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Case Report

A radiological footprint equivalent to liquefactive necrosis observed in the course of disappearing liver metastases in rectal cancer: A case report and review of the literature [☆]

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ABSTRACT

A 72-year-old female diagnosed with rectal cancer treated with a surgical procedure was reported. As 3 liver metastases (LMs) appeared in multidetector CT, adjuvant chemotherapy using Bevacizumab combined with modified FOLFOX-6 was completed. LMs were changed to cystic lesions during the follow-up period, consistent with liquefactive necrosis. These cystic lesions that appeared in the course of disappearing LMs (DLMs) were identified by CT as homogeneous low signal intensity in hepatocyte specific Gd-enhanced MRI. This might be pathognomonic radiological footprint equivalent to liquefactive necrosis observed in the process of DLM and must be carefully followed in the course of radiological complete response. The radiological changing findings of LMs to cystic changes, high sensitivity of detecting DLM, and limitations of Gd-MRI might be meaningful to clinicians.

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Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide [1]. Almost one thirds of CRC patients had liver metastases (LMs), resulting in two thirds of their death [1]. Patients with CRC have incidence of LM in 25%-30% [2]. A 60-month overall survival (OS) in patients without and

with LM were reported 60.9% and 14.8%, respectively [3]. This might mean that LM seems an influential factor of OS in patients with CRC. Meanwhile, there have been cases where LMs disappeared after chemotherapy due to improved efficacy. The prevalence of DLM varies between 7 and 48% [4]. Conservative management of radiologically disappeared LM (DLM) resulted in 19%-74% local recurrence, mostly within 2 years [5]. The DLM is defined radiological complete response with no

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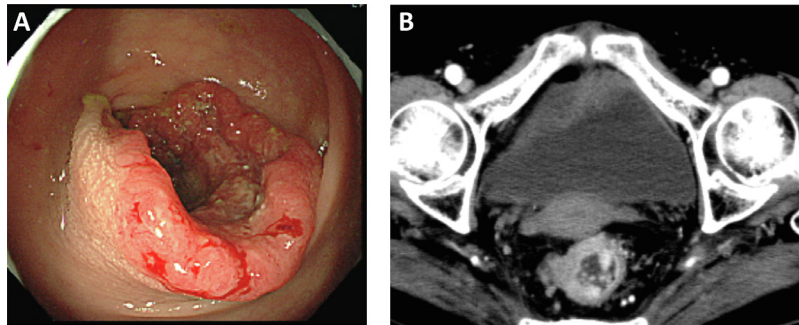


Fig. 1 – The picture of colonoscopy examination at rectum (Rb region) and enhanced-CT image at her first visit. (A) The colonoscopy pictures showed type II, mound (round wall) on whole circumference at 10cm orally from an anal verge. (B) The enhanced-CT of the rectum showed marked heterogeneous enhanced asymmetric colonic wall thickening with pararectal lymph nodes swelling.

recurrence radiological findings for two years [6]. The latest systematic review and meta-analysis of the accuracy of imaging modalities to predict complete pathological response of DLM concluded that intraoperative ultrasound (IOUS) and MRI using gadoxetate discodium (Gd-MRI) are the most preferred modalities, with pooled negative predictive value (NPV) of 0.79 (95% confidential interval (CI): 0.53-0.96) and 0.73 (95% CI: 0.58-0.85), respectively [7]. Without surgical intervention for patients with DLM from CRC, Gd-MRI seems the most reliable to confirm DLM. In this case report, we describe the unique radiological cystic changes and this change seems equivalent to the liquefactive necrosis observed in the process of DLM confirmed using Gd-MRI.

Case report

A 72 years old female presented at the emergency department with abdominal pain. An urgent colonoscopy showed a type 2 at 10cm orally from an anal verge with a mound existing in the whole circumference (Fig. 1). The pathologic examination of rectal mucosa revealed class V cytology, and the diagnosis of rectal cancer at Rb lesion was confirmed. The chest and abdominal contrast-enhanced computed tomography (CT) to investigate systemic metastases showed no lesions of the lung, liver and abdominal lymph nodes. On the 14th day after first visit to our hospital, she had undertaken Hartmann's operation, in which the surgical resection of the rectosigmoid colon with a closure of the anorectal stump and an end colostomy were created (Fig. 2). A pathological work-up of resected surgical specimen revealed moderately differentiated tubular adenocarcinoma with no metastases to 13 dissected regional lymph nodes. Pathological stage classification was determined as stage 2 with TMN classification of pT3 (SS), pN0, cM0 with microvascular invasions.

In DNA analysis using the surgical specimen to decide chemotherapy regimen, the result of RAS [KRAS and NRAS] mutation was positive. This meant that patient was

potentially resistant to inhibitors for anti-epidermal growth factor receptor (EGFR) mutation [1] and was eligible for Bevacizumab with FOLFOX-6 [4]. Due to RAS positive result, tailored adjuvant chemotherapy was used: intravenous Bevacizumab (Avastin Genentech Inc., San Francisco, CA) combined with modified FOLFOX-6 [levo-folinic acid, 5-fluorouracil, and oxaliplatin]. A total 8 biweekly cycles were completed (Fig. 2). The serial abdominal multidetector CT (MDCT) showed that 3 liver metastases were found 7 months after Hartmann's operation (Fig. 2, top line). These hepatic metastatic lesions scattered over 4 segments of the liver and seemed unresectable. The enhanced MDCT showed the contrast-enhancement effect at peripheral rings (Fig. 3A,3B). During the 10 weeks interval between the MDCT and subsequent CT images (Fig 3C,3D), 8 cycles of the abovementioned adjuvant chemotherapy had been completed. At the end of chemotherapy regimen, radiological sizes of ILMs had been decreased, and enhancement effect had disappeared (Fig. 3C,3D). At the 21st week after LMs were first discovered, three LMs had changed to cysts (Fig. 4A,4B). At 2 years and 9 months after LMs were identified, cystic lesions were no longer identified (Fig. 4C,4D). The Gadoteric acid - enhanced MR images (Gd-MRI) using hepatocyte-specific contrast media was added at this time because there could be latent residual metastatic areas despite that carcinoembryonic antigen (CEA) had shown no LMs. This Gd-enhanced MRI also showed cystic lesions without enhanced effect in the arterials phase (Fig. 5A, 5B, and 5C) and low-intensity in the hepatocellular phases (Fig. 5D, 5E, and 5F). From these MRI findings, cystic lesion at S3,4 was the same as previously seen (Fig. 4A, 4B, data, not shown), and no LMs were identified. As a conclusion from the results of MDCT and Gd-enhanced MRI work-up, DLM with rectal cancer and radiologic complete response were confirmed. These radiological changes were interpreted that cystic lesions of LMs were identified as disappearing liquefactive necrotic changes and might be a clinical pathognomonic sign of DLM.

During these radiological investigations between September 2015 and January 2022, the serum concentration of CEA as a tumor marker of HCC peaked in April 2016 (290 ng/mL). According to effective adjuvant chemotherapy, it decreased and

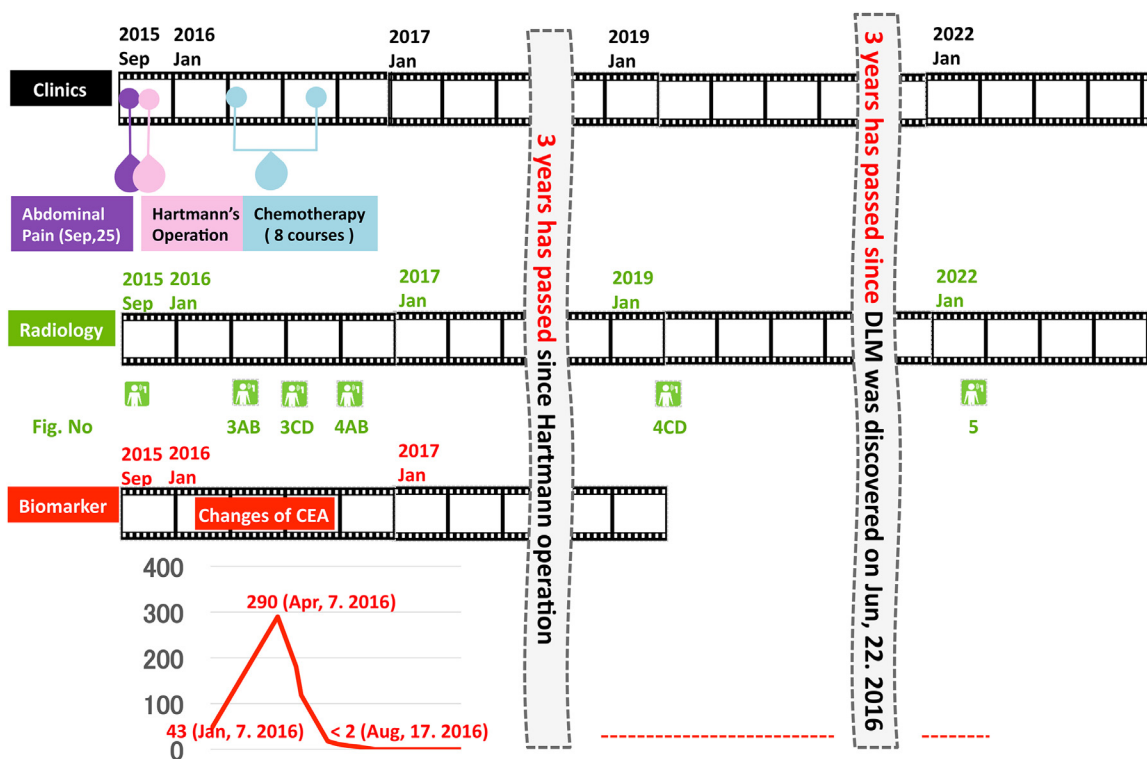


Fig. 2 – Timeline. Graphic illustration of the patient's calendar. Top line: events including symptom and treatments of operation and chemotherapy were plotted. Middle line: the time of x-ray exam for liver metastases including computed tomography (CT) and contrast-MR images (Gd-EOB-MRI) were shown. Bottom line: changes of serum carcinoembryonic antigen (CEA) as pathognomonic tumor marker of HCC were shown until Feb. 18, 2022.

remained at the lowest level for 306 weeks without elevations (<2.0 ng/mL) (Fig. 2, bottom line).

Discussion

According to the definition of DLM as a continuing radiological complete response (RCR) for at least two years [6], this case is diagnosed DLM from CRC, and this DLM status has continued for more than 5 years. We would discuss this case report from two viewpoints: (1) radiological footprint of liquefactive necrosis appearing in the process of DLM, and (2) as a radiological modality to identify DLM, a high sensitivity of Gd-enhanced MRI to diagnose RCR of DLM through liquefactive necrosis. To our knowledge, this is the first report of radiological changes resulting in DLM from CRC.

Radiological footprints equivalent to a Liquefactive necrosis observed in a process of DLM

Histological findings of LMs of CRC reveal dominant features classified into four groups: cellular, fibrotic, necrotic, and

mixed features. Meanwhile, MRI findings of LMs are classified into three categories, including rim, uniform, and variegate according to diffusion-weighted MRI (DW-MRI) features consistent with the high-intensity pattern of surrounding, uniform, and variegate, respectively [8]. Comparing the former pathological classification with the latter MRI findings classification, 68% had rim appearance, and 80% were necrotic, being the most common pathological patterns [8]. However, cystic lesions of the liver in our case, as seen in Gd-enhanced MR images, showed non-enhanced and homogenous low-signal intensity pattern. Comparing with the previously reported findings, DLM lesions disappeared completely, and cystic lesions were observed. These cystic lesions have been observed also in CT shown (Fig.3 and 4, images of cystic lesions were not shown). The cystic lesions observed in Gd-MRI were not necrotic changes but hepatic cyst. From this context, the course of DLM might not be visualized by enhanced CT images or hepatocyte-specific Gd-enhanced MR images and identified disappeared completely. In other word, as conclusion from the findings of enhanced CT and Gd-MR images, the liquefactive necrosis seen as cystic appearance is bound to disappear as a RCR [4,6].

From the standpoints of cell biology in CRC LM, tumor cells of CRC in the primary site escape into the bloodstream via a

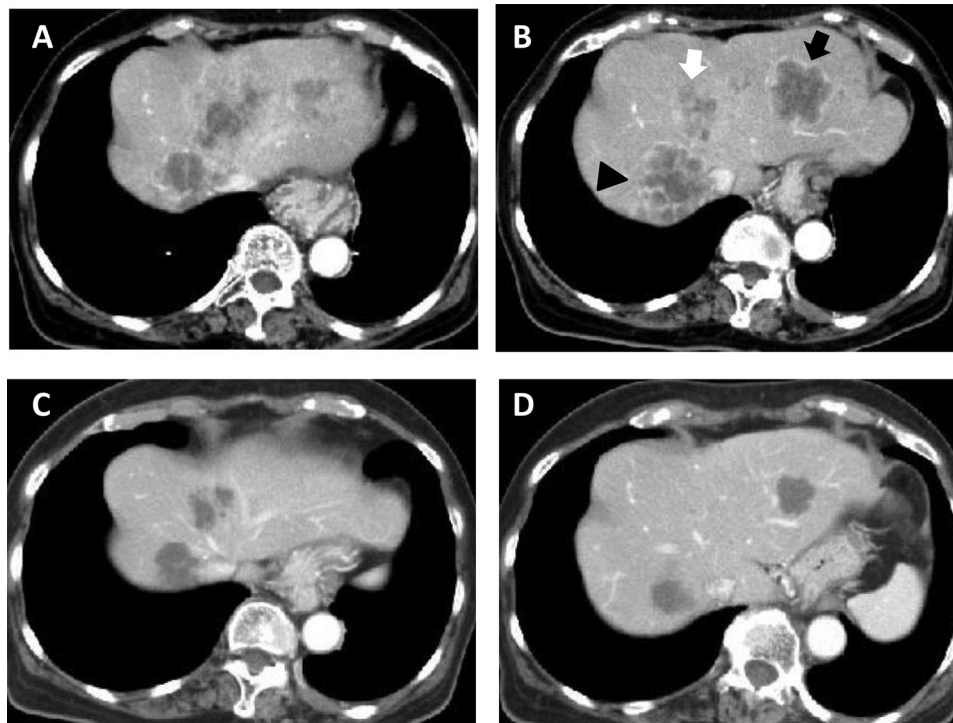


Fig. 3 – The enhanced-CT images 26 weeks and 36 weeks later since Hartmann’s operation. (A, B) (26 weeks after Hartmann’s procedure was performed: Apr. 7, 2016): The low-density metastatic areas were observed at S2-3 (black arrow), S4 (white arrow), and S7 (triangle) in the liver at 6 months after Hartmann’s procedure. All tumors were peripherally enhanced. (C, D) (10 weeks after time of Fig. 3A, 3B: Jun, 22, 2016): The metastasis of S4 was disappeared and regions of S2-3 and S4 showed homogenous low-density and no peripheral enhancement. The number and sizes of liver metastases were decreased.

portal circulation even in the rectum or systematic venous circulation and are lodged in the hepatic parenchyma [9]. The post-tumor invasion period (niche) consists of four phases: microvascular, pre-angiogenic, angiogenic, and growth phase [9]. These four phases in tumor invasion occur not in plates of hepatocytes but the hepatic parenchyma. Therefore, when anti-cancer agents are effectively cytotoxic, liquefactive necrosis is observed as cystic change in CT images in hepatic parenchyma followed by substituting of fibrosis. The liver atrophy observed in Fig. 3C and 3D could be explained by the fibrotic change that occurred after liquefactive necrosis. In summary, liquefactive necrosis is observed in the course of DLM. It disappeared, as the RCR, and is replaced by fibrotic tissues.

However, it was reported that RCR is not the same as pathological complete response (pCR) as one of the surgically resected 20 DLM sites was proved to be bile duct adenoma [10]. This might imply that RCR could not be identified identical to pCR. Furthermore, it is noteworthy that we could identify radiological change from contrast-enhanced at peripheral ring appearance to cystic before the disappearance of LMs and fibrosis. This cystic lesion is consistent with liquefactive necrosis and is a pathological finding.

High sensitivity of EOB-MR Imaging to diagnose radiological complete response of disappearing liver metastases through a Liquefactive necrosis

This case has been mainly followed by CT scan to identify RCR of disappearing tumors in the liver. However, in comparing the sensitivity of radiological modalities between CT and Gd-enhanced MRI to confirm DLM, Gd-MRI has been reported significantly higher in predictive positive value than that on contrast-enhanced CT scan (78.0% vs 35.2%, $P < .001$) [11]. Additionally, a meta-analysis also showed preferability of Gd-MRI to diagnose DLM with high NPV as mentioned in the introduction section [7]. This is why Gd-MR images was offered in this case to re-confirm the absence and disappearing of rectal cancer LM after chemotherapy. In comparing the recurrence of LMs or residual tumor, Gd-MRI seems superior to CT images. After radiological examination using CT and Gd-MRI, the recurrence rate was 31%-33% and 6%-11%, respectively [11,12]. However, radiologists and the other hepatological specialists must keep in mind that detectability of Gd-MRI is not 100%, and the recurrent rate of residual LMs has not been zero but remained 6%-11%, as shown before.

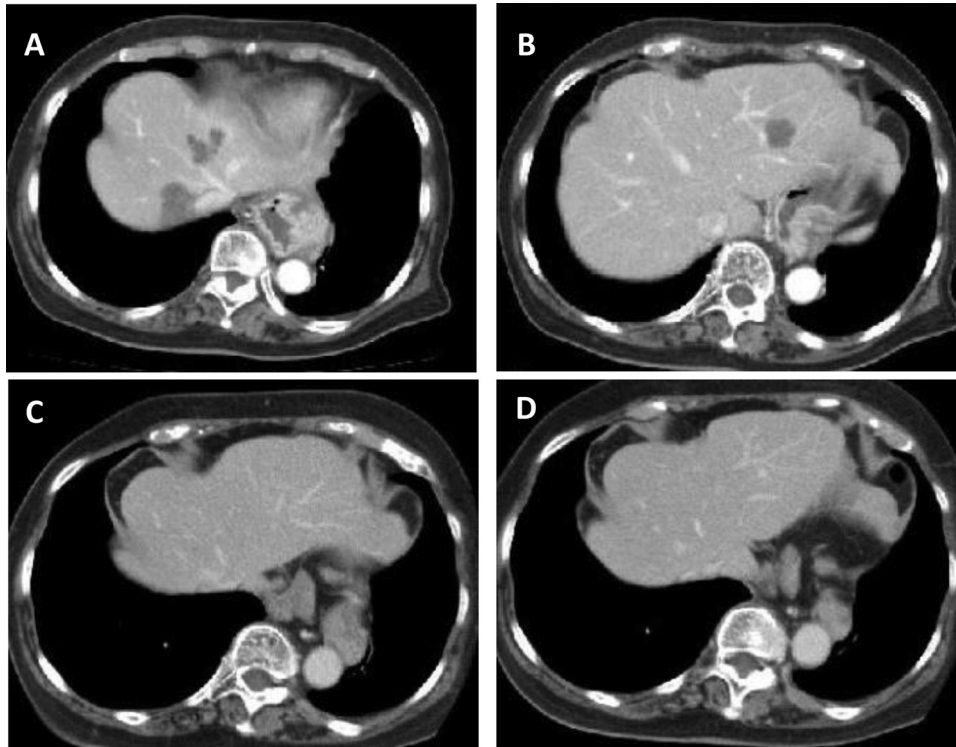


Fig. 4 – The enhanced-CT images 31 weeks and 2 7/12 years after liver metastases were first identified at [Fig. 3A, 3B](#). (A, B) (21 weeks after time of [Fig. 3C, 3D](#): Sep. 1, 2016): The liver metastatic lesions have changed to cystic and considered as “liquefactive necrosis”. (C, D) (2 9/12 years after [Fig. 3C, 3D](#): Mar. 4, 2019): All metastatic lesions had been disappeared. These disappearances of liver metastases were identified as disappearing liver metastases (DLM).

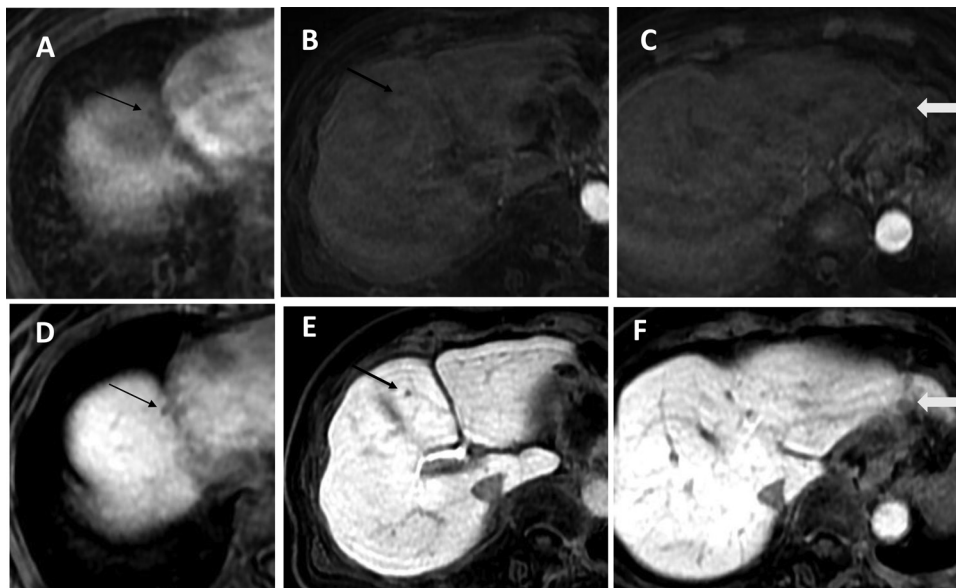


Fig. 5 – The Gd-EOB MR images (3 years after [Fig. 3C, 3D](#)). To confirm DLM by hepatocyte-specific contrast medium, EOB-MRI was taken 3 years after DLM was discovered by [Fig. 3C, 3D](#) (Feb. 18, 2022). The timing of MRI were the follows: A, B, C- 25 seconds after injection of Gd-contrast medium, arterial phases. D, E, F: 15 minutes after injection of Gd-injection, hepatocellular phases. In both phases, no liver metastases were identified and DLM was confirmed. In addition, in arterial phase, contrast-enhanced effect was not observed in cystic lesion at S3,4 segments. In hepatocellular phase, this cystic lesion showed low-intensity. Considering these findings of no enhancement and low-intensity at S3-4, S3,4 lesion seemed that no recurrence of hepatic metastatic lesion from rectal cancer and consisting cystic lesion were identified.

Chemotherapy often decreases hepatic parenchyma enhancement effect through steatosis, associated with 5-fluorouracil [13], or sinusoidal obstruction syndrome with oxaliplatin treatment [13]; both were used in our case. The mechanism through which the hepatocyte-specific agents enter the hepatic parenchyma during the hepatobiliary phase with high signal intensity [11] is radiologically observed as rib appearance. The necrotic process observed as central necrosis after chemotherapy is radiologically seen with peripheral high signal intensity shown as rim appearance. Although it was unclear what changes are followed from our observation, the homogenous low signal intensity seems to occur after rib appearance if LMs exhibit continuing disappearance. In other words, DLM led the healing process as homogenous low signal intensity through rib appearance, followed by necrotic changes spreading to peripheral direction seen as having a homogenous appearance. This radiological process in DLM might be of value in diagnosing DLM by Gd-enhanced MR imaging studies after chemotherapy and understanding the process of DLM.

Conclusion

A 72-year-old female diagnosed with rectal cancer treated with a surgical procedure was reported. As three LMs appeared in MDCT, adjuvant chemotherapy using Bevacizumab combined with modified FOLFOX-6 was completed. LMs were changed to cystic lesions during the follow-up period, consistent with liquefactive necrosis. These cystic lesions that appeared in the course of DLM were identified by CT as homogeneous low signal intensity in hepatocyte-specific Gd-enhanced MRI. This might be pathognomonic radiological footprint equivalent to liquefactive necrosis observed in the process of DLM and must be carefully followed in the course of RCR. The radiological changing findings of LMs to cystic changes, high sensitivity of detecting DLM, and limitations of Gd-MRI might be meaningful to clinicians.

Patient consent

Informed consent was obtained from the patient for the publication of this case report after her death. This case report was approved by the hospital ethic committee and the approval number was 22-03.

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