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Case Report

Nodal involvement by marginal zone B-cell lymphoma harboring t(14;22)(q32;q11) involving immunoglobulin heavy chain and light chain lambda as the sole karyotypically recognizable abnormality in a patient with systemic lupus erythematosus

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Abstract: Recurrent non-random balanced chromosomal translocation, usually involving the immunoglobulin heavy chain (IgH) gene or an immunoglobulin light chain gene and a proto-oncogene, which results in the overexpression of the latter under the control of an enhancer or promoter of the former, is a hallmark of many types of non-Hodgkin lymphoma (NHL) of B-cell origin. However, translocations between IgH and the immunoglobulin (Ig) light chain lambda gene (IgL), namely, a t(14;22)(q32;q11), have rarely been described in B-cell NHL. Herein we report the first case of marginal zone B-cell lymphoma harboring a t(14;22)(q32;q11) as its sole genetic abnormality in a patient with a 12-year history of systemic lupus erythematosus (SLE). Other interesting findings of this case include: 1) the neoplastic B-cells lack expression of both surface and cytoplasmic Ig light chain as revealed by flow cytometry and 2) monoclonal rearrangement of Ig light chain kappa (IgK) only due to k-deleting element (kde) recombination event. This case illustrates the necessity of utilizing a multi-modality approach in the diagnosis of B-cell NHL.

Keywords: t(14;22)(q32;q11), K-deleting element, marginal zone B-cell lymphoma, systemic lupus erythematosus

Introduction

Non-random recurrent balanced chromosomal translocations, usually involving between the immunoglobulin heavy chain (IgH) or light chain and proto-oncogene, which result in the overexpression of the latter under the control of an enhancer or promoter of the former, are a hallmark of many types of non-Hodgkin lymphoma (NHL) of B-cell origin [1]. The IgH locus located on chromosome 14q32 is the most commonly involved gene in B-cell NHL, such as seen in the t(14;18) in follicular lymphoma, the t(11;14) in mantle cell lymphoma, and the t(8;14) in Burkitt lymphoma.

The chromosome 22q11 locus contains at least two important genes pertinent to lymphoma/leukemia, one of which is the BCR gene, which is fused with the ABL1 gene on chromosome 9q34 in chronic myeloid leukemia (CML). Another is the immunoglobulin light chain lambda gene (IgL), which is seldomly involved in the translocations seen in B-cell NHLs.

Balanced and reciprocal translocation between 14q32 and 22q11 involving the IgH and IgL genes, respectively, has been previously reported in 7 cases of B-cell NHLs, including 4 cases of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), 1 case of hairy cell leukemia (HCL), 1 case of variant HCL(HCL-v), and 1 case of diffuse large B-cell lymphoma (DLBCL) [2-7]; however, to the best of our knowledge, such a translocation has not yet been reported in marginal zone B-cell lymphoma (MZBCL).
Various investigations have long shown that patients with autoimmune disorders such as systemic lupus erythematosus (SLE) are at greater risk for developing B-cell NHL, in particular DLBCL [8, 9]. While no MZBCL was identified among 6438 SLE patients spanning 31 years [8], others have shown that SLE patients have 2.8-7.5-fold increased risk of developing MZBCL [9].

Herein, we describe the first case of MZBCL with a t(14;22)(q32;q11) involving the IgH and IgL genes in a patient with a 12-year history of SLE. In addition, this case also possesses other unusual findings including a lack of both surface and cytoplasmic Ig light chain expression, and the presence of monoclonal Ig kappa (IgK) rearrangement due to k-deleting element (kde) recombination event without monoclonal rearrangement of IgH, IgL or recombination of variable (Vk) and joining (Jk) regions of IgK.

**Materials and methods**

**Clinical history**

The patient is a 41-year-old woman with a history of SLE, which was diagnosed in 2000. Her SLE has been managed with only hydroxychloroquine (Plaquenil) and intermittent pulses of prednisone but not since 2004, and she has never been treated with methotrexate. She has mild pulmonary hypertension managed with tadalafil (Adcirca) and immune thrombocytopenic purpura (ITP), status post splenectomy in 1988. She had a recent hospital admission with complications of renal failure and transaminits with Streptococcus bovis bacteremia in September 2011. At that time, a computed tomography (CT) showed external iliac and peri-aortic lymphadenopathy; however, the patient denied any B-symptoms such as weight loss, fever or night sweat. Her anti-double stranded...
DNA antibody was 180 I.U. (ref. interval: 0-24 I.U.), and anti-nuclear antibody was positive with a titer of > 1/640 (ref. interval: < 1/40), she also had an anti-cardiolipin antibody of 103 GPL (ref. interval: < 15 GPL negative; 15-20 GPL borderline; 21-80 GPL: low-medium positive; > 80 GPL high positive). In January 2012, she presented to the Head and Neck service with bilateral cervical lymphadenopathy, at which time an excisional lymph node biopsy from the right neck was performed, and a MZBCL was diagnosed. Six weeks later, an excisional biopsy of a left iliac lymph node was performed, and MZBCL was again diagnosed. The patient has been placed on a Rituximab only treatment regime since April 2012, and she shows improvement in hyper-metabolic adenopathy.

**Morphologic assessments**

After procuring fresh tissue for flow cytometric and conventional karyotypic studies, the remaining tissues were fixed in 10% PBS-buffered neutral formalin. After series dehydration, the tissue was embedded in paraffin and stained with hematoxylin and eosin (H&E) according to the standard protocol.

**Multi-color multi-parameter flow cytometry**

Four-color flow cytometric analysis of single cell suspension from the fresh lymph node tissue of both lymph nodes was carried out according to the previously published protocol. The following fluorochrome-conjugated monoclonal antibodies against CD3, CD4, CD5, CD8, CD19, CD20, CD23, CD38, CD79a, and FMC-7, polyclonal surface and cytoplasmic kappa, polyclonal surface and cytoplasmic lambda were used. The antibodies specific against CD3, CD4, CD5, CD8, CD19, CD20, CD23, CD38, CD79a, and FMC-7 were purchased from Becton Dickinson (San Jose, CA, USA). The polyclonal anti-kappa and anti-lambda antibody preparations used

Figure 2. (A, B) Among the CD3(+) small T-cells (A) are increased number of CD19(+) larger B-cells (B), most of which have relative abundant cytoplasm (A: CD3, original magnification 200x; B: CD19, original magnification 200x). (C) Ki-67 shows approximately 10% proliferation index (original magnification 200x). (D) Infrequent EBV(+) cells are appreciated by the in situ hybridization for EBER (original magnification 200x).
for surface expression evaluation were purchased from Dako (Dako Inc., Carpinteria, CA, USA), and the polyclonal anti-kappa and anti-lambda antibodies used for cytoplasmic expression studies were purchased from Beckman Coulter (Beckman Coulter Inc., Brea, CA, USA). The analysis of acquired data was conducted using Paint-A-Gate software (Becton Dickinson, San Jose, CA, USA).

**Immunohistochemistry and in situ hybridization**

Immunohistochemistry was performed on a Dako Autostainer using Envision (+) Detection Kit (Dako Inc.). The dilution of each antibody and its source are as follows: CD3 (1:50; Thermo Scientific, Waltham, MA, USA), CD19 (1:30; Epitomics Inc., Burlingame, CA, USA), CD20 (1:250; Dako), CD138 (1:60; abD Serotec, Taleigh, NC, USA), Ki-67 (1:120; Dako), IgA (1:30,000; Dako), IgG (1:1600; Thermo Scientific), IgM (1:5600; Dako), kappa (1:1600; Thermo Scientific), and lambda (1:16000; Dako).

In situ hybridization for Epstein-Barr virus (EBV)-encoded RNA (EBER) was performed by using the EBER1 DNP probe (Ventana Medical Systems, Inc., Tucson, AZ, USA) according to the manufacturer’s recommendations.

**Conventional karyotype and fluorescence in situ hybridization (FISH)**

Conventional karyotype by G-banding using fresh tissue was carried out according to a standard protocol, and 20 metaphase cells were examined. Interphase FISH using dual color break-apart probes specific for IgH at 14q32 and IgL at 22q11 (Abbott Molecular Inc., IL, USA), respectively, was performed according to the manufacturer’s instruction. Two hundred interphase nuclei were examined for each FISH probe.

Figure 3. (A-C) The majority of the lymphoma cells are positive for IgG (A) but negative for IgM (B) and IgA (C) (original magnification for (A-C) are 200x, 100x, and 100x, respectively). Please note, the IgM highlights the mantle zone B-cells (B). (D) Very rare CD138(+) plasma cells are noted (original magnification 200x).
Gene rearrangements studies for IgH, IgK, IgL, and T-cell receptor (TCR)

Genomic DNA was purified from formalin-fixed paraffin-embedded (FFPE) tissue sections using the QIAamp DNA Mini Kit (QIAGEN Inc, Valencia, CA, USA) according to the manufacturer’s protocol. Polymerase chain reaction (PCR) assays for IgH, IgK, IgL and TCR gamma (TCRγ) were performed using the IdentiClone IgH + IgK B Cell Clonality Assay, the IgL Gene Clonality Assay and the IdentiClone TCRγ Gene Rearrangement Assay (InVivoScribe Technologies Inc., San Diego, CA, USA). Please note two sets of master mix primers were used for IgK: one targeting the variable (V) and the joining (J) regions of IgK, the other targeting the V and the intragenic Jκ-Cκ regions of IgK (InVivoScribe Technologies Inc).

Results

Pathological findings

H&E sections from excisional biopsies of both cervical and iliac lymph nodes showed similar if
not identical morphologic features, namely both specimens showed an overall preserved nodal architecture but with expansion of the inter-follicular regions (Figure 1A) composed of predominantly small lymphocytes intermixed with increased number of small to medium sized atypical lymphoid cells with irregular nuclear contours, abundant pale to clear cytoplasm, and conspicuous nucleoli (Figure 1B, 1C). No expansion of marginal zone was noted. However, frequent secondary reactive germinal centers with different size and shape and containing frequent mitoses were easily appreciated (Figure 1D). No necrosis or granulomas were seen.

Immunohistochemistry showed that amongst the small inter-follicular CD3(+) T-cells (Figure 2A) are CD19(+) (Figure 2B), CD20(+) (not shown), and CD79a(+) (not shown) small to medium-sized B-cells, which are negative for BCL-1, CD5, CD10, and CD15 (not shown). The B-cells are generally larger than T-cells (Figure 2A, 2B). Ki-67 showed approximately 20% proliferation index (Figure 2C). Epstein-Barr virus (EBV) in situ hybridization (ISH) for EBV-encoded RNA (EBER) showed frequent positive larger cells (Figure 2D).

Further analysis of the immunoglobulin heavy chain expression showed that amongst the small inter-follicular CD3(+) T-cells (Figure 2A) are CD19(+) (Figure 2B), CD20(+) (not shown), and CD79a(+) (not shown) small to medium-sized B-cells, which are negative for BCL-1, CD5, CD10, and CD15 (not shown). The B-cells are generally larger than T-cells (Figure 2A, 2B). Ki-67 showed approximately 20% proliferation index (Figure 2C). Epstein-Barr virus (EBV) in situ hybridization (ISH) for EBV-encoded RNA (EBER) showed frequent positive larger cells (Figure 2D).

Based on the morphologic features and immunohistochemical profiles, a diagnosis of low-
grade mature B-cell lymphoma, best classified as MZBCL possibly arising in the background of SLE lymphadenitis, was rendered.

Flow cytometry

Flow cytometric analysis revealed approximately 9.9-12% larger B-cells (red population, Figure 4A) that are brighter positive for CD19 (Figure 4B), brighter positive for CD20 (Figure 4C and 4D), positive for FMC-7 (Figure 4E), but negative for both surface (Figure 4F) and cytoplasmic (Figure 4G) immunoglobulin light chains compared to smaller mature normal polytypic B-cells (blue population, Figure 4A-G). In addition, these cells were negative for CD10 (data not shown). Small normal mature T-cells (green population, Figure 4A-C, 4E and 4H) showed normal CD4:CD8 ratio (Figure 4H).

Conventional karyotype and FISH

Conventional G-banding karyotype of the lymph nodes revealed 13 out of 20 analyzed cells with balanced and reciprocal translocations between 14q32 and 22q11.2. The karyotype is as follows: 46,XX,t(14;22)(q32;q11.2)[13]/46,XX- [7] (Figure 5A). To further define the karyotype and to investigate which genes are involved in this balanced translocation, interphase FISH analysis using dual color break-apart probes for the IgH locus at 14q32 and the IgL locus at 22q11.2, respectively, was performed. A signal separation pattern consistent with a translocation involving the IgH (Figure 5B) and IgL (Figure 5C) loci was observed in 22.5% (45/200) and 17% (34/200) of the cells examined, respectively. FISH using a dual color break-apart probe set for BCL-6 on chromosome 3 at band q27 showed no evidence of a BCL-6 rearrangement (not shown).

Since BCR, often translocated in CML, is also located at 22q11, analysis with a dual color dual fusion probe set for BCR/ABL was also performed. Of 200 interphase nuclei examined, 99.5% (199/200) showed a normal signal pattern (not shown) confirming the lack of perturbations of either the BCR or ABL1 locus and the absence of a BCR/ABL1 fusion.

IgH, IgK, IgL, TCRγ gene rearrangements

PCR analysis for a monoclonal IgH rearrangement was negative on both specimens (data not shown), despite presence of polyclonal amplification in the background indicative of good DNA quality.

Since the IgH showed a germline configuration, we decided to pursue IgK rearrangement. To
Marginal zone B-cell lymphoma with t(14;22) in SLE

Table 1. Summary of B-cell lymphoma with t(14;22)(q32;q11)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Karyotype</th>
<th>FISH</th>
<th>Authors/reference</th>
<th>[#]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>46,XX,t(14;22)(q24-32;q11)</td>
<td>ND</td>
<td>Nowell et al./[2]</td>
<td></td>
</tr>
<tr>
<td>HCL</td>
<td>46,XY,del(1)(q32.1q32.3)t(14;22)(q32;q11.2)</td>
<td>ND</td>
<td>Nishida et al./[3]</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>46,XX,t(14;22)(q32;q11)</td>
<td>ND</td>
<td>Nowell et al./[4]</td>
<td></td>
</tr>
<tr>
<td>HCL-v</td>
<td>46,XY;14;22(q32q11)([6]/46,XY,del(12)(p13)x2,t(14;22)(q32;q11)(2)/46,XY(2)</td>
<td>ND</td>
<td>Brit-Babapulle et al./[5]</td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>46,XX[16]/47.XX.+12[2]/47,ldem,t(14;22)(q32;11)[2]</td>
<td>ND</td>
<td>Gozzetti et al./[6]</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>52.XY,+y;der(3)(3;3)(p11;p21),del(3)(q21);+7,+9,der(9)(3;9)(p11;p21)</td>
<td>14q32-lgH-lgK</td>
<td>Aamot et al./[7]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21q(14;22)(q32;q11);del(15);t(1;15)(q21;p21)</td>
<td></td>
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</tbody>
</table>


our surprise, no monoclonal rearrangement of IgK (not shown) was observed for either lymph node with primer sets targeting the V (Vk) and J (Jk) regions of IgK; however, monoclonal rearrangement of the IgK deleting element (kde) (Figure 6) was demonstrated for both lymph nodes with primer sets targeting the V (Vk) and the intragenic Jk-Ck region. The size of the product from both specimens is identical, suggesting that lymphoma cells are derived from the same clone although sequencing is required for confirmation.

No monoclonal rearrangements of the IgL or the TCRγ genes were detected in either specimen (data not shown).

Discussion

This is an unique and interesting case from multiple aspects: first, this MZBCL occurs in an immunocompromised patient in a form of long-standing SLE and intermittent use of steroid; secondly, the neoplastic B-cells show an insidious inter-follicular growth pattern in a background of reactive follicular hyperplasia with features of SLE lymphadenitis; thirdly, there is no surface or cytoplasmic Ig light chain expression among the lymphoma cells by flow cytometry; fourthly, the translocation involves the IgH gene at 14q32 and the IgL gene at 22q11.2, and this is the first documented t(14;22) (q32;q11.2) observed in MZBCL; and finally, there is a monoclonal rearrangement of IgK involving the Vk and kde element rather than the most often observed Vk and Jk.

Translocation between the IgH gene at 14q32 and the IgL gene at 22q11 occurs rarely. To the best of our knowledge, based on published English literature, only seven cases of B-cell NHL with a t(14;22)(q32;q11) have ever been reported (Table 1); four cases of CLL/SLL [2, 4, 6, 7], one HCL [3], one variant HCL [5], and one DLBCL [7]. Thus this is the first case of MZBCL harboring a t(14;22), the forth case of B-cell NHL in which a t(14;22)(q32;q11) is the sole karyotypically recognizable genetic abnormality, and the eighth case of B-cell NHL harboring a t(14;22)(q32;q11). Please note, only 2 out of 7 previously reported cases with a t(14;22) (q32;q11) were confirmed by FISH analysis to involve the IgH and IgL genes [6].

Lymphomogenesis with an underlying t(14;22) (q32;q11.2) is not known. Unlike the majority of B-cell NHL, in which the translocation occurs between IgH or IgK/IgL and a proto-oncogene through which the resultant fusion protein promotes cell proliferation and/or inhibits apoptosis, the reciprocal translocation between 14q32 and 22q11.2 does not involve a proto-oncogene at all. Together with this case, there are total of 4 reported B-cell NHLs harboring the t(14;22)(q32;q11) as their sole karyotypically recognizable genetic abnormality. Therefore, the t(14;22)(q32;q11) is presumed to be responsible, at least in part, for the pathogenesis. Among the remaining 4 cases, there are other genetic alterations in addition to the t(14;22) and 22q11.2 does not involve a proto-oncogene at all. Together with this case, there are total of 4 reported B-cell NHLs harboring the t(14;22)(q32;q11) as their sole karyotypically recognizable genetic abnormality. Therefore, the t(14;22)(q32;q11) is presumed to be responsible, at least in part, for the pathogenesis. Among the remaining 4 cases, there are other genetic alterations in addition to the t(14;22)(q32;q11.2). For example, one case of CLL [6] that contained a t(14;22)(q32;q11) also had trisomy 12, which is often associated with a moderately aggressive disease process and resistance to chemotherapy, but it was reported that the patient had been in good health and untreated for seven years, indicating a possible positive influence of the t(14;22) on the disease progression as postulated by the authors. All of the reported cases of HCL, HCL-v, and DLBCL which harbored a t(14;22)(q32;q11) also displayed additional cytogenetic aberrancies [3, 5, 7]. Although there is no definitive evidence for a pathogenetic role of the t(14;22) in these
cases, the t(14;22) is nevertheless believed to be an essential aberration in these cases.

Several interesting and unexpected aspects of the case are noteworthy. First of all, flow cytometry for Ig light chains kappa and lambda revealed no surface or cytoplasmic light chain restriction amongst the neoplastic B-cells; secondly, there is only IgK rearrangement between Vk and kde elements with no IgH, IgK (Vk-Jk) and IgL monoclonal rearrangements by PCR. These findings, although seemingly unusual, are not inconsistent with each other or with the aforementioned diagnosis. While it is well known that mature B-cell lymphomas can rarely lack surface Ig light chain expression [10, 11], the lack of cytoplasmic Ig light chain expression in mature B-cell NHL has also been rarely well documented, especially in primary effusion lymphoma [12]. Due to loss of targeting sequences resulting from ongoing somatic hypermutation of immunoglobulin gene variable region segments, it is not surprising that IgH PCR can only detect approximately 82% of B-cell lymphomas [13]. Analysis of IgK and/or IgL in addition to IgH can increase the detection rate of monoclonality [13, 14], and the previously reported cases showed either kappa or lambda monoclonal rearrangement.

While no monoclonal rearrangements of IgH, IgK (Vk-Jk) or IgL were detected in the current case, there were detectable monoclonal Vk-Kde rearrangements. This could reflect the fact that kde rearrangements, unlike typical heavy or light chain variable-to-joining region rearrangements, are assumed to be free of somatic hypermutation and thus less likely to be undetectable by PCR [13]. Kde remained in its germline form on all successful IgK-producing alleles [15], and the kde rearrangement occurs in virtually all IgK-positive B-cell malignancies [13]. Thus, based on the monoclonally rearranged kde, one would assume the lymphoma cells will most likely have rearranged IgL. However, there was no IgL monoclonal rearrangement in our case, which suggested that either there is somatic hypermutation of the IgL that leads to undetectable by PCR or the lymphoma cells used aberrant or cryptic B-cell receptor signal pathways to proliferate. Based on the single peak of kde (Figure 6), a monoallelic monoclonal rearrangement of kde is most likely. In addition, although a translocation involving the IgH and IgL genes is confirmed by FISH analysis in our case, it is conceivable that this translocation, at the nucleotide level, results in a significant disruption of the DNA sequence of each gene. Such a disruption could be responsible for eliminating protein expression as well as detectability of rearrangement by PCR analysis.

In the case of HCL reported by Nishida et al, the neoplastic cells showed a chromosomal translocation between the IgH and IgL genes, and the neoplastic cells exhibited restricted surface IgK expression [3]. In their other case of DLBCL with a t(2;14) involving the IgH and IgK genes, the neoplastic cells showed restricted surface IgL expression [7]. Both of these cases revealed mismatches between the restricted expression Ig light chain and the gene involved in the translocation [3, 7]. However, in our case, no surface or cytoplasmic IgK or IgL light chain expression was identified by flow cytometry, despite the fact that the IgL gene was involved in the translocation.

Accumulated literature has shown that patients with autoimmune diseases including SLE are at an increased risk for developing B-cell NHL. While DLBCL was the predominant subtype of B-cell NHL from the Swedish national SLE cohort [8], SLE was found to have a 2.7-fold increased risk of developing MZBCL [9]. Our patient possessed significant risk factors for developing MZBCL: female and more than 10 years of disease [9]. The underlying mechanism for lymphomagenesis in SLE is multi-step and multi-factorial, which includes genetic and extrinsic factors such as overstimulation, defective apoptosis, and inflammation [16]. It has also been suggested that anti-phospholipid antibodies can be a risk factor for hematological malignancies [17], and our patient did indeed have an elevated anti-cardiolipin antibody level of 103 GPL. Infectious agents such as EBV can indirectly cause NHL [18]. Although our patient’s EBV test by PCR was negative, there were scattered EBV positive cells by ISH within the lymph node (Figure 2D). This would further put our patient at risk for development of lymphoma.

Another possible mechanism of lymphomagenesis in patients with autoimmune disorders stems from treatment in the form of immunosuppression [19]. Immune modulators may increase the risk of lymphoma by specific inhib-
itory actions on the immune system, which then allow expansion and proliferation of clonal B-cells. Whether immunosuppressive drugs are directly responsible is still up for debate. One population-based study found that use of NSAIDs, systemic corticosteroids, or other immunosuppressive agents was associated with an increased risk of NHL in patients with rheumatoid arthritis, but not in patients with SLE [19]. This is in agreement with Smedby et al in that corticosteroid/immunosuppressive drug use does not modify the risk of developing NHL [9]. It is of interest to mention that methotrexate is another important immunosuppressive agent that is associated with increased risk of developing lymphoproliferative disorders, which often show spontaneous remission after discontinuation [20].

Treatment for NHL in patients with autoimmune disease is similar to conventional therapy. Rituximab appears to be a popular agent in most cases. In fact, when administered with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), rituximab was shown to be effective not only the lymphoma but also the underlying rheumatologic disease [21]. However, the efficacy of rituximab in patients with SLE remains unclear.

In summary, the significance of a t(14;22) (q32;q11) involving IgH and IgL in lymphogenesis of B-cell NHL has yet to be fully elucidated, partly due to the low number of such cases and the lack of understanding as to how the juxtaposition of the two immunoglobulin genes might contribute to the pathogenesis. Additional cases with long term follow-up are required to determine the prognostic significance of t(14;22) either alone or in the presence of other genetic abnormalities.

Disclosure of conflict of interest

None.

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