

Uterine adenomyotic cyst with markedly elevated serum CA19-9 and CA125 levels: A case report

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Abstract. Adenomyotic cysts are small cysts with a diameter of <5 mm, usually containing hemorrhagic material. The present study reported on a patient with a large adenomyotic cyst with abnormally high serum levels of CA19-9 (>1,000 U/ml) and CA125 (642 U/ml) and a complaint of pelvic pain. MRI scans were critical in diagnosing the case. Adhering to the principle of tumor-free implantation, a laparotomy was performed. After the operation, six weeks were required to normalize the serum level of CA19-9 and four weeks for CA125. Elevated tumor markers are frequently observed in malignancies, but the outcome reported in the present case was a benign lesion and the prognosis was favorable. In the present case, it was unusual that CA19-9 was elevated in addition to CA125, as it is commonly reported that only CA125 is elevated in cases of large adenomyotic cyst.

Introduction

Uterine cystic adenomyosis is an uncommon gynecological disease (1). Its characteristic features include ectopic endometrial glands, stromal invasion of the myometrium, cystic part of old blood, with diffuse or focal widening of the junctional zone and bright foci or linear striations in the myometrium on T2-weighted magnetic resonance imaging (MRI) scans.

Buerger and Petzing (2) pointed out that, although uterine adenomyosis may have a cystic part of old blood, the scope of the area is small, generally not >5 mm, and large cystic lesions are rare, which are called adenomyoma bone cyst (adenomyotic cyst), bursa sex gland fibroids (cystic adenomyoma)

or bursa sex steroid myopathy (cystic adenomyosis). Large adenomyotic cysts (≥ 1 cm in diameter) are uncommon; to date, only ~70 cases of this type of lesion have been reported worldwide according to a literature search performed in MEDLINE and the Foreign Medical Literature Retrievals Service database using search term 'adenomyotic cyst' from 1992 to 2022.

The serum concentration of cancer antigen 125 (CA125) has been revealed to increase during endometriosis and measurement of the serum CA125 concentration is widely used as a supplementary test for diagnosing the disease and evaluating therapeutic effects (3). Another cancer antigen, CA19-9, has recently been reported to increase endometriosis, but it rarely increases above 1,000 U/ml (4). However, the literature has reported only seven cases of adenomyotic cyst with elevated CA19-9 or CA125 levels (Table I).

The present report presents a case of a uterine adenomyotic cyst with markedly elevated serum CA19-9 and CA125 levels.

Case report

Case presentation. A 32-year-old female [gravida 3 (referred for artificial abortion due to abnormal fetal development in 2019; one missed abortion in 2020), para 1 (gave birth to a live healthy full-term baby in 2011)] presented at the Northwest Women's and Children's Hospital (Xi'an, China). Ultrasonography was performed during the follow-up after the missed abortion, revealing an intrauterine cystic lesion without any symptoms of menorrhagia, chronic pelvic pain or dysmenorrhea. Following that, a hematologic examination and tumor marker detection were performed, which revealed CA125 levels of 175 U/ml and CA19-9 of >1,000 U/ml. Given the abnormally high tumor marker levels, abdominal CT scanning and gastroscopy were all completed but did not reveal any evidence of gastrointestinal malignant lesions. The patient suddenly experienced pelvic pain and was referred to the department for a thorough gynecological evaluation.

Measurement of serum CA19-9 and CA125 levels. Blood samples were taken and serum was obtained according to standard protocols. CA125 (normal ranges: CA125, 0-35 U/ml; CA19-9, 0-27 U/ml) were measured using the electrochemiluminescence immunoassay on a Roche Cobas e 801 analyzer (Roche Diagnostics).

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Table I. Details of previous similar studies.

First author, year	Region	Patient age, years	Elevation of CA125 or CA19-9 ^a (U/ml)	Case description	(Refs.)
Kammerer-Doak, 1996	Maricopa, USA	37	CA125: >1,000	Benign gynecologic condition presented in a case report. After excision of the affected areas, the CA125 levels returned to normal	(10)
Imaoka, 2005	Tenri, Japan	41	CA125: 673; CA19-9: 846	Cystic adenomyosis with florid glandular mass present as a huge exophytic cystic mimicking an ovarian malignancy	(12)
Cucinella, 2013	Palermo, Italy	25	CA125: 38.00; CA19-9: 88.19	A 4.5-cm adenomyotic cyst in a 25-year-old nulliparous female with severe dysmenorrhea and pelvic pain	(5)
Pontrelli, 2015	Negrar, Italy	27	CA125: 96	Rare case of giant cystic adenomyoma (8.0 cm) mimicking an uterine malformation, diagnosed and treated by hysteroscopy	(9)
Isik, 2014	Kirikkale, Turkey	47	CA125: 63	A giant adenomyotic cyst originating from the cervix with an elevated serum concentration of CA125	(4)
Fan, 2019	Jilin Province, China	39	CA125: 1,212.00	Two cases of intrauterine cystic adenomyosis were treated by hysterectomy or hysteroscopy to release the liquid inside, one of which had elevated serum levels of CA125	(11)
Zhao, 2021	Chongqing, China	30	CA125: 76.20	A rare case of a cystic adenomyotic lesion that was treated by laparoscopic surgery; CA125 levels were elevated	(8)

^aNormal ranges: CA125, 0-35 U/ml; CA19-9, 0-27 U/ml.

Imaging. CT scanning parameters were 128x0.628 mm collimation with a reconstruction interval of 1 mm, rotation time of 0.75 sec, tube voltage of 120 kV and 200 mAs (Brilliance iCT; Philips Healthcare).

A Color Doppler Ultrasound (U22; Philips Healthcare) diagnostic instrument was adopted with 7.5 MHz endovaginal probe. MRI was performed with a 1.5-T superconductive magnet unit (Picker International Co. Ltd.). T1-weighted spin-echo images (T1-WI; repetition time, 600 msec; echo time, 20 msec) and T2 weighted spin-echo images (T2-WI; repetition time, 2,000 msec; echo time, 80 msec) were obtained.

Immunohistochemistry. Tissue samples were fixed in a 10% (v/v) solution of buffered formalin for 24 h at 4°C and then dehydrated, cleared in xylene and embedded in paraffin. Paraffin sections (5 mm) were mounted on silane-coated slides, de-waxed and rehydrated. For antigen retrieval, the sections were treated with 10 mM citrate buffer, pH 6.0 in a water bath (30 min at 95°C), then treated with 1.5% (v/v) H₂O₂ in methanol for 10 min for quenching the endogenous peroxidase activity and finally equilibrated in 10 mM PBS-0.05% v/v Tween 20 pH 7.5. Nonspecific binding was reduced by incubation in 1% BSA (Cytiva) for 60 min. Subsequently, the slides were incubated with rabbit polyclonal anti-CA125

(cat. no. HPA065600; dilution, 1:100; MilliporeSigma) or mouse monoclonal antibody anti-CA19-9 (cat. no. 399S; dilution, 1:100; MilliporeSigma) in a humidified chamber for 22 h at 4°C. After washing in PBS-Tween 20, the sections were incubated with biotinylated goat anti-rabbit or horse anti-mouse immunoglobulin (cat. no. CY-4500 or CY-2500, respectively; 1:100 dilution; Vector Laboratories, Inc.; Maravai LifeSciences) for 30 min at 25°C, and then treated with avidin-biotinylated peroxidase complex (Vector Laboratories, Inc.; Maravai LifeSciences) for 30 min at 28°C. The bound antibodies were visualized with diaminobenzidine and H₂O₂ in PBS, pH 7.5 according to the manufacturer's instructions (Vector Laboratories, Inc.; Maravai LifeSciences). Finally, the tissues were stained with Gill's hematoxylin, dehydrated and mounted with coverslips. Negative controls were prepared by substituting the primary antibodies with rabbit IgG (cat. no. 0023305; dilution, 1:20; Thermo Fisher Scientific, Inc.) or mouse IgG (cat. no. 12371; dilution, 1:20; EMD Millipore).

History of menstruation. The patient had attained menarche at the age of 14 years. The patient had a history of a 28-day regular menstrual cycle without hypermenorrhea.

Pelvic examination. The uterus was displaced to the right of the median line and was estimated to be larger than a

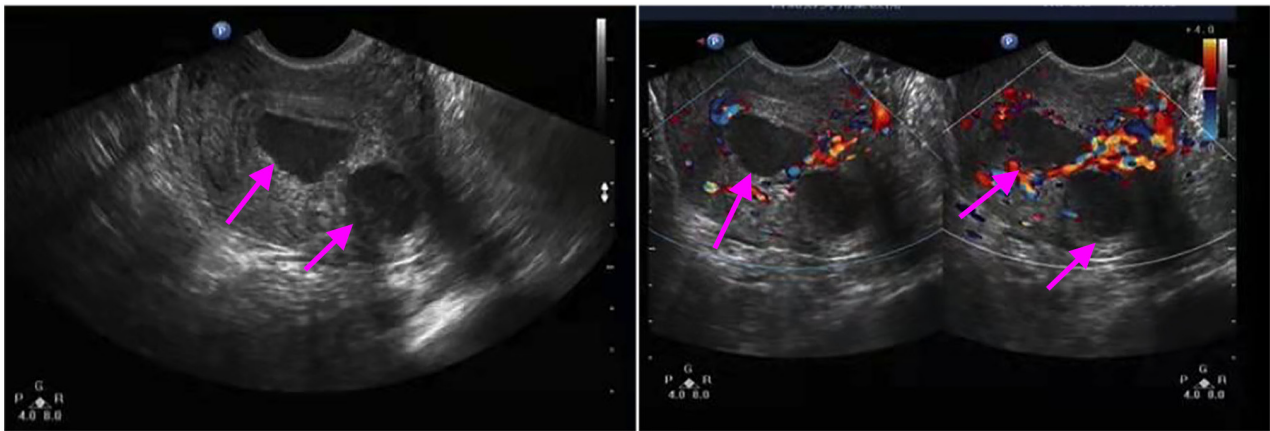


Figure 1. Transvaginal ultrasound scan of the uterus indicating the lesion with an adenomyotic cyst (the left panel arrows). Doppler flow examination (right panel) demonstrated blood flow to the lesions (arrows).

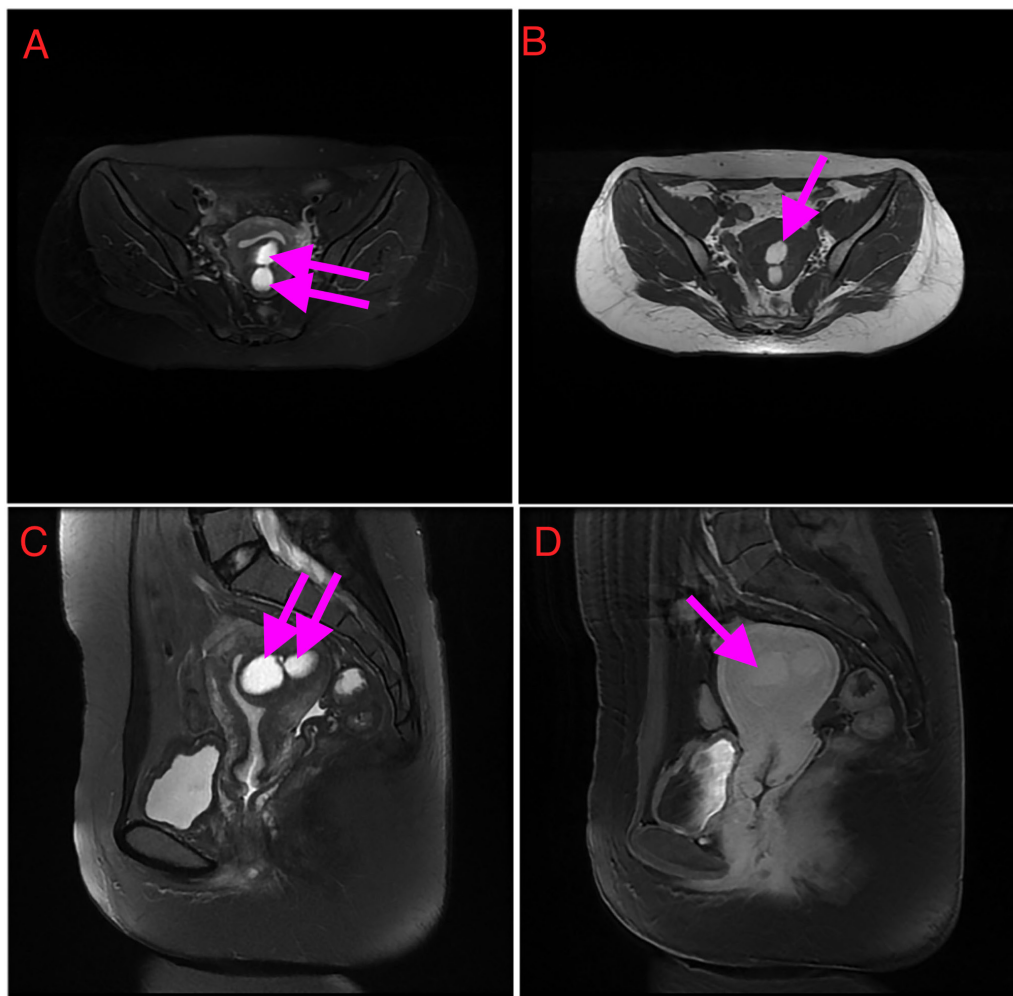


Figure 2. Magnetic resonance imaging revealed the uterine adenomyotic cyst. (A) Axial T2-weighted image with fat suppression shows hyperintense lesion of uterine adenomyotic cyst (arrows). (B) Axial T1-weighted imaging. demonstrates the cystic lesion (arrows). (C) Sagittal T2-weighted image shows the hyperintense cystic lesion (arrows). (D) Sagittal contrast-enhanced T1-weighted image shows the cystic mass (arrows).

goose egg. There were no pelvic tenderness or nodules. Pelvic examination revealed a normal vagina, vulva and adnexa and an enlarged retroflexed uterus.

Hematologic examination. Laboratory tests revealed anemia (hemoglobin concentration, 102 g/l (normal range,

115-150 g/l). The biochemical profile was otherwise unremarkable. The serum concentration of CA125 and CA19-9 was elevated at 642 U/ml and >1,000 U/ml, respectively.

Ultrasonic examination. Ultrasonography displayed a multi-locular cystic mass on the posterior wall of the uterus.

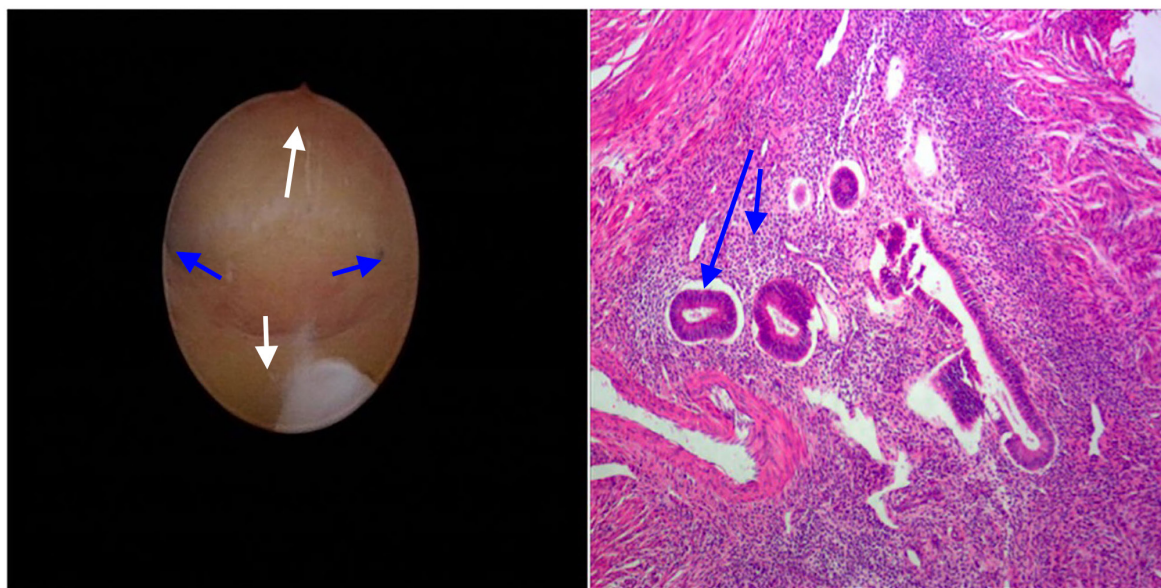


Figure 3. Hysteroscopy visualized a normal uterine cavity (white arrows) and bilaterally patent tubal ostia (blue arrows; left-hand panel). The adenomyotic tissues excised from the posterior part of the uterus was used for pathology examination. The histologic image confirms lesions (H&E; magnification, x100; long arrow refers to the endometrial glands while short arrow shows the stroma; right-hand panel).

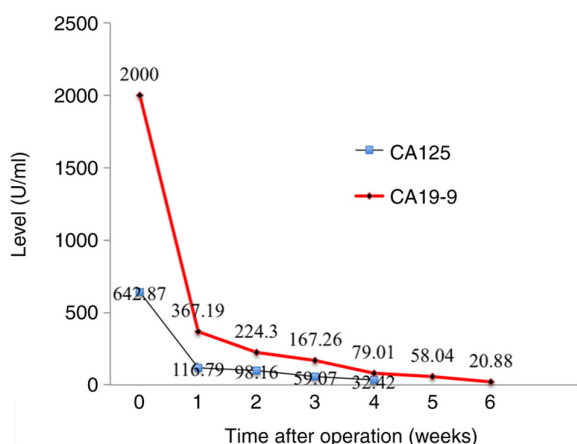


Figure 4. Changes in serum CA19-9 and CA125 after the operation.

Color power Doppler revealed a difference from a leiomyoma. The mass was diagnosed as uterine adenomyoma (Fig. 1). The ultrasound of the hepatobiliary duct, pancreas and spleen exhibited no abnormalities. An abdominal CT scan indicated no abnormal density lesions in the liver, bile duct, pancreas, spleen or gastrointestinal tract.

MRI findings. From the MRI findings (Fig. 2), the abnormal signal shadow and central hemorrhagic cystic in the posterior compartment of the uterus were considered adenomyoma. The mass measured 53x48x41 mm and T2-WI displayed the cyst as an area of high intensity. The normal uterine cavity was visualized as a line near the cyst. It was slightly hyperintense on T1- and T2-WI, with an internal fluid level, typical for the layering of simple and hemorrhagic or proteinaceous fluids.

Hysteroscopy check. Hysteroscopy visualized a normal uterine cavity and bilaterally patent tubal ostia (Fig. 3).

Intraoperative findings. Laparotomy surgery was performed. The surgery was very similar to that in the case

report of Cucinella *et al* (5). Enlargement of the posterior wall of the uterus was seen and chocolate-colored fluid flowed out of the posterior wall after incision. No abnormality was found in the appearance of bilateral fallopian tubes and ovaries. The excised lesion was sent for pathological examination (Fig. 3).

Tissue distribution of CA19-9 and CA125. The resected specimens were fixed in 10% formalin, embedded in paraffin and examined by immunohistochemical staining with anti-CA125 and anti-CA19-9 to determine the tissue distribution of each tumor marker. CA19-9 and CA125 were not expressed in the adenomyotic cyst which results not shown.

Changes in serum CA19-9 and CA125 levels. Both tumor markers were assayed using commercially available radioimmunoassay kits (Centocor) once per week. CA125 decreased below the cut-off level (0-35 U/ml) at ≥ 4 weeks after the operation, but CA19-9 did not decrease below the cut-off level (0-37 U/ml) until ≥ 6 weeks after the operation (Fig. 4). The patient underwent GnRha therapy for six months and there was no evidence of recurrence throughout the follow-up.

Discussion

CA19-9, first reported by Koprowski *et al* (6), is mainly found in the fetal stomach, intestinal epithelial cells and pancreas, and as a carbohydrate antigen recognized by a monoclonal antibody in a human colon cancer cell line. In addition to being a highly sensitive tumor marker for pancreatic and bile duct cancers, it has been reported to be highly sensitive for gynecologic tumors, such as endometrial carcinoma or ovarian cancer. Recently, CA19-9 was also reported to be increased in patients with endometriosis and adenomyosis (7), but it rarely exceeds 1,000 U/ml, as it did in the present case.

Increased serum CA125 levels have also been proposed as a diagnostic tool for cystic adenomyosis. Cucinella *et al* (5) and Zhao *et al* (8) respectively described a large adenomyotic

cyst with slightly elevated CA125. Furthermore, two cases of giant adenomyotic cyst originating from the cervix with raised CA125 levels were also reported by Pontrelli *et al* (9) and Isik *et al* (4). Certain studies reported that preoperative CA125 levels as high as 1,212.00 U/ml returned to normal after excision of these areas (10,11). Serum CA125 levels are generally elevated in patients with giant adenomyotic cyst.

A large-magnitude increase in the serum levels of both CA125 and CA19-9 in patients with cystic adenomyosis is rare (12,13). In the present case, serum CA125 was 642 U/ml and CA19-9 was as high as >1,000 U/ml prior to surgery, which decreased after tumor removal, consistent with previous reports. The present study expands the knowledge on cases with significantly increased CA19-9. However, it was not possible to determine the reason for the abnormally high serum level of CA19-9. Similarly, MRI and other imaging studies (14,15) suggest that hemorrhage in uterine adenomyosis lesions in the present case may damage the ovaries, uterus and nearby tissues, causing surrounding tissue adhesion, damaging the peritoneal barrier and possibly causing CA19-9 leakage into the circulation. In benign biliary tract diseases such as acute cholangitis, the bile duct epithelium is reported to be damaged by inflammation and biliary CA19-9 and CA125 may leak into the circulation (3). The differential diagnosis (such as biliary tract diseases, ovarian disease and enteropathy), was excluded by ultrasonic examination, MRI findings, CT scan, hysteroscopy check and pathological results.

MRI imaging and 3D ultrasound have recently been clinically applied in the gynecologic field, with reports that may be useful for the diagnosis of adenomyosis (16). MRI may now detect the normal junctional zone and adenomyotic cysts (17). The Myometrial location (intramural, submucous, subserous), Uterine site (midline, paramedian, lateral); Structure (cystic, mixed, polypoid), Contents (clear, hemorrhagic), Level (fundus, body, cervix) and Endometrial or inner lining (endometrium, metaplastic) (MUSCLE) classification was suggested for evaluating cystic adenomyosis (18). The patient of the present study may be classified as an intramural cystadenoma, namely M1 U1 S1 C2 L2 E2. MRI is considered clinically valuable in this respect. To distinguish the condition from other types of intramural cyst, histological diagnosis is necessary to identify the endometrial inner layering and the presence of outer myometrium.

To prevent malignant tumor spread, a laparotomy operation was performed. There is doubt regarding the nature of such rare voluminous cysts in young females prior to surgery, considering patient age at symptom occurrence (8).

The postoperative decrease of CA19-9 was slower than that of CA125. It remains unclear whether this difference was caused by a difference in the half-life of these two tumor markers in the circulation. However, unlike CA125 in adenomyotic cyst, CA19-9 appears to not be a sensitive marker of adenomyotic cyst.

In conclusion, larger adenomyotic cysts are rare, while small adenomyotic cysts of <5 mm in diameter have been detected in hysterectomy specimens. In addition, 70 cases of adenomyotic cyst have so far been reported in the literature. In the case of the present study, serum CA19-9 and CA125 levels were significantly increased, which has been rarely reported. Due to these laboratory test results, it was not possible to make a confident differentiation of benign vs. malignant tumors. The

ultrasound results and MRI suggested a diagnosis of a mass of uterine origin. In addition, the operation and pathology examination confirmed cystic lesions. However, additional case reports are required to further elucidate the pathogenesis and clinical characteristics of this rare disorder.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LZ substantially contributed to the conception or design of the work, as well as the acquisition, analysis and interpretation of data for the work. LS performed the experiments, analyzed the data and drafted the manuscript. FC made contributions to the analysis and interpretation of data. All authors checked and approved the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Medical Ethics committee of Northwest Women's and Children's Hospital (Xi'an, China; approval no. 21-039).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the details of her medical case and any accompanying images.

Competing interests

The authors have no competing interests to declare.

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