HDAC2 in cases of PTCL-NOS and between that of HDAC2 and that of HDAC3 in cases of DLBCL ($p < 0.05$) (Table 3).

Western blot analysis

We lost many cases while preparing for a western blot analysis of the formalin-fixed, paraffin-embedded tissue samples. Besides, we also had no sufficient number of remaining cases that are available for the current study. Despite a small number of remaining cases, however, we have obtained the significant results as shown below: the density of protein band was reduced because the western blot analysis showed very strong protein bands for HAT1. This indicates that the density of protein bands was negative for cases of RLH. But the weak density was

Table 3. Spearman correlation between the expressions of proteins

p-value	Ki-67	HAT1	HDAC1	HDAC2	HDAC3
Ki-67	1	0.0022[a]	0.0133[a]		
HAT1		1	0.0008[a]		
HDAC1		0.0124[b]	1		
HDAC2	0.0064[b]		0.0332[c]	1	0.0059[a]
HDAC3					1

HAT1, histone acetyltransferase 1; HDAC, histone deacetylase.
Blank, $p > 0.05$ in three types of lymphomas; [a]Diffuse large B-cell lymphomas; [b]NK/T-cell lymphomas, nasal type; [c]Peripheral T-cell lymphomas, not otherwise specified.

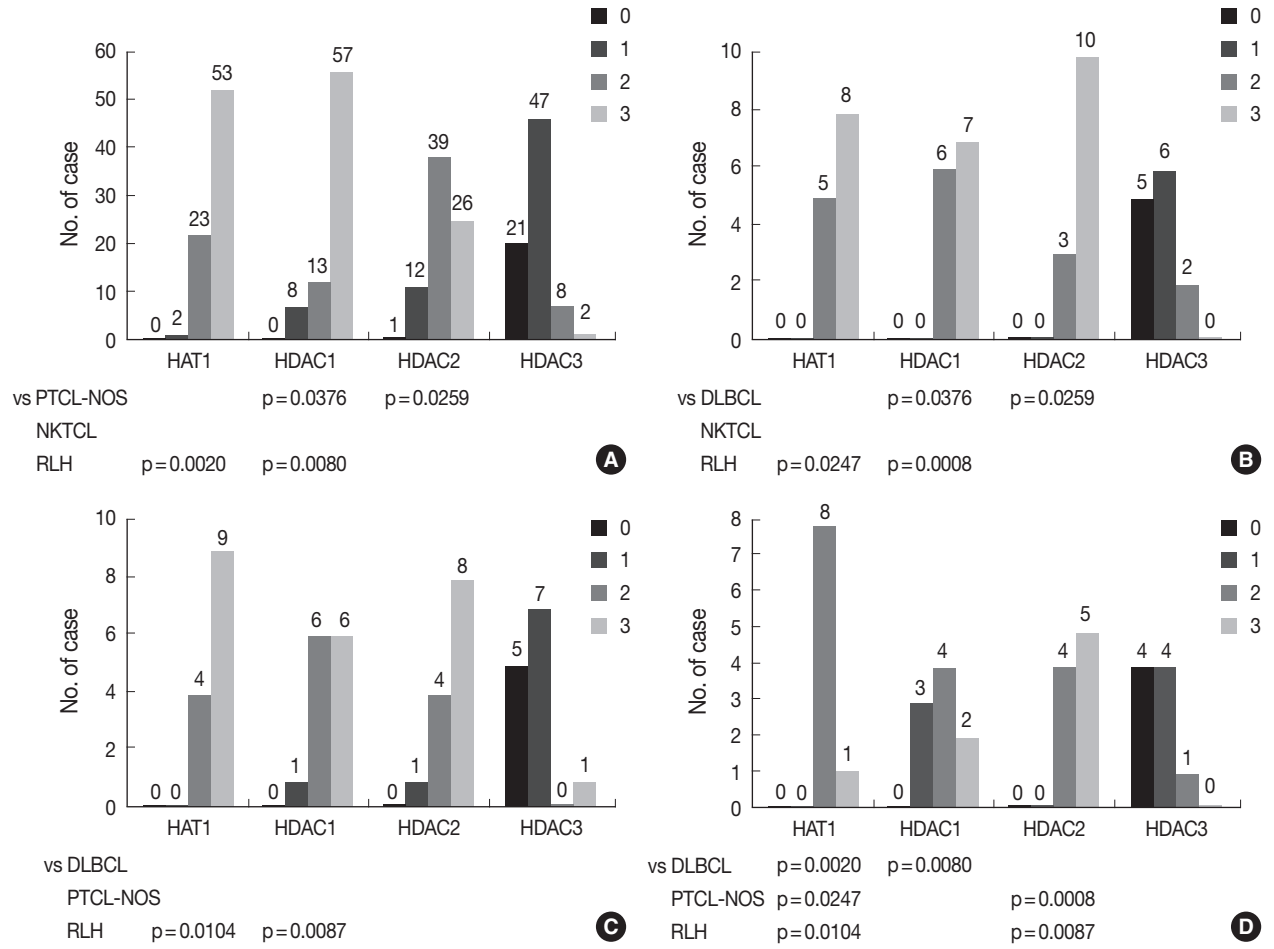

Fig. 3. The comparative histograms for malignant lymphomas including diffuse large B-cell lymphomas (DLBCL) (A), peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS) (B), and NK/T-cell lymphomas, nasal type (NKTCL) (C) and reactive lymphoid hyperplasia (RLH) (D). HAT1, histone acetyltransferase 1; HDAC, histone deacetylase. blank; $p > 0.05$.

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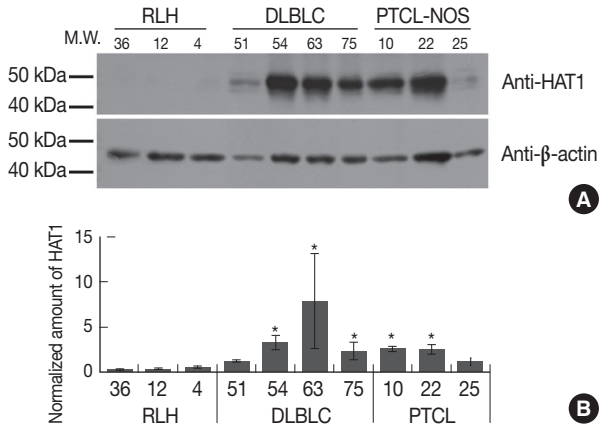

Fig. 4. A higher degree of expression of histone acetyltransferase 1 (HAT1) in cases of malignant lymphoma than those of reactive lymphoid hyperplasia (RLH). Following a comparison with the degree of the expression in cases of RLH, the degree of the expression of HAT1 is significantly higher in cases of diffuse large B-cell lymphomas (DLBLC) (3/4) or peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS) (2/3). Western blot analysis of HAT1 (A). Anti-actin antibodies are used as a loading control. The normal degree of the expression of HAT1 (B). Asterisks indicate $p < 0.05$. Statistical significance is analyzed using a t-test.

observed in case 4 as shown in Fig. 4A. The degree of the expression of HAT1 was significantly higher in cases of DLBCL (3/4) and those of PTCL-NOS (2/3) as compared with those of RLH ($p < 0.05$). In the remaining cases of DLBCL (1/4) or PTCL-NOS (1/3), however, the degree of the expression of HAT1 was higher as compared with those of RLH. But this difference did not reach a statistical significance (Fig. 4). In addition, there were no any significant results in case of HDAC1.

Survival rate

Following an analysis of the survival curve, the degree of the expression of HAT1 and HDAC1 was higher in association with a poorer survival in cases of DLBCL and those of PTCL-NOS. But this did not reach a statistical significance ($p > 0.05$). In addition, the degree of the expression of HDAC3 was also higher in association with a better survival in cases of NKTCL. But this also did not reach a statistical significance ($p > 0.05$) (Fig. 5).

DISCUSSION

It is well established not only that the carcinogenesis is commonly associated with the alteration of DNA sequences but also that epigenetic alterations are found in various types of cancers. Aberrant methylation of CpG islands in promoter regions causes the silencing of tumor suppressor genes in some cancers including malignant lymphoma.[13,14] The imbalance between acetylation and deacetylation of histone protein induces the development, invasion and metastasis of the tumor. Increased histone acetylation may lead to the development of malignant lymphoma.[2] Yasui *et al*.[4] maintained, however, that the decrease of histone acetylation is involved not only in the development of tumor, but also its invasion and metastasis. The histone hypoacetylation is induced by a decrease in the activity of HAT or an increase in that of HDAC. The altered expression of HDAC proteins has also been reported to occur in cases of tumor. These alterations include the increased expression of HDAC1 in cases of gastric,[15] prostate,[16] colon,[17,18] or breast cancer.[19] Besides, it has also been disclosed that the increased expression of HDAC2 was present in cases of cervical,[20] gastric,[21] and colorectal cancer.[20,22] A higher degree of the expression of HDAC3 was observed in cases of colon cancer.[23] According to studies about hematopoietic malignancies, the degree of the expression of such histone-related proteins as HDAC1, HDAC2, and HDAC6 was significantly higher in cases of DLBCL or PTCL than normal lymphoid tissue.[24] In addition, Marquard *et al*.[25] maintained that a high degree of the expression of HDAC2 is more commonly seen in cases of aggressive CTCL rather than indolent cases. These authors also noted that the degree of the expression of HDAC6 is associated with a favorable outcome.[25] Following the treatment with rituximab in cases of B-cell lymphoma, the degree of the expression of HDAC was associated with downregulation of CD20 expression. The expression of CD20 mRNA and protein was repressed by recruitment of a histone deacetylase protein complex to the CD20 gene promoter.[26] In addition, Agata *et al*.[2] reported that histone acetylation determines an accessibility to the recombination of T-cell receptor γ-chain genes that play a direct role in executing a developmental switch in cell fate determination.

Our results showed that the degree of the expression of HAT1 was significantly higher in cases of DLBCL, PTCL-NOS or NKTCL as compared with those of RLH ($p < 0.05$). This is closely associated with the role of histone acetylation in inducing the expression of loose chromatin and thereby promoting the transcription. Epigenetics may play a secondary role in the development of tumor. It can therefore be inferred that the effects of histone acetylation would depend on the target oncogenes. The hypoacetylation of oncogenes would lead to the decreased oncogenesis. But opposite results are expected in tumor suppressor genes. Our results showed no specific oncogenes that play a critical role in the malignant transformation. In the current study, however, histone acetylation plays a critical role in

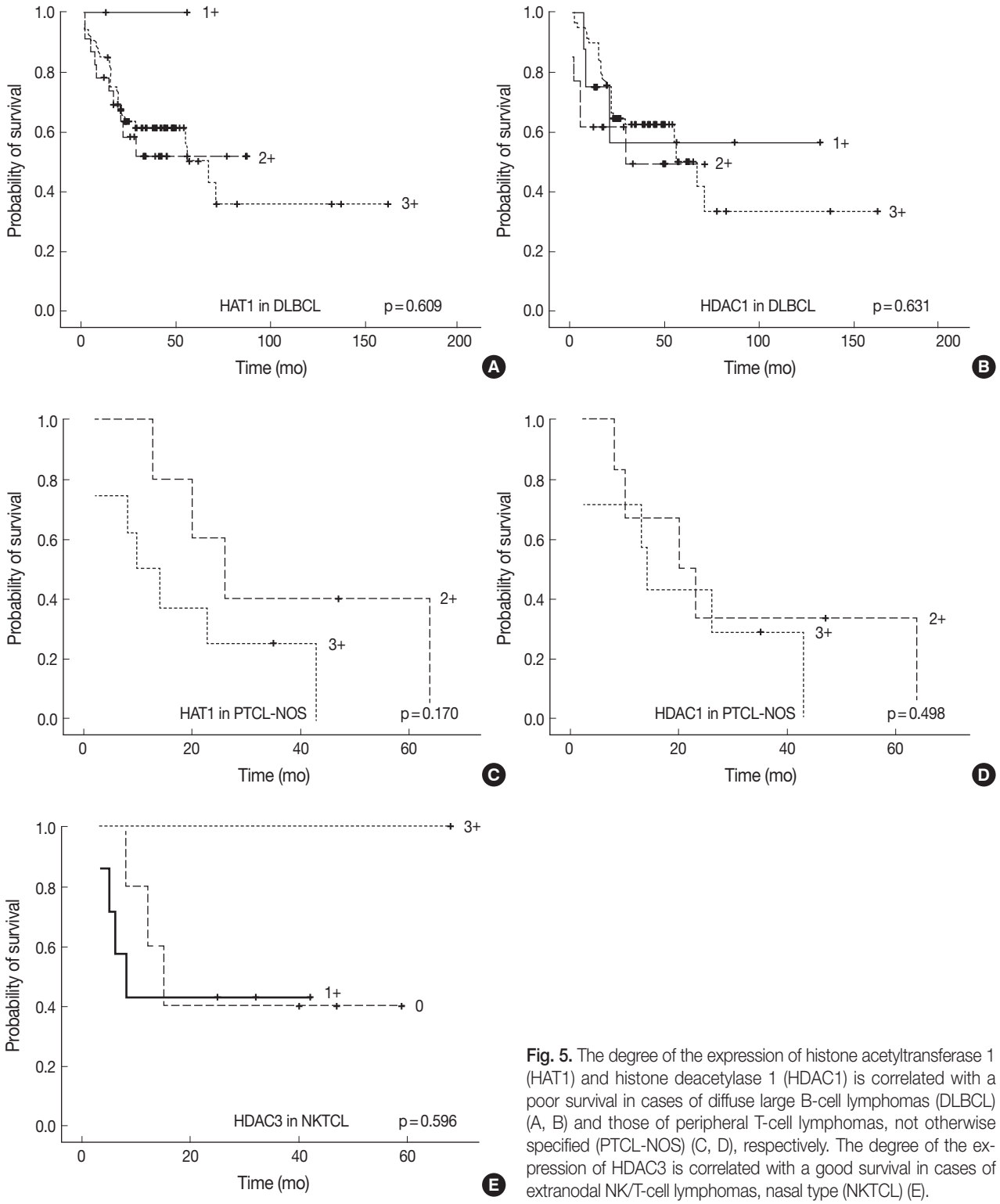

Fig. 5. The degree of the expression of histone acetyltransferase 1 (HAT1) and histone deacetylase 1 (HDAC1) is correlated with a poor survival in cases of diffuse large B-cell lymphomas (DLBCL) (A, B) and those of peripheral T-cell lymphomas, not otherwise specified (PTCL-NOS) (C, D), respectively. The degree of the expression of HDAC3 is correlated with a good survival in cases of extranodal NK/T-cell lymphomas, nasal type (NKTCL) (E).

the development of such cancers as DLBCL, PTCL-NOS, and NKTCL.

On the other hand, many studies have examined the effects of HDAC inhibitors. In addition, the indications of SAHA have been approved for the treatment of CTCL by the US FDA. It has been known that HDAC inhibitors are involved in cell

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cycle arrest, differentiation and apoptosis in tumor cells. Some authors argue that isotype-specific HDAC inhibitors may be a more effective and safe agent that causes less adverse effects. Nevertheless, isotype-specific HDAC inhibitors are not popular up to present.[27]

In the current study, the degree of the expression of HDAC1 was significantly higher in cases of DLBCL and those of HDAC2 in cases of PTCL-NOS and NKTCL as compared with RLH ($p < 0.05$). This is in agreement with previous reports.[24] Based on our results, it can be inferred that HDACs are involved in the expression of dense chromatin and this is associated with the repression of certain types of tumor suppressor genes, even though we did not disclose what these tumor suppressor genes are. HDAC1 plays a critical role in cases of DLBCL. But HDAC2 plays a critical role in cases of PTCL-NOS or NKTCL. This suggests that HDAC1- and HDAC2-specific inhibitors would be more effective for the treatment of DLBCL and that of PTCL-NOS and NKTCL, respectively.

On the other hand, we could not verify the relationship between the expression of HDAC1 and HDAC2 and the survival of patients. Our results showed, however, not only that the degree of the expression of HAT1 and HDAC1 was significantly higher in relation to a poorer survival in cases of DLBCL or PTCL-NOS but also that the degree of the expression of HDAC3 was significantly lower in relation to a poorer survival in cases of NKTCL ($p > 0.05$).

In addition, the expressions of HAT1 were correlated with HDAC1 in cases of DLBCL ($p < 0.05$). The proliferation index was significantly correlated with the degree of the expression of HAT1 and HDAC1 in cases of DLBCL ($p < 0.05$). These results indicate that HAT1 and HDAC1 have a synergistic effect in development of DLBCL, both of which are involved in its aggressiveness as cooperating factors.

Our results are also in agreement with the reports that both HATs and HDACs are involved in the development of cancer through a multi-step process together with several cooperating factors. In other words, HDACs act on specific genome regions by recruitment of DNA binding factors including transcription factors, nuclear receptors and epigenetic modifiers (methyl binding proteins, DNA methyltransferases, and histone methyltransferases). Considering these factors further specific studies are warranted to clarify the accurate mechanisms by which lymphoreticular malignancies occur. This will also be helpful for elucidating the effects of HDAC inhibitors against malignant lymphomas.

In summary, our results are as follows:

1) The degree of the expression of HAT1 was higher in cases of DLBCL, PTCL-NOS or NKTCL as compared with RLH.

2) Presumably, HAT1 might act on some types of oncogene and thereby contribute to the development of such cancers as DLBCL, PTCL-NOS, and NKTCL.

3) The degree of the expression of HDAC1 and HDAC2 was higher in cases of DLBCL, PTCL-NOS, and NKTCL as compared with RLH. Both HDAC1 and HDAC2 are involved in the repression of certain types of tumor suppressor genes.

In conclusion, both histone acetylation and deacetylation play a critical role in the development of such cancers as DLBCL, PTCL-NOS, and NKTCL. In addition, it can also be concluded that both HAT1 and HDAC1 might be indicators for a poor prognosis in cases of DLBCL, which is based on the following results:

1) HAT1 and HDAC1 have a synergistic effect in the development of DLBCL.

2) The proliferation index was correlated to the degree of the expression of HAT1 and HDAC1 in cases of DLBCL.

3) Following an analysis of the survival curve, the degree of the expression of HAT1 and HDAC1 was higher in association with the aggressiveness and a poor survival in cases of DLBCL. In addition, HDAC1- and HDAC2-specific inhibitors would be more effective for the treatment of DLBCL and that of PTCL-NOS and NKTCL, respectively.

Our results indicate not only that the degree of the expression of HAT1 and HDAC1 might have a prognostic value in predicting the clinical behavior of DLBCL but also that the specific use of HDAC inhibitors might lead to better treatment outcomes of the chemotherapy in cases of malignant lymphoma.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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