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Original Article

# Therapeutic Outcome of Epstein-Barr Virus Positive T/NK Cell Lymphoma in the Upper Aerodigestive Tract

**Jee Sook Hahn[1], Seung Tae Lee[1], Yoo Hong Min[1], Yun Woong Ko[1], Woo Ick Yang[2], and Gwi Eon Kim[3]**

*Departments of [1]Internal Medicine, [2]Pathology, [3]Radiation Oncology, Yonsei University College of Medicine, Seoul, Korea.*

Expression of the natural killer (NK) cell antigen CD56 is uncommon in malignant lymphoma, but when it is, it is almost exclusively of the non-B cell lineage and show a preference for the nasal and nasopharyngeal region. T/NK cell lymphoma is known to be aggressive and refractory to treatment. It is highly associated with the Epstein-Barr Virus (EBV), but clinical investigations are rarely reported, that is until recently. We report here, on the clinical features and therapeutic outcomes of patients with T/NK cell lymphomas and its association with EBV. We reviewed fifty-four cases with peripheral T cell lymphomas in the upper aerodigestive tract between Jan. 1987 and Aug. 1998 from the Severance Hospital, Yonsei University College of Medicine. The diagnosis of T/NK cell lymphoma was made according to the expression of the NK cell markers, CD56 antigen and cytoplasmic CD3 ε , in tumor specimens, by immunohistochemistry. Epstein-Barr early region (EBER) RNA was detected using in situ hybridization on paraffin-embedded sections. Among the 54 cases with malignant lymphomas occurring in the upper aerodigestive tract, 20 had T/NK cell lymphoma (37%). The primary sites of T/NK cell lymphomas were the nasal cavity, 12 cases (60%), the tonsils, 4 cases (20%), the nasopharynx, 2 cases (10%), and the oropharynx, 2 case (10%). There were no differences between the features, at diagnosis or therapeutic modalities for patients with T/NK cell lymphoma and non-T/NK cell lymphoma. The complete remission rate of T/NK cell lymphomas was lower than non-T/NK cell lymphomas (65% vs 85%, $p$=0.02). The overall survival of T/NK cell lymphomas was 13 months (1 - 74 month), which was significantly lower than non-T/NK cell lymphomas [60.6% with a median follow up of 22 months (1 - 101 month, $p$=0.02)]. Disease free survival of T/NK cell lymphomas was 22 months (4 - 66 month), significantly lower than non-T/NK cell lymphomas [73.8% with a median follow up of 22 months (2 - 95 month), $p$=0.04]. The overall survival rates for T/NK cell lymphomas were significantly lower than for EBV positive non-T/NK cell lymphomas ($p$=0.018). EBER RNA was detected in the paraffin-embedded tissue sections of all T/NK cell lymphomas, compared to only 17.6% (6 of 34 cases) for non-T/NK cell lymphomas. In conclusion, as patients with T/NK cell lymphomas showed poor clinical outcomes, and a high association with EBV positivity, clinical trials with more investigational therapeutic strategies, and further research into the relationship of EBV infection with pathogenesis of T/NK cell lymphoma is warranted.

**Key Words:** CD 56+, T/NK cell lymphoma, Epstein-Barr virus

## INTRODUCTION

Malignant lymphomas arising in the nasal cavity and paranasal sinuses are unusual. Many cases of nasal lymphomas have been described in Oriental populations,[1-4] whereas relatively few cases have been described in Western populations.[5-9] Nasal lymphomas include tumors clinically presented as lethal midline granuloma, often displaying histologic features of pleomorphic malignant tumors, which are variably associated with angiocentricity, angioinvasion, and necrosis. When these features are present, the term polymorphic reticulosis has been used, although the alternative terms, angiocentric immunoproliferative lesions and angiocentric lymphoproliferative disorders, have been proposed recently.[10] In recent years there has been much evidence showing most of these nasal lymphomas are related to malignant T-cell disorders, and the term nasal

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*Reprint address: requests to Dr. Jee Sook Hahn, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5418, Fax: 82-2-393-6884, E-mail: medi@yumc.yonsei.ac.kr*

T-cell lymphoma has been used to describe these lesion.[1,9] However, immunohistochemical studies have revealed that in more than half the cases examined, lymphoma cells expressed natural killer (NK) cell related markers, such as CD56 and CD16, but lacked mature T-cell antigens, such as CD34.[9,11] In addition, in some patients there were no rearrangements of T-cell receptor (TCR) genes. These findings suggest that some nasal lymphomas are derived from NK cells and not from T cells.[4,7,12]

Interestingly, T/NK cell lymphomas show a predilection for the nasal cavity and upper aerodigestive tract, although skin and soft tissue infiltration have also been observed.[13]

T/NK cell lymphomas are known to be aggressive and refractory to treatment. It is highly associated with EBV, but reports on clinical investigations have been rare, until recently. We report here, the clinical features, and therapeutic outcomes, of the patients with T/NK cell lymphomas and their association with EBV.

## MATERIALS AND METHODS

### Patients and methods

Fifty-four cases with peripheral T-cell lymphoma of the upper aerodigestive tract, between January 1987 and August 1998 at the Severance Hospital, Yonsei University College of Medicine, were reviewed. Immunohistochemistry, on paraffin sections, were applied with the following markers: UCHL1 (Dako, Carpenteria, CA, USA), CD3 ε (Dako), CD56 (NKH-1; Zymed Laboratories Inc., San Francisco, CA, USA) for the diagnosis of T/NK cell lymphomas. To detect EBV within the tumor cells we studied the EBV early region RNAs (EBER) (NCL-EBV; Novocastra Laboratories Ltd., Newcastle, UK) in the paraffin embedded sections, by in situ hybridization. The Ann Arbor staging system was used. Staging procedures included physical examination, blood chemistry, bilateral marrow aspiration and biopsy, chest X-ray, computerized tomography of the neck, chest, abdomino-pelvis, whole body bone scans and Gallium scans.

### Treatment

Radiotherapy only, and combination chemotherapy, with or without radiotherapy, was used according to the clinical stage of the patients. Briefly, some cases with non-bulky stage I disease received only radiotherapy, according to the physician's judgment, the rest received chemotherapy only, or combined chemoradiotherapy. Combination chemotherapy consisted of a minimum of six courses of adriamycin-containinig regimen. The dose of radiotherapy was 40-45 Gy, using a lateral opposing field, covering the nasal region, paranasal cavities, nasopharynx, and the Waldeyer's ring.

### Assessment and statistical analysis

To investigate the treatment response, restaging work-up was performed after 3 and 6 courses of chemotherapy. Complete remission was defined as complete disappearance of all clinical and radiological evidence of the disease. Partial response was defined as a $> 50\%$ response in measurable disease, and no response was defined as a $< 50\%$ response in measurable disease or disease progression. Disease-free survival was measured from the date of first complete remission to the date of first relapse. The overall survival time was measured from the date of diagnosis to the date of death, or last follow-up. Differences between groups were determined by the Mann-Whitney U test. Distribution between categorical variables was examined by (2 tests. Kaplan-Meier plots were used to generate disease-ree survival and overall survival curves, which were compared for statistical difference with log-rank analyses. Statistical analysis was performed using the SPSS software (SPSS, Chicago, IL, USA). A statistical difference was defined as a $p$ value $< 0.05$.

## RESULTS

### Patients characteristics

Of the fifty-four cases of peripheral T-cell lymphoma occurring in upper aerodigestive tract,

20 were T/NK cell lymphoma (37%). The immunophenotypic features of the 34 cases with non-T/NK cell lymphomas were as follows: 70.6% (n=24) had B cell phenotype, 20.6% (n=7) had T cell and 8.8% (n=3) had null cell. The comparative characteristics of patients with T/NK cell lymphoma and non-T/NK cell lymphoma are shown in Table 1. The primary sites for patients with T/NK cell lymphomas were, nasal cavity 60% (n=12), tonsil 20% (n=4), nasopharynx 10% (n=2) and oropharynx 10% (n=2). For the non-T/ NK cell lymphomas, the sites were, nasal cavity 64.7% (n=22), tonsil 23.5%(n=8), nasopharynx 5.9% (n=2) and paranasal sinus 5.9% (n=2). All the presented clinical characteristics, such as age, sex, primary site, stage, performance status, and presence of B symptoms, were well balanced between the two groups.

### Therapeutic modality

There were no different therapeutic modalities between the two groups. 19 cases with the stage I disease received only radiotherapy (7 T/NK cell lymphomas and 12 non-T/NK cell lymphomas). The other 11 cases received both chemotherapy and radiotherapy. 14 cases received only chemotherapy (4 T/NK cell lymphomas and 10 non-T/NK cell lymphomas), and 21 cases received both chemotherapy and radiotherapy (9 T/NK cell lymphomas and 12 non-T/NK cell lymphomas) (see Table 2).

### Association with EBV

The presence of EBV was detected in the paraffin-embedded tissue sections of all the patients with T/NK cell lymphomas, compared to 6 out of the 34 cases (17.6%) with non-T/NK cell lymphomas (see Table 3).

### Treatment outcome

It was possible to evaluate all the patients for their response to therapy.The complete remission rates for T/NK cell lymphomas were lower than for non-T/NK cell lymphomas (65% vs 85%, $p$= 0.02, Table 2). The overall survival rates for T/NK cell lymphomas were 13 months (1-74 month), which was significantly lower than for the non-T/NK cell lymphomas [60.6% with a median follow up of 22 months (1-101 month), $p$=0.02] (Fig.

**Table 1.** Patients Characteristics

| | T/NK cell lymphoma (n=20) | Non T/NK cell lymphoma (n=34) | $p$ value |
|---|---|---|---|
| Age | 39 (20 - 73) | 50 (18 - 78) | NS |
| M/F | 11/9 | 21/13 | NS |
| Primary site | | | NS |
| Nasal cavity | 12 (60%) | 22 (64.7%) | |
| Tonsil | 4 (20%) | 8 (23.8%) | |
| Nasopharynx | 2 (10%) | 2 (5.9%) | |
| Oropharynx | 2 (10%) | - | |
| Paranasal sinus | - | 2 (5.9%) | |
| Stage | | | NS |
| I | 14 (70%) | 16 (47%) | |
| II | 4 (20%) | 11 (32.4%) | |
| III | 1 (5%) | 5 (14.7%) | |
| IV | 1 (5%) | 2 (5.9%) | |
| B symptom ( + ) | 7 (35%) | 10 (29.4%) | NS |
| ECOG $\geq$ 2 | 3 (15%) | 5 (14.7%) | NS |

CR, complete remission; PR, partial response; NR, no response.

**Table 2.** Treatment Modality and Outcome

| | T/NK cell lymphoma | Non T/NK cell lymphoma | *p* value |
|---|---|---|---|
| Treatment | | | NS |
| RTx alone | 7 (35%) | 12 (35.3%) | |
| CTx alone | 4 (20%) | 10 (29.4%) | |
| RTx + CTx | 9 (45%) | 12 (35.3%) | |
| Response Rate | | | |
| CR | 13/20 (65%) | 29/34 (85%) | 0.02 |
| PR | 2 (10%) | 3 (8.8%) | NS |
| NR | 5 (25%) | 2 (5.9%) | NS |

CR, complete remission; PR, partial response; NR, no response.

**Table. 3.** EBER RNA Positivity in T/NK- and Non T/NK Cell Lymphoma

| | T/NK cell lymphoma | Non T/NK cell lymphoma |
|---|---|---|
| EBER | 20/20 (100%) | 6/34 (17.6%) |

EBER, Epstein-Barr early region.

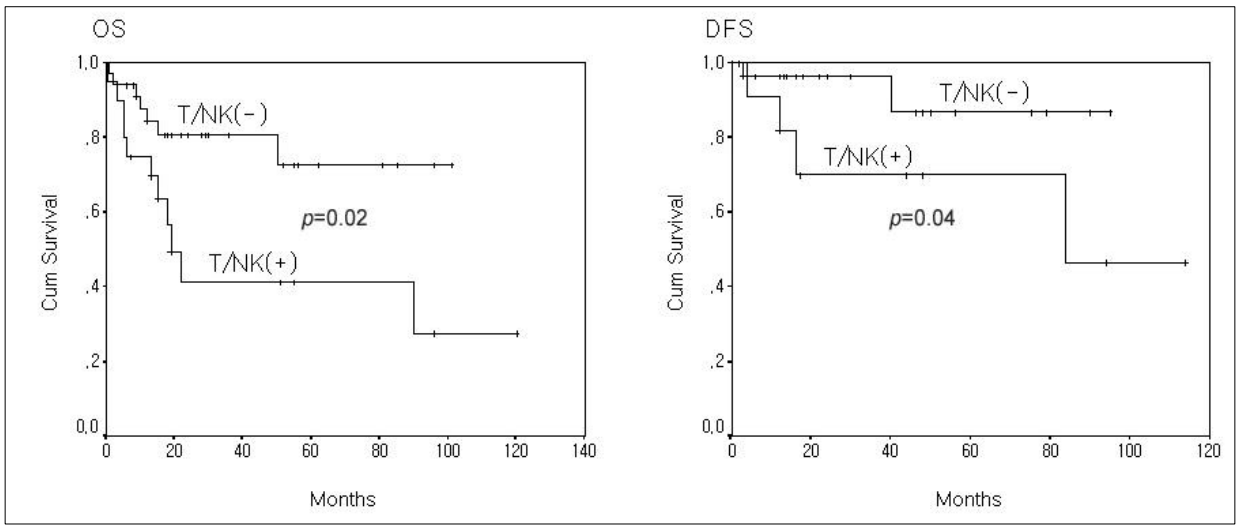


**Fig. 1.** Overall survival and Disease-free survival of T/NK (+) and T/NK (-) lymphoma.

1). Disease free survival for T/NK cell lymphomas was 22 months (4 - 66 month), which was also lower than for the non-T/NK cell lymphomas [73.8% with a median follow up of 22 months (2 - 95 month), $p$=0.04] (Fig. 1). We also compared survival rates between T/NK cell lymphomas and 2 subgroups with non-T/NK cell lymphomas, according to EBV positivity (Fig. 2). The overall survival rates for EBV positive, non-T/NK cell lymphomas were significantly higher than for T/NK cell lymphomas, even though it was only a small number of cases ($p$=0.018). Disease-free survival could not reach statistical significance. EBV negative, non-T/NK cell lymphomas, also showed trends toward better overall and disease-free survival rates, compared to those for T/NK cell lymphomas, although there was no statistical significance due to the small number of cases.

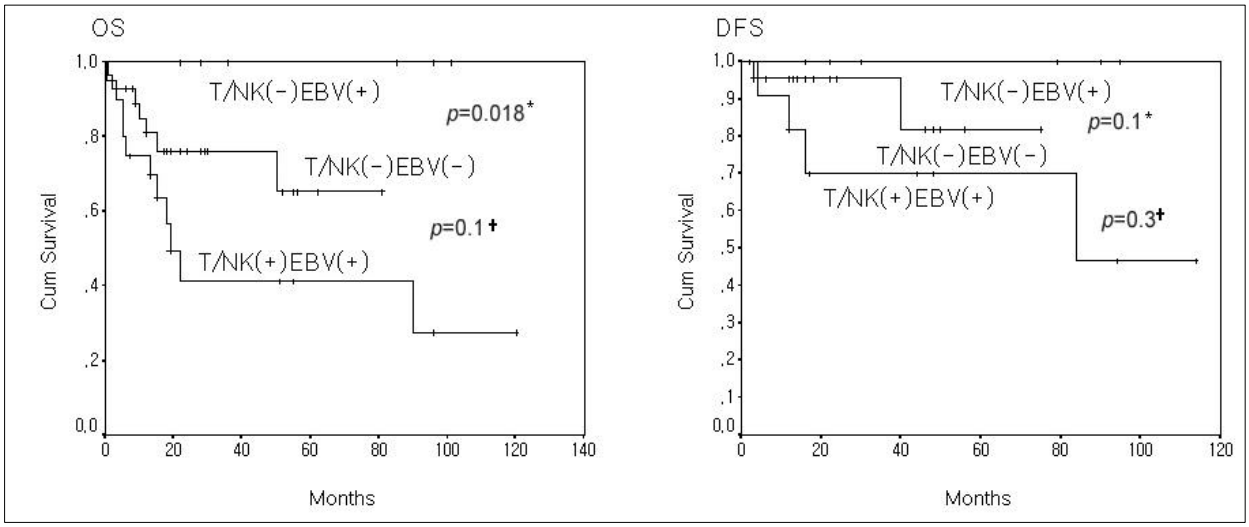


**Fig. 2.** Overall survival and Disease-free survival of T/NK(+)/EBV(+), T/NK(-)/EBV(+) and T/NK(-)/EBV(-) lymphoma. *T/NK(-)EBV(+) vs T/NK(+)EBV(+); T/NK(-)EBV(-) vs T/NK(+)EBV(+)

## DISCUSSION

Non-Hodgkin's lymphomas of the sinonasal tract are an uncommon group of neoplasms that account for 6 - 7% of all non-Hodgkin's lymphoma in Japan[14] and Hong Kong,[15] and 1.5% in the USA.[16] A relatively high incidence of nasal lymphomas has been observed in Orientals. Besides the differences in occurrence, other dissimilarities between Eastern and Western cases have been reported. These primarily include the finding of T-cell phenotype lymphomas in Asian countries[2,17] and B-cell lymphomas in Western countries.[6,18] Non-Hodgkin's lymphomas of the sinonasal tract, as reported in our previous study, were 5.5% of all non-Hodgkin's lymphomas in our hospital.[19]

Until recently, nasal T-cell lymphomas have been considered to be of true T-cell lineage. This is based primarily on the reactivity of antibodies, directed to T-cell antigens, to lymphoma cells. However, recent reports favored the NK cell lineage of nasal T-cell lymphomas. T cells and NK cells share various T cell-related antigens. For example, a universally distributed monoclonal antibody UCHL-1, which directs to CD45RO antigen in paraffin-embedded and fresh frozen tissues, was believed to react exclusively with T cells, but this antibody has recently been shown to react with activated NK cells also.[20] There have been many reports demonstrating germ-line configuration of TCR genes in nasal T-cell lymphomas;[7,12,21-25] most cases of nasal T-cell lymphomas in Orientals exhibit germ-line configuration of TCR genes. Taken together, many, but not all, T-cell lymphomas will be of NK-cell lineage.

NK cells are cytolytic cells, active against tumor cells, and cells infected with bacteria or viruses. NK cells are developed in the marrow from biopotential progenitors capable of differentiation into T and NK cells.[26] Phenotypically, NK cells appear as large lymphocytes with azurophilic granules, and immunophenotypically they express the characteristic marker CD56.[27] Functionally, they mediate major histocompatibility complex, (MHC)-unrestricted cytolytic, reactions that do not require expression of class I or II MHC molecules on the target cells.[28]

The diagnosis of T/NK cell lymphomas was based on morphology, surface phenotype and/or TCR genes of the germ-line configuration. Morphologically, NK cells are large granular lymphocytes. Phenotypically, they do not express surface CD3 or TCR antigens, although they commonly express CD16 and CD56 antigens. When all these criteria are fulfilled, the lymphomas are defined as T/NK cell lymphomas. We could describe our cases as T/NK cell lymphomas by positivity of their cytoplasmic CD3ε and CD56 immunohis-

tochemically.[29]

The initial sites for involvement in the T/NK cell lymphomas include; skin,[30-32] spleen,[30,32-33] liver,[32] lymph nodes,[30,32-33] jejunum,[32] rectum,[34] salivary glands,[32] and testis,[35] in addition to the sinonasal tract.[11,36] Ng et al[11] reviewed 149 cases of non-Hodgkin's lymphomas occurring in Chinese patients. There were 95 B-cell and 51 T-cell lymphomas. Seventeen T-cell lymphomas (33%) expressed CD56, CD57, and/or CD16. In comparison with the NK marker-negative T-cell lymphomas, the NK marker-positive lymphomas showed a predilection for the nasal and paranasal region. The predilection for the nasal cavity of CD56+ lymphomas was confirmed in a series of 11 cases from the USA.[36]

The association of EBV with nasal lymphomas has suggested a viral pathogenetic role.[26,27,37-39] The presence of the EBV receptor CD21 antigen on normally and abnormally expanded NK cells implies EBV gains entry into the NK cells via CD21 molecules, and transforms them.[29] To elucidate the pathogenetic role of EBV, the EBV infection of normal NK cells *in vitro*, and their transformation, must be examined. In this study, EBV was detected in all the patients with T/NK cell lymphomas, strongly suggesting a pathogenetic role for the virus. This is because infection must have been established at an early stage of lymphomagenesis prior to the clonal expansion of the infected cell.[29] The prognostic value of EBV positivity in lymphoma has not been known until recently, and this should be further elucidated. In this study, 6 cases with EBV positive non-T/NK cell lymphomas showed unexpectedly good survival rates. All 6 cases achieved CR, and they all maintained it, with a median follow-up duration of 60.5 months (range: 22 - 101 months) from the time of analysis. We could speculate, even though EBV was demonstrated in lymphoma cells in these cases of non-T/NK cell lymphoma, viruses did not contribute clonal expansion of the lymphoma cells. Further clinical studies of more cases with EBV positive non-NK cell lymphomas are warranted.

The occasional association of nasal lymphomas with hemophagocytic syndrome has been described.[7,40] It is well known that hemophagocytic syndrome is frequently observed in peripheral T-cell lymphomas[41,42] and angiocentric immunoproliferative lesions,[43] and represents a major cause of death. The true incidence of T/NK cell lymphomas in these conditions is not known, but patients with T/NK cell lymphomas may develop hemophagocytic syndrome This is because normal activated NK cells can produce macrophage activation cytokines, including; interferon-$\gamma$, macrophage colony-stimulation factor and granulocyte-macrophage colony stimulating factor, which in turn may activate the macrophages to induce hemophagocytosis.[44,45] The cytokines responsible for hemophagocytosis must be identified in T/NK cell lymphomas. However, we did not observe any cases of hemophagocytic syndrome.

Because of the rarity of the disease, there has been no general consensus on the optimal management of T/NK cell lymphomas. Patients with clinically localized disease usually receive only local radiotherapy or combination chemotherapy and radiotherapy. For the advanced disease, combination chemotherapy with, or without, additional radiotherapy is given.

According to Liang et al.[46] the treatment results for nasal lymphomas depends on the clinical stage of the disease. Appreciably higher complete remission rates were observed in patients in the early stages of the disease, and in those without B symptoms. Superior disease-free survival after complete remission was observed in patients in stages I and II of the disease. In Liang's report, T/NK cell lymphomas were not described, and were probably included with T-cell lymphoma, and, therefore, the treatment results for the T/NK cell lymphomas are unknown. Patients with nasal lymphomas, usually show local nasal symptoms, and the tumor is often clinically localized. However, the prognosis is generally poor, compared with their nodal counterparts.[47] Durable remission is only seen in around 50% of stage I patients, and the disease is invariably fatal if disseminated. Kim et al.[48] described a 50% local recurrence, and 25% systemic failure following radiotherapy alone, for patients with stage I and II angiocentric lymphomas, suggesting more systemic, multimodal, therapeutic strategies are required. For patients with the relapsed disease, the prognosis is also dismal, as almost all of them die from the progressive disease within 1 year from the time of

relapse. Liang et al.[47] recently reported on autologous stem cell rescue after high dose chemotherapy in 2 cases with T/NK cell lymphomas, reporting a good response after transplantation. According to Maeda et al.[3] favorable prognostic factors in nasal lymphomas include; ordinary lymphoma of an absent feature of midline malignant reticulosis, stage I disease, absence of ulceration in the lesions, and a tendency for local tumor formation. Compared to the nodal counterparts, patients with T/NK cell lymphomas seem to have a poorer prognosis, and their clinical course is not significantly altered by the use of chemotherapy instead local radiotherapy, or the use of doxorubicin-containing regimens. Normal NK cells express MDR 1-coded P-glycoprotein.[49] The lymphoma cells of patients with T/NK cell lymphomas also expressed P-glycoprotein. This may be why T/NK cell lymphomas are resistant to combination chemotherapy. In this study, complete remission rates for T/NK cell lymphomas were significantly lower than for non-T/NK cell lymphomas. Overall and disease-free survival rate also were clearly lower in T/NK cell lymphomas compared to those for non-T/NK cell lymphomas.

In conclusion, as the patients with T/NK cell lymphomas had poorer survival rates and high association with EBV, clinical trials with more aggressive therapeutic strategies and further investigation, of pathogenesis of T/NK cell lymphomas associated with EBV, may be warranted.

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