Indications for bone marrow examination in autoimmune disorders with concurrent haematologic alterations

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Abstract

Objectives
The aim of this study was to evaluate the aetiology of “unexplained” cytopenias in patients with autoimmune disorders, as well as to identify parameters that should alert clinicians to the need for bone marrow examination.

Methods
During the study period (2005–2010), 110 consecutive patients with an underlying systemic autoimmune disease, excluding Sjogren’s syndrome, were referred for haematological consultation and bone marrow examination, due to cytopenias without evident cause including blood loss, haemolysis, nutritional deficiencies and haemoglobin disorders.

Results
Systemic lupus erythaematosus was the most frequent underlying condition (38/110, 34.5%), and anaemia (haemoglobin<12g/dl) the most common haematologic abnormality (81/110, 74%). Prior to evaluation, more than half of the patients received cytotoxic or immunosuppressive drugs, with methotrexate being the most commonly administrated agent (29/110, 26.4%). Evaluation was informative in 31 (28.2%) of the cases. Twenty-four (21.8%) cases of haematologic clonal disease were diagnosed; 11 myelodysplastic syndromes, 6 lymphoproliferative disorders, 6 plasma cell dyscrasias and one myeloproliferative neoplasm. Seven cases (6.4%) with bone marrow toxicity were also noted. Male gender, serum iron >90 μg/dl, mean corpuscular volume (MCV) >90fl, and serum monoclonal band were significant predictors of specific diagnosis including clonal haematologic disorder or bone marrow toxicity. All other correlations were insignificant.

Conclusion
Clonal haematologic disorders and toxicity are frequent findings in patients with autoimmunity referred for haematologic consultation, owing to otherwise unexplained cytopenias. Patients with high serum iron, high MCV and presence of serum monoclonal band should undergo bone marrow examination to exclude haematologic malignancy or bone marrow toxicity.

Key words
autoimmunity, cytopenias, myelodysplastic syndromes, lymphomas
Introduction
Physicians are acquainted with hematologic manifestations of systemic autoimmune diseases, insofar as these can be attributed to the disease itself or to a pre-existing disorder (1-6). However, hematologic alterations may occur as a result of an offending drug, or a coexistent hematologic malignancy. Bone marrow aspiration and biopsy may solve the puzzle, but can appear unjustified for disease-related cytopenias. On the other hand, the misconception of a myelodysplastic syndrome as “disease-related anaemia” is a straightforward misdiagnosis that could cause serious clinical, ethical and legal problems. Therefore, the clinical dilemma may become apparent, especially in cases where the cause of cytopenia is not obvious or, worse still, when more than one factor (disease, drug, clonal disease) is involved. In this retrospective single-centre study, we present our cumulative experience of patients with systemic autoimmune diseases that were referred to our department with the conundrum of one or more otherwise “unexplained” cytopenias.

Patients and methods
Patient eligibility and data accrual
This is a retrospective, single-centre cohort study from 2005 to 2010. The target population consisted of patients with systemic autoimmune diseases that were evaluated by the hematology section of our department for one or more hematologic abnormalities. Eligibility criteria for the study were: a) a pre-existing or synchronous diagnosis of a systemic autoimmune disorder (excluding Sjögren’s syndrome), b) the presence of one or more “unexplained” cytopenias – *i.e.* leukopenia (<4000/mm³), anaemia (Hb <12gr/dl), or thrombocytopenia (<100,000/mm³). The term “unexplained” denotes the absence of acute blood loss, active autoimmune haemolysis, haemoglobin disorders (thalassemia), iron, B12 and folic acid deficiency, thrombotic microangiopathy or anaemia of chronic disease; it further refers to the presence of deteriorating hematologic parameters between subsequent visits or the presence of hematologic abnormalities as predominant manifestations of disease. Patients diagnosed with Sjögren’s syndrome who were referred for hematologic evaluation were excluded from the cohort, since studies up to date have established the increased risk of lymphoma development in this setting (7, 8). Thereby the exclusion of Sjögren’s syndrome from the study cohort guarantees a non-biased result. Medical charts of eligible patients were retrieved and evaluated with regard to bone marrow aspiration and biopsy data (including iron stain, cytogenetics with or without immunophenotyping), demographics, prior treatments and serum hematologic indices, including serum iron, ferritin, vitamin B12, folic acid and MCV. Disease activity in the systemic lupus erythematosus (SLE) group was determined at entry using the European Consensus Lupus Activity Measurement (ECLAM) (9). On the other hand, patients with rheumatoid arthritis (RA) were evaluated using the Disease Activity Score (DAS) questionnaire (10). Disease duration (in years) was calculated by subtracting the date of entry from the date of diagnosis.

Definition of outcomes
The bone marrow data were classified as informative (diagnosis of underlying clonal disorder or toxicity) and non-informative (“reactive” or myelodysplastic-like or non-specific findings) (11-13). Clonal disorders were subdivided into myelodysplastic syndromes (MDS), plasma cell dyscrasias (PCD) and lymphoproliferative disorders (LPD) such as non-Hodgkin’s lymphomas (NHLs) and chronic lymphocytic leukemia (CLL). MDS diagnoses were made according to WHO classification (14). According to the proposal of the International Working Group on Morphology of MDS (IWGM-MDS) and in accordance with WHO criteria, at least 10% of all cells in a given lineage should display morphological signs of dysplasia in bone marrow smears in order to count as a diagnostic criterion for MDS (10% cut-off) (15). When morphologic criteria for MDS were not met, the diagnosis of MDS can still be established in a cytopenic patient if a typical (MDS-related) karyotypic anomaly was
found. In each patient, it was important to study the peripheral blood and bone marrow cytology and histology to exclude dysplasia (10% cut-off) in any of the 3 major lineages. The differential diagnosis on PCD was based on the criteria used by the International Myeloma Working Group, namely the presence of end organ involvement (manifested as increased calcium, renal insufficiency, anaemia, or bone lesions) related to plasma cell disease, bone marrow clonal infiltration and quantification of monoclonal protein (16). The diagnosis of drug-induced bone marrow toxicity was based on the presence of hypersegmented neutrophils and macrocytosis in the peripheral blood, evidence of bone marrow hypoplasia and megaloblastic hemopoiesis and recovering of all these abnormalities after withdrawal of the immunosuppressive drug.

Statistical analysis
Patient data were summarised and presented in table format. Continuous variables were presented as mean±SD under normality assumption or alternatively, as median (Interquartile Range, IQR). Subgroups were compared using the non-parametric Mann-Whitney U-test. Count outcomes were tabulated and presented as % frequencies. A non-parametric, receiver operating characteristics (ROC) analysis for blood and serum indices was initially performed to identify potentially useful variables for an informative outcome. The area under the ROC curve (AUC) was reported as a measure of diagnostic performance. In a second step, disease types, demographics and haematologic indices were entered as independent covariates in multinomial logistic regression model for the prespecified informative outcomes (dependent variables). Odds ratios along with their 95% confidence intervals (95%CI) were estimated and reported. Significance level was set at \( p=0.05 \). Only the significant covariates were identified to highlight those cases warranting a bone marrow study, provided they had at least one or more of the significant adverse factors. The corresponding sensitivity and specificity for diagnosis of an informative outcome was then calculated.
Table I. Outcome of haematologic evaluation, stratified for underlying autoimmune disorder.

<table>
<thead>
<tr>
<th>Dx</th>
<th>MDS</th>
<th>MGUS</th>
<th>MM</th>
<th>Other NHL</th>
<th>CLL</th>
<th>Toxicity</th>
<th>MPD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA (n=29)</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>SLE (n=38)</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Vasc (n=19)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>PR (n=6)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>MCTD (n=5)</td>
<td>2</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>APS (n=8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Still (n=2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Scl (n=2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>n=110 (100%)</td>
<td>11 (10%)</td>
<td>4 (3.6%)</td>
<td>2 (1.8%)</td>
<td>4 (3.6%)</td>
<td>2 (1.8%)</td>
<td>7 (6.4%)</td>
<td>1 (1.0%)</td>
<td>31 (28.2%)</td>
</tr>
</tbody>
</table>

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; Vasc: systemic vasculitis; PR: polymyalgia rheumatica; MCTD: mixed connective tissue disease; APS: antiphospholipid syndrome; SCI: systemic scleroderma.

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67) with a 2.1:1 female to male ratio (75 female vs. 35 male). SLE was the most frequent underlying condition (38/110, 34.5%) (Fig. 1A) and anaemia (81/110, 74%) the most common haematologic abnormality (Fig. 1B). Median disease duration was 4 years (IQR 1–9 years). Prior to evaluation, over half the patients received cytotoxic or immunomodulatory drugs, with methotrexate (MTX) being the most frequently administered drug (29/110, 26.4%) (Fig. 1C). The average profile (mean±SD) of the referred patient is characterised by anaemia (haemoglobin 10.6±1.9 gr/dl) with normal or increased indices, including serum iron (68.2±45.3 μg/dl), ferritin (582±1443 ng/ml), vitamin B12 (608±425 pg/ml) and MCV (87.8±10fl). Average WBC was 6.2±3.6x10^9/μl, platelet count 245±147x10^9/μl, neutrophil count 4.1±3.1x10^9/μl and lymphocyte count 1.5±0.9x10^9/μl, respectively. Thrombocytosis (>450x10^9/μl) was an exception to the pattern of cytopenia (7 cases).

Bone marrow aspiration was informative in 31 cases (28.2%) and included 24 cases with clonal haematologic disorder and 7 cases displaying evidence of marrow toxicity. The most predominant clonal disorder was MDS (11/31, 35.5%), followed by LPD (6/31, 19.4%) and PCD (6/31, 19.4%). The MDS group consisted of 5 cases with refractory anaemia with excess blasts-1 (RAEB-1), 1 case with refractory anaemia with ring sideroblasts (RARS), 3 cases with refractory cytopenia with unilineage dysplasia (RCUD) and 2 cases with refractory cytopenia with multilineage dysplasia (RCMD). Cytogenetic analysis in these cases revealed karyotypic abnormalities in 6 out of 11 patients. More specifically, 3 patients karyotypically expressed monosomy 7, 2 expressed trisomy 8 and 1 patient expressed an inv(9)(p12q13)inv(16)(p11.2q13–21) karyotype. Four patients of the LPD group were diagnosed with NHL (2 diffuse large B-cell lymphomas, 1 lymphoplasmacytic lymphoma, 1 marginal zone lymphoma) and 2 with CLL. All LPD patients were HCV seronegative. Two out of four patients diagnosed with NHL received immunomodulatory therapy prior to the NHL diagnosis. Immunophenotyping was a useful tool in the diagnosis of two CLL cases, where physical examination or blood counts were unrevealing. The first patient had atypical extranodal manifestations, presenting with anaemia, and lower motor neuron disease. Bone marrow immunophenotype was diagnostic for B-CLL. Muscle biopsy revealed infiltration of tissue and vessels by CLL cells. The second case had anaemia and lymphocytosis with small, mature-appearing lymphocytes in the peripheral blood, and diagnosed with bone marrow histology and immunophenotyping, in the absence of significant lymphadenopathy (as Binet stage B, B-CLL). A third patient with bicytopenia and fever was initially diagnosed with DLCBL from bone marrow histology in the absence of nodal involvement or splenomegaly. A lung biopsy of pulmonary nodule post BM biopsy revealed DLCBL. Another patient with anaemia, was diagnosed with DLCBL from the bone marrow aspiration, and work-up identified DLCBL of the stomach as the primary site involved.

Two multiple myeloma and 4 monoclonal gammopathy of undetermined significance (MGUS) cases were recorded in the PCD group. None of the patients diagnosed with SLE or RA and clonal haematologic disorder expressed disease activity at the time of diagnosis. Six out of 7 patients with thrombocytosis had reactive (secondary) thrombocytosis and only one an underlying myeloproliferative disorder (MPD). The type of MPD was essential thrombocythaemia with jak2 mutation positivity. The bone marrow findings in patients with no specific diagnosis revealed hypocellularity, dyspoiesis in any lineage not fulfilling the MDS criteria, bone marrow necrosis and fibrosis. These non specific histopathological findings were the most common picture in the bone marrow biopsies, being much more prominent in SLE patients. Table I summarises the outcome of the diagnostic evaluation, stratified for the underlying autoimmune disorder. Median time lapse from diagnosis of autoimmune condition to the diagnosis of clonal disorder was 3 years for MDS (range 1–10), 7 years for lymphoproliferative disorder (range 1–8) and 10 years for PCD (range 1–19), with all comparisons insignificant (Mann-Whitney U-test p>0.05). There was no distinctive pattern of haematologic alteration between different outcomes (all comparisons insignificant), as presented in Figure 2.
ROC curve analysis of count variables presented in Table IIA confirmed that blood counts and serum indices perform poorly and, therefore, have limited diagnostic utility, with regard to an informative outcome. 

In multinomial logistic regression, MDS was less frequent among females (OR 0.14, 95%CI 0.35–0.58), whereas a 10-μg increase in serum iron correlated with increased risk of MDS (OR 1.20, 95%CI 1.04–1.40). Increased MCV correlated with an increased risk for toxicity (OR 1.14, 95%CI 1.00–1.31, per unit increase), and a monoclonal band in serum electrophoresis correlated strongly with PCD (OR 15.7, 95%CI 2.37–104.5) (Table IIB). All other correlations were insignificant. 

The identification of these influential factors for an informative outcome can classify patients as high risk, thereby warranting bone marrow evaluation. MCV and serum iron cut-offs were set to 90 fl and 90 μg/dl, rounded closest to their 75% quartile. The presence of at least one factor (male sex, high MCV, high serum iron, or monoclonal band) is highly sensitive but not specific for all outcomes (Table III). This model is not informative for NHL diagnosis, as opposed to other discrete outcomes emphasising the need for extensive clinical evaluation of this group of patients.

Discussion

The exclusion of underlying clonal disorder or drug toxicity is fundamental to the management of patients with systemic autoimmune disorders, seeking medical attention for otherwise unexplained haematologic alterations. In our series, almost a fifth of patients referred for evaluation of an otherwise unexplained cytopenia, mainly anaemia, had MDS, PCD, or lymphoma. In the largest up-to-date series of bone marrow studies in autoimmunity, Richer et al. (17) found a similar proportion (17/146, 12%) of haematologic disorders (including MDS/acute leukemia, MPD and NHL). MDS was distributed among SLE and RA patients with a median latent period of 3 years after diagnosis of autoimmunity, and showed a male predominance. Autoimmunity has just recently been linked by Anderson et al. to myeloid malignancies (OR 1.50, 95%CI 1.35–1.66), using population-based data from US Surveillance and epidemiology (SEER) (18). MDS was significantly associated with both SLE (OR 1.82, 95%CI 1.04–3.16) and RA (OR 1.52, 95%CI 1.27–1.81). The distinction between MDS and SLE-related bone marrow histology is not always straightforward and may require the skills of an expert haemocytopathologist, especially in the case of low blast bone marrow count and the absence of a cytogenetic abnormality. SLE bone marrow may also exhibit dysplastic features affecting all haematopoietic lineages (dysmyelopoiesis, dyserythropoiesis, dysmegakaryopoie-
s) that resemble MDS dysplasia, with differences limited to decreased overall cellularity and the presence of stromal alterations in SLE, as extensively presented by Voulgarelis et al. (11).

On the other hand, the increased risk of lymphomas in systemic autoimmunity is well-established by Zintzaras et al. (8), using standardised incidence rates (SIRs) as measures of association: the SIR point estimates were 7.4 for SLE, 3.9 for RA and the highest for Sjögren’s syndrome at 18.8. In respect to RA, in particular, the risk of NHL may reach with the use of biologic agents (SIR 11.5). Sjögren’s haematologic features and lymphoproliferation have already been presented in the context of previous studies and are not discussed here (7, 8).

PCD, including monoclonal gammopathies and multiple myeloma, have been identified during the course of RA and SLE, but evidence of association with other systemic autoimmunities remains circumstantial (18-21).

Bone marrow toxicity is another clinically significant outcome, given that the majority of patients are exposed to offending drugs, with MTX being the most frequently prescribed drug to possibly affect blood counts. In our series, toxicity rate reached 6.4%. Methotrexate is considered a generally safe and well-tolerated drug, even for prolonged periods of administration. However, neither prolonged therapy nor a stable dose diminishes the risk of haematologic toxicity. Haematologic toxicities (mainly neutropenia and thrombocytopenia) may occur late (median 16.9 and 9.4 months, respectively) after initiation of MTX, in contrast to other disease-modifying drugs, where haematologic toxicity is an early manifestation. Additionally, half of the toxicities occur after one year of administration with patients having been on a stable dose for at least six months (22). MTX-induced pancytopenia in RA or psoriatic arthritis is described as a severe complication with an abrupt onset and a mortality rate (due to infection) approximating one out of two affected individuals (23). Azathioprine may also be associated with bone marrow suppression and cytopenias, but these are usually asymptomatic. In a series of 760 patients with inflammatory bowel disease and a three-decade follow-up, the drug was withdrawn due to toxicity in only 5%, including two infection-related deaths (24). With regard to cyclophosphamide, the incidence of severe haematologic toxicity and drug discontinuation is extremely low. In a series of patients treated with intravenous cyclophosphamide mainly for SLE nephritis, Katsifis et al. (25) estimated the rates for severe leucopenia (<1000/mm$^3$), severe neutropenia (<500/mm$^3$) and severe thrombocytopenia (50,000/mm$^3$) at 1.0%, 1.0% and 0% respectively in any drug course, with the discontinuation rate being only 0.12 per 100 doses administered. Thrombocytosis, on the other hand, denotes a secondary reactive process due to inflammation, with systemic vasculitides and rheumatoid arthritis often present with thrombocytosis (27-29).

Our study also addressed the issue of developing a predictive rule to identify those patients at high risk for underlying clonal haematologic disorder for whom bone marrow evaluation should be a sine qua non. Previous authors had suggested that a changing (deteriorating) haematologic profile, neutropenia <2500/mm$^3$, or thrombocytopenia <100,000/mm$^3$, should prompt for bone marrow examination. In our study, blood counts, including white blood cells, haemoglobin level and platelet number, as well as single or multiple cytopenias, were not associated with a significant clinical outcome as proven histologically by bone marrow biopsy. Furthermore, the association of pre-existing autoimmune condition, demographics, and common haematologic indices was not informative. Our study, however, managed to

### Table II. A. Non-parametric, ROC curve analysis of count variables, with informative outcome as reference index.

<table>
<thead>
<tr>
<th>Classification variable</th>
<th>AUC</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (µl)</td>
<td>0.54</td>
<td>0.39–0.66</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>0.53</td>
<td>0.40–0.66</td>
</tr>
<tr>
<td>Platelets (x10$^9$/µl)</td>
<td>0.48</td>
<td>0.35–0.61</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>0.66</td>
<td>0.52–0.81</td>
</tr>
<tr>
<td>Serum iron (µg/dl)</td>
<td>0.57</td>
<td>0.42–0.71</td>
</tr>
<tr>
<td>Ferritin (ng/ml)</td>
<td>0.50</td>
<td>0.35–0.65</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>0.56</td>
<td>0.41–0.71</td>
</tr>
</tbody>
</table>

### Table III. Specificity, sensitivity and positive predictive values by outcome, for at least one high risk factor (male sex or MCV>90 or iron>90 or presence of monoclonal band).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>All outcomes</td>
<td>0.84</td>
<td>0.21</td>
<td>0.74</td>
</tr>
<tr>
<td>MDS</td>
<td>1.0</td>
<td>0.22</td>
<td>–</td>
</tr>
<tr>
<td>Toxicity</td>
<td>0.86</td>
<td>0.19</td>
<td>–</td>
</tr>
<tr>
<td>PCD</td>
<td>0.83</td>
<td>0.19</td>
<td>–</td>
</tr>
<tr>
<td>Lymphoproliferation</td>
<td>0.50</td>
<td>0.17</td>
<td>–</td>
</tr>
</tbody>
</table>
identify some notable exceptions – i.e. gender, serum iron, MCV and monoclonal band in serum electrophoresis. Male predominance is a well-defined feature of MDS with a sex ratio of two that has remained stable over the years (30, 31). Serum iron is suppressed in anaemia of chronic disease related to systemic autoimmune disorders, an effect that is not anticipated in MDS patients (32, 33). On the contrary, ferritin levels cannot discriminate anaemia of chronic disease from myelodysplasia, since they increase in both conditions (34, 35). An elevated MCV could denote an increased probability of bone marrow toxicity, an effect which is already described in autoimmune conditions and inflammatory bowel disease treated with azathioprine, and in RA treated with MTX, and haematologic and solid neoplasias during chemotherapy (36-39). Finally, the presence of a monoclonal band on serum electrophoresis will disclose an underlying PCD. Bone marrow biopsy is generally recommended in these cases, as it aids to the discrimination of MGUS from MM. The latter requires evidence of end-organ damage and >10% infiltration of plasma cells in the bone marrow (16). Although MGUS is considered the non-malignant counterpart of MM, the annual risk of evolution to MM is estimated at 1%, necessitating a close follow-up (40, 41).

The proposed model has low sensitivity in cases of lymphoma. The diagnosis of lymphoproliferation still relies on identification and histology of involved sites (lymph nodes, spleen, extranodal sites). Physical examination and imaging studies are considered the first step. Bone marrow biopsy usually follows for staging purposes, especially in cases of aggressive lymphomas where bone marrow involvement is not the rule, approximating merely 10% in large, recent series (42, 43). Bone marrow biopsy may be helpful in diagnosis of indolent lymphomas, including CLL, where disseminated stage is the rule at presentation, whereas not informative in cases of mucosa associated lymphoid tissue (MALT) types related to Sjögren’s syndrome, and other gastric and non-gastric MALT (44, 45). We were unable to establish validated criteria as to when to perform a bone marrow biopsy in patients with autoimmune disorders, even in cases of unexplained cytopenias where one third of patients may disclose underlying clonal haematologic disorder or, at best, myelotoxicity. However, we did successfully identify a group of simple parameters (male sex, MCV, serum iron, and monoclonal band) the presence of any of which classifies the patient as “high risk”, hence warranting a bone marrow evaluation. This model achieves a high sensitivity and positive predictive value for all outcomes of interest, with the exception of lymphomas. However, the development of any predictive model can only be supportive to the role of physical examination and clinical suspicion, in the presence of new emerging signs, symptoms, or laboratory findings. Our study is limited by the small sample size and its retrospective design; the proposed model needs validation and further investigation in a future prospective cohort.

References

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