Contrast-enhanced ultrasound characteristics in orbital cavernous venous malformation

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Abstract. This study aimed to analyze and subsequently recapitulate the contrast-enhanced ultrasound (CEUS) characteristics in orbital cavernous venous malformation (CVM), exploring the key aspects of differential diagnosis. Several orbital CVM cases (n=56) confirmed by surgery and pathology at Sichuan Provincial People's Hospital (Chengdu, China) were analyzed retrospectively. The conventional ultrasound showed mostly hypoechoic orbital CVM lesions (64.2%), with clear boundaries (98.2%) and quasi-circular (100%) characteristics. However, the blood flow signals were not rich enough, overlapping with other orbital space-occupying lesions to a considerable extent. The CEUS imaging showed a characteristic progressive enhancement pattern of focal nodules in CVM lesions. In conclusion, CEUS may offer certain specificity and positive significance for the preoperative qualitative diagnosis of orbital CVM.

Background

Orbital cavernous venous malformation (CVM), previously referred to as 'orbital cavernous hemangioma', is one of the most common primary orbital lesion in adults (1). Typically, the CVM condition causes a series of concerning effects on the patient's vision and appearance, such as visual deterioration and exophthalmos due to pushing the eyeball (2,3). The pathological CVM condition is often characterized by a single mass with a capsule. However, it should be noted that, in certain instances, it is highly challenging to distinguish between schwannoma and pleomorphic adenoma conditions (4). In recent times, the application potential of contrast-enhanced ultrasound (CEUS) imaging technology has been recognized by numerous researchers. However, there are still few studies on orbital CVM (5-7).

Motivated by these considerations, the present study aimed to analyze the characteristics of CEUS in orbital CVM to improve its diagnostic accuracy. Considering the reported literature, this work may provide valuable insights into the potential of CEUS for preoperative diagnosis. In this light, the present findings may facilitate and improve the differentiation of CVM from other orbital lesions, addressing important diagnostic challenges and potentiating its applicability (8).

Patients and methods

Patients. In the present study, patients (n=56) diagnosed with orbital CVM admitted to Sichuan Provincial People's Hospital (Chengdu, China) from January 2018 to September 2023 were analyzed retrospectively. These patients (22 males and 34 females) were in the age range of 23 to 73 years, with an average age of 47.6 (47.6±14.1) years. Notably, the orbital CVM condition of all subjects was confirmed by postoperative pathological observations. Conventional ultrasound and CEUS were performed prior to surgery. Written informed consent for the publication of imaging and clinical data was obtained from each subject recruited for the study. Furthermore, the study protocol was designed to conform to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the Ethics Committee of Sichuan Provincial People's Hospital (Chengdu, China).

The inclusion criteria were set as follows: i) Patients who had a confirmed diagnosis of orbital CVM based on postoperative pathology; ii) patients who underwent both conventional ultrasound and CEUS before surgery; iii) patients who had provided written informed consent for participating in the study.

The exclusion criteria were set as follows: i) Patients with incomplete imaging data or poor-quality ultrasound images;

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ii) patients with previous orbital surgery or a history of other orbital pathologies that could affect the imaging results; iii) patients who disagree with the use of ultrasound contrast agents.

Methods. The study protocol was approved by the Medical Ethics Committee of Sichuan Provincial People's Hospital (Chengdu, China; approval no. 2017-642). The ultrasound procedure was performed using the method as stated. The ultrasound examinations were performed using MyLab 90 and Logic E9 from GE Healthcare equipped with a 7-12 MHz linear-array transducer. Initially, patients were directed to rest on the table on their backs with their eyes closed. Conventional ultrasound was then performed to observe various characteristics of the lesions, including the location, size, shape, internal echo, calcification, liquefaction and blood flow. Blood flow signals were further assessed using Color Doppler Flow Imaging (CDFI). The examination was performed using a 7-12 MHz linear-array transducer, with the color Doppler parameters set to a pulse repetition frequency of 0.7-1.2 kHz and a wall filter of 50-100 Hz, depending on the lesion depth and size. Blood flow signals were classified according to the Alder classification: Grade 0 (no flow), Grade 1 (minimal flow), Grade 2 (moderate flow) and Grade 3 (abundant flow). Further, the CEUS examination was performed in the vein on the section with rich blood flow or the largest section of the lesion. Subsequently, a suspension was prepared by mixing 25 mg of a contrast agent (SonoVue; Bracco) with 5 ml of normal saline using manual oscillation for injection. Then, 1.0 ml of suspension was injected through the antecubital vein, which was quickly followed by 5 ml of normal saline. Further, the CEUS dynamic images in the whole process (~1 min) were recorded. Finally, the focus was completely fan-scanned, displaying the blood perfusion in the mass and the infiltration of surrounding tissues.

Evaluation. The recorded images were reviewed and analyzed by two senior radiologists. Accordingly, the location, size, boundary, morphology, echo and blood flow signals (based on the Alder classification) of the lesions were analyzed by conventional ultrasound (9).

Furthermore, the characteristics of CEUS were observed, including the enhancement features of CVM in the early phase (enhancement of lesions earlier/simultaneously/later) and the enhancement features of CVM in the late phase (lesions washout earlier/simultaneously/later) compared to surrounding tissues, as well as the enhancement patterns of CVM (diffuse enhancement/progressive enhancement) and the peak enhancement of CVM (hyperenhancement/isoenhancement/hypoenhancement/non-enhancement). Notably, the results were evaluated without considering the enhancement pattern (homogeneous or inhomogeneous) or lesion enlargement (present or absent).

Statistical analysis. Data were analyzed in SPSS 19.0 (IBM Corp.). Data are presented as the mean ± standard deviation for continuous variables and as n (%) for categorical variables, unless otherwise specified. Descriptive statistics were used to summarize the characteristics of the study population and the imaging findings. No statistical hypothesis testing was conducted in this study.

Table I. Population characteristics (n=56).

Characteristic	Value
Sex	
Male	30 (53.6)
Female	26 (46.4)
Age, years	45±12.3
Lesion location	
Orbital floor	20 (35.7)
Orbital roof	10 (17.9)
Medial wall	15 (26.8)
Lateral wall	11 (19.6)

Values are expressed as n (%) or the mean ± standard deviation.

Results

Population characteristics. In the present study, the ultrasound examination of all patients (n=56) with 56 lesions showed single, round and space-occupying lesions in the unilateral orbit. The cohort included 30 male patients (53.6%) and 26 female patients (46.4%), with a mean age of 45±12.3 years. The lesions were located in different orbital regions: 20 cases (35.7%) in the orbital floor, 10 cases (17.9%) in the orbital roof, 15 cases (26.8%) in the medial wall, and 11 cases (19.6%) in the lateral wall. The diameter of the lesions was 18±6.3 mm, with a minimum diameter of ~8 mm and a maximum diameter of 36 mm (Table I).

Conventional two-dimensional (2D) ultrasound findings. Considering the echo of 2D ultrasound, these lesions were classified into hyperechoic, isoechoic and hypoechoic types in accordance with the surrounding soft tissues at the same level. Accordingly, the conventional 2D ultrasound findings revealed 36 hypoechoic lesions (64.2%), 15 isoechoic lesions (26.8%) and 5 hyperechoic lesions (8.9%). All of these lesions (100%) were quasi-circular in shape and most of the lesions (55/56, 98.2%) showed clear boundaries. The CDFI results showed weak or absent blood flow signals in 50 cases (89.3%) (Figs. 1A and 2B), with only 6 cases (10.7%) showing weak blood flow. The characteristics are summarized in Table II.

CEUS enhancement patterns and washout characteristics. The CEUS characteristics showed a gradual enhancement pattern of the progressive enhancement pattern of focal nodules (94.6%), which was slightly synchronized with the surrounding soft tissues. Among the selected lesions, several lesions (n=50, 89.2%) showed simultaneous enhancement or slightly later than the surrounding tissues. Certain lesions (n=3, 5.4%) displayed a diffuse enhancement pattern without the progressive fill-in pattern that was observed in most of the lesions. Several lesions (54/56, 96.4%) displayed inhomogeneous enhancement at the peak time, with incomplete filling of the contrast agent, while only 2 lesions (3.6%) showed complete fill-in. All lesions showed synchronous washout with surrounding tissues after 90 sec of enhancement (Table III).

Table II. Summary of the conventional ultrasound findings of orbital cavernous venous malformation in patients (n=56).

		Location		Boundary		Calcification		Fluid sonolucent area		Blood flow signal		
Category	n	Left	Right	Clear	Unclear	No	Yes	Yes	No	0	I	II
Low echo	36	19	17	36	0	35	1	12	24	18	15	3
Equal echo	12	6	6	11	1	12	0	0	12	7	3	2
High echo	8	6	2	8	0	8	0	2	6	4	3	1

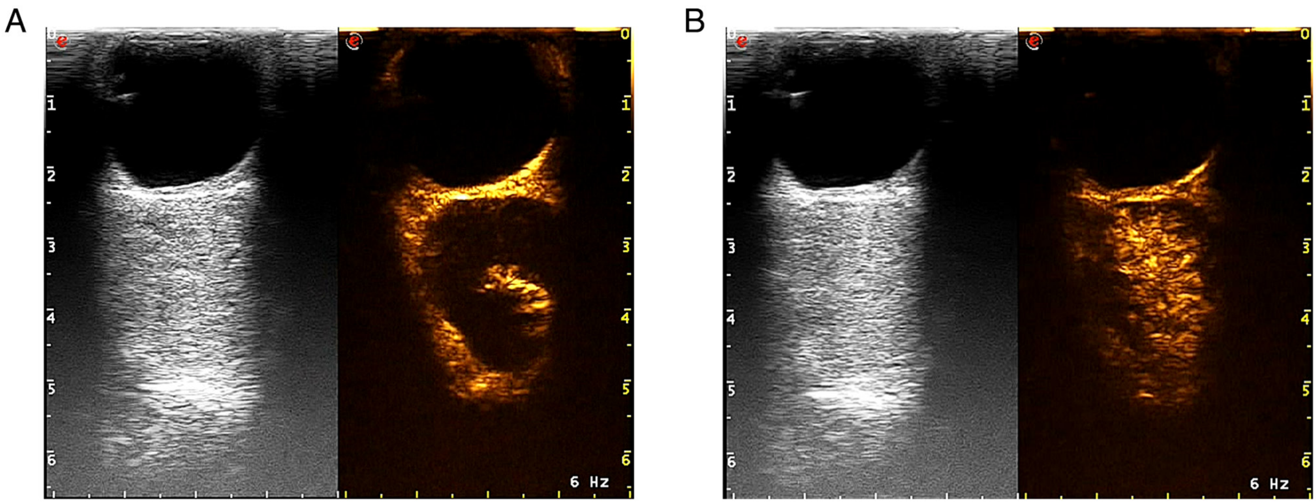

Figure 1. Images showing the typical progressive enhancement pattern of orbital cavernous venous malformation in a 44-year-old male patient with cavernous malformation. (A) Internal nodular enhancement of the lesion in 31 sec. (B) Progressive fill-in and eventually incomplete enhancement in 120 sec. The gray image is a conventional ultrasound image and the golden image is a contrast-enhanced ultrasound image.

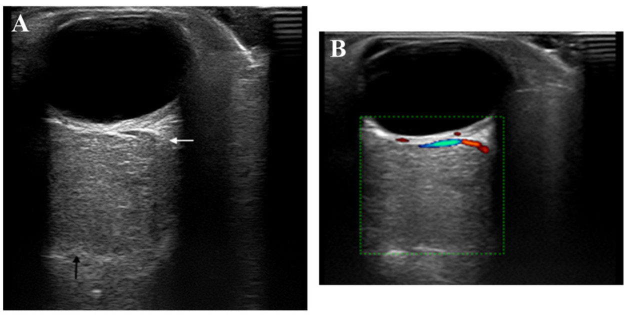

Figure 2. The representative Color Doppler flow imaging results showed a small amount or no signs of internal blood flow. (A) The optic nerve (white arrow) is displaced by the lesion (black arrow) in a 44-year-old male patient. (B) No obvious blood flow signal was observed within the lesion in a 44-year-old male patient.

Despite the changes, the lesions eventually showed complete or incomplete fill-in (Fig. 2A and B), which were not observed in the CEUS of other orbital space-occupying lesions. The other 3 lesions showed diffused enhancement without a progressive enhancement pattern (Fig. 3A and B). After the examination, all patients rested in the lounge for 30 min and were carefully asked for any visual or other abnormal sensations. No positive findings were found. The patients reported no visual changes or other abnormal sensations. Therefore, these findings suggested that no obvious changes were observed in the vision of all subjects before and after the examination.

Discussion

Orbital CVM has emerged as one of the most common space-occupying lesions in adults, posing a challenge regarding its differentiation from other similar orbital lesions. Despite the useful insights, the applicability of conventional imaging techniques, such as magnetic resonance imaging (MRI) and traditional 2D ultrasound, is limited due to their diagnostic specificity. Although CEUS has been well-established in the diagnosis of hepatic and subcutaneous cavernous venous malformations (10), the application of this technique in orbital CVM is relatively novel. Previous studies on orbital masses relied heavily on MRI and conventional 2D ultrasound (11,12). However, these exceptional techniques suffer from major limitations in differentiating CVM from other lesions. The present study intended to demonstrate the potential of CEUS to offer superior diagnostic specificity in a non-invasive manner. The CEUS imaging of orbital CVM showed a typical progressive enhancement pattern with inhomogeneous enhancement, which could serve as a distinct feature for preoperative diagnosis. The resultant patterns may provide additional diagnostic clarity, distinguishing CVM from other orbital lesions, such as fibromas, schwannomas or lymphomas, and lacking these specific CEUS characteristics.

Typically, CVM is one of the most common types of non-dilated venous malformations (13-16). Although there were related case reports of infants, no obvious clinical symptoms were evident before adulthood. In the present study, adults were selected as patients with a broad age range of 23 to 73 years, with an average age of 47.6 years. As evident from the previous studies, most cases occurred between 40 and 60 years of age (12). Accordingly, no substantial age-related variations in CEUS characteristics or lesion presentation were observed. Previous findings suggested that orbital CVM followed a relatively consistent imaging pattern across different age groups (17,18). However, the predilection for middle-aged adults, particularly women, indicated a possible hormonal influence, as reported previously (6,7). In the current study, the majority of cases (34/56, 61%) were females, which was consistent with the previous report showing in several long-term follow-up studies the enlargement or decrease of the lesions may be related to the level of progesterone (17). Contrarily, the lesions in the estrogen supplementation group showed no signs of enlargement (8,19).

Previous reports suggested that the most common clinical symptoms of orbital CVM were axial exophthalmos, resulting in the worsening of varied degrees of vision (20,21). In addition, certain patients presented with ocular movement impairment, strabismus and rare localized pain (17). The orbital CVM tended to occur in the preorbital area and orbital muscle cones. Compared with lesions that occurred in other tissues, these lesions generally showed an intact envelope (18). Therefore, the orbital CVM often appeared as a solitary mass with a clear boundary on imaging examination. Considering the fulfillment of orbital CVM with stagnant blood in a resting state, the reflectivity was normally medium to high, with no signs of internal vascularization. Therefore, the conventional 2D ultrasound images of orbital CVM mostly appeared as isoechoic or slightly hyperechoic masses with clear boundaries and regular shapes. The CDFI results showed a small amount or no signs of internal blood flow. In addition, the relationship between the lesion and the eyeball wall and optic nerve could be observed during the dynamic scanning to observe the location of the eyeball wall and optic nerve.

Considering its real-time imaging capabilities, CEUS can offer valuable insights during preoperative evaluation, allowing for accurate differentiation between CVM and other orbital lesions, such as schwannomas and lymphomas (22-24). Accordingly, CEUS offers substantial utility for the diagnosis of orbital masses. For instance, surgeons may improve their approach with a more definitive preoperative diagnosis, potentially reducing surgical risks and complications (25). An accurate preoperative diagnosis plays an important role in clinicians' selection of appropriate treatment options. CVM lesions are often benign, requiring precise surgical intervention based on their location and relationship with surrounding tissues. In terms of clinical implications, the study demonstrated that CEUS could provide exceptional diagnostic specificity by identifying the characteristic progressive enhancement pattern and

Table III. Summary of the contrast-enhanced ultrasound findings of orbital cavernous venous malformation in patients (n=56).

		Early enhancement phase			Enhancement patterns		Peak enhancement			Homogeneous		Enlarged[a]	
Category	n	Later	Synchronization	Earlier	Diffuse	Progressive	Hypo-	Iso-	Hyper-	Yes	No	Yes	No
Low echo	36	15	16	5	3	33	2	7	27	2	34	0	36
Equal echo	12	7	5	0	0	12	3	2	7	0	12	0	12
High echo	8	2	4	2	0	8	1	0	7	0	8	0	8

[a]Enlarged: Comparison of lesion size after contrast imaging with conventional ultrasound lesion size display.

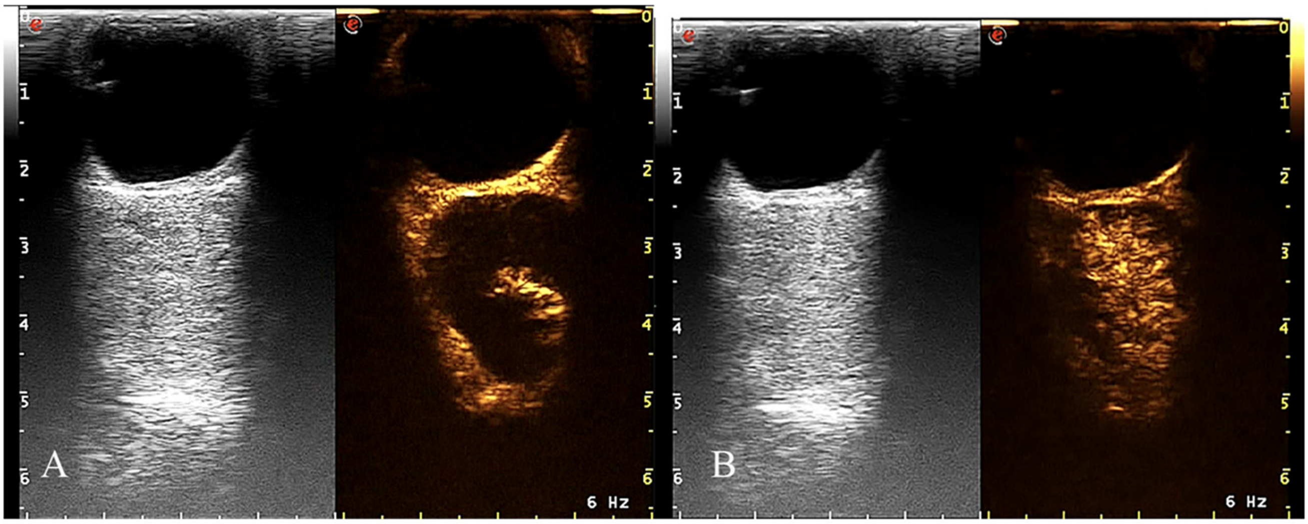

Figure 3. Diffuse enhancement pattern of orbital cavernous venous malformation in a 33-year-old female patient with cavernous malformation. (A) The lesions show no typical nodular enhancement in 14 sec. (B) The lesions show overall heterogeneous enhancement in 22 sec. The gray image is a conventional ultrasound image and the gold image is a contrast-enhanced ultrasound image.

inhomogeneous enhancement of orbital CVM. The unique imaging features could distinguish CVM from other orbital space-occupying lesions that may present with similar characteristics on conventional 2D ultrasound, such as fibromas, schwannomas or lymphomas. The ability of CEUS to reveal these distinct patterns may highlight its potential in terms of reducing diagnostic uncertainty, making it a valuable tool for clinical decision-making. In several cases where conventional ultrasound failed to provide sufficient detail, CEUS could provide critical vascular information that may aid in the precise diagnosis and treatment planning for orbital CVM.

Despite the advantages, several features of CEUS must be considered for its replacement of other diagnostic modalities, such as MRI, or serve as a complementary tool (25). Although CEUS offers real-time dynamic imaging and excellent visualization of vascular structures, MRI remains the gold standard for detailed anatomical resolution and assessment of soft tissue involvement. MRI provides superior visualization of the relationship between the lesion and critical structures, such as the optic nerve, orbital walls and adjacent tissues, which is vital for complex surgical planning. Considering these attributes, CEUS remains a complementary tool to MRI rather than a replacement. However, the combined use of CEUS and MRI may enhance the accuracy of orbital CVM diagnosis and management (26). Coupled with detailed anatomical information by MRI, the real-time imaging ability of CEUS provides a comprehensive diagnostic approach to assess blood flow dynamics. The combination of CEUS and MRI could result in a more accurate preoperative assessment. Thus, this approach could improve treatment outcomes by guiding clinicians to choose the most appropriate surgical approach based on the specific characteristics of lesions.

Several reports demonstrated that CEUS applied to the orbit may result in certain adverse effects on the retina or vision. In the present study, the parameter settings of CEUS were set, including the mechanical index (MI; 0.06-0.08) and thermal index (TI; <0.01), which were lower than the guidelines for the safe use of diagnostic ultrasound equipment adopted by the European Federation of Societies for ultrasound in Medicine and Biology (EFSUMB). The recommended values by EFSUMB were MI of <0.7 and TI of <1 (8) to avoid the occurrence of cavitation effects. Although the clinical application of ocular CEUS has been carried out for >10 years, no related reports on visual impairment appear to exist (6,10,14,27,28). Furthermore, no precise enhancement staging of the arterial phase, portal-venous phase and delayed phase was developed due to the difference in the blood supply between the eye and liver. During CEUS, the onset of enhancement time of the lesions was observed compared with surrounding tissues. The results showed that 50 (89.2%) lesions enhanced simultaneously with or later than surrounding tissues. Among the selected 56 orbital CVMs, 53 (94.6%) lesions showed a progressive enhancement pattern that was similar to the CEUS of hepatic cavernous hemangioma (29). The periphery or center of the lesions was enhanced in the early phase with progressive fill-in and gradual enlargement of the extent of nodular enhancement. Despite the changes, the lesions eventually showed complete or incomplete fill-in, which were not observed in the CEUS of other orbital space-occupying lesions. The other 3 lesions showed diffused enhancement without a progressive enhancement pattern. It could be speculated that the changes may be related to the larger sinus cavity inside of the venous malformation in pathology, which should be a high-flow type. In the present study, 54 (96.4%) lesions eventually showed incomplete enhancement, namely inhomogeneity enhancement. Consistent with the report by Rootman and Rootman, orbital CVMs were more prone to intraluminal thrombosis (30).

In conclusion, the conventional ultrasound manifestations of orbital CVM may be similar to those of other orbital space-occupying lesions. The CEUS of orbital CVM showed a typical progressive enhancement pattern with an inhomogeneous enhancement at the peak time. The combination of the two image features could be highly characteristic, showing great value in the preoperative qualitative diagnosis. However, one of the limitations of the present study is the lack of statistical analysis. This was primarily due to the different characteristics of two diagnostic methods employed. Conventional ultrasound and CEUS differ significantly in their approaches and observational parameters. Conventional ultrasound focuses on the detection of the lesion's size, morphology, echogenicity and blood flow, whereas CEUS involves the administration of contrast agents to evaluate the lesion's perfusion characteristics after enhancement. As the two methods observe entirely different parameters, a direct statistical comparison between them was not feasible. While descriptive data and imaging characteristics were systematically analyzed, the absence of statistical testing precluded definitive conclusions about associations or differences between specific subgroups. Future studies with larger cohorts should incorporate rigorous statistical analysis to validate the findings and assess the diagnostic accuracy of CEUS in comparison to other modalities.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

XL, LF, QZ and HW mainly participated in the literature search, study design, writing and critical revision, and prepared Figs. 1-3. QZ, HW, JC, QCC and QC mainly participated in data collection, data analysis and data interpretation, and prepared Tables I and II. XL and LF checked and confirmed the authenticity of the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in its prior approval by the Ethics Committee of Sichuan Provincial People's Hospital (Chengdu, China; approval no. 2017-642).

Patient consent for publication

Informed consent for the publication of imaging and clinical data was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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