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A case of segmental hepatic necrosis complicating oxaliplatin and capecitabine chemotherapy: a case report and review of the literature

Chemotherapy is associated with different patterns of histopathological changes of the non-tumor-bearing liver. Hepatic infarction represents a relatively rare condition; the prevalence in several series of consecutive autopsies is 1.1%. To the best of our knowledge, no cases of liver infarction secondary to chemotherapy have been reported to date. We report a case of segmental hepatic infarction following the adjuvant chemotherapy with Oxaliplatin and Capecitabine in a patient who had undergone total gastrectomy and distal esophagectomy for gastric cancer. Liver infarction is usually managed by conservative therapy; interventional procedures such as percutaneous imaging-guided drainage or surgical evacuation should be reserved in cases where septic complications occur, with development of a hepatic abscess from the necrotic area. It is important to avoid misdiagnoses with liver metastases in order to define the most appropriate clinical management strategy.

KEY WORDS: Adjuvant chemotherapy, Gastric cancer, Liver infarction, Hepatic necrosis

Introduction

Chemotherapy is associated with different patterns of histopathological changes of the non-tumor-bearing liver [1]. Hepatic infarction is a rare condition and has a 1.1% prevalence in several series of consecutive autopsies [2]. To the best of our knowledge, no cases of liver infarction secondary to chemotherapy have been reported to date. Gastric cancer represents the third leading cause of cancer death [3]; even after a curative-intent surgical resection, relapse-related death remains a major issue [4] and hematogenous metastases from gastric carcinoma most commonly involve the liver [5]. We report a case of segmental hepatic infarction following the adjuvant chemotherapy with Oxaliplatin and Capecitabine in a patient who had undergone total gastrectomy and distal esophagectomy for gastric cancer. It is important to avoid misdiagnosis with liver metastasis in order to define the most appropriate clinical management strategy.

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Case Report

On July 2018, a 71-year-old Caucasian man was referred to our hospital complaining with gastric pain and received an upper gastrointestinal endoscopy; a 7cm tumor arising from the greater curvature of the gastric corpus was found. His past medical history was negative for significant pathology; his anamnesis was negative for drug allergy and/or use of drugs and alcohol. He also underwent a whole-body CT scan using a first-generation 640-slice CT scanner (Aquilion One, Toshiba Medical Systems, Japan), that showed the neoplasm arising from the greater curvature of the gastric corpus, measuring about 1.5x7cm, without signs of distant metastases (Fig. 1). On August 2018, he underwent total gastrectomy with distal esophagectomy, omentectomy, regional lymphadenectomy (D2) and reconstruction by Roux-en-Y anastomosis; the histopathological diagnosis was signet-ring gastric adenocarcinoma G3 and 13 lymphnodes were negative for metastatic disease (pT3 pN0 R0; stage IIA according to the 8th Edition of the TNM Classification).

After surgery, he was referred to the Department of Oncology and he underwent a whole-body CT scan using a first-generation 640-slice CT scanner (Aquilion One, Toshiba Medical Systems, Japan), that showed the esophago-jejunal anastomosis, without sign of residual disease and/or liver injury (Fig. 2A). Thereafter, between September 2018 and January 2019, he received adjuvant chemotherapy consisting of a modulated schedule of the XELOX® regimen, consisting of Oxaliplatin 120mg/m^2 on day 1 and Capecitabine 825mg/mq^2 twice a day for 14 days in a 21-days cycle [6]. During the first four cycles, he developed grade (G) 1 diarrhoea (according to Common Terminology Criteria for Adverse Events, CTCAE version 4.02), and his hepatic function was normal. On February 2019, 5 days after the fifth cycles of chemotherapy, he developed severe diarrhoea (G3 according to CTCAE), abdominal distension, fatigue and was admitted to hospital.

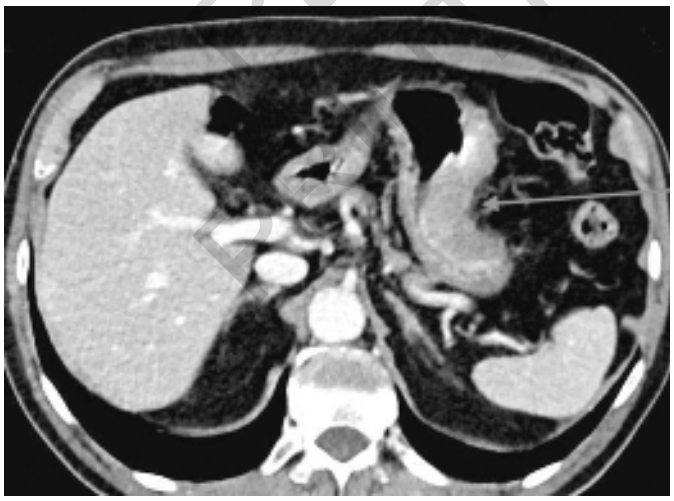

Fig. 1: Axial CT venous phase shows the irregular wall thickening in the greater curvature of the gastric corpus (red arrow) referable to the primary gastric neoplasm.

On physical examination he had moderate abdominal distension and bilateral pitting pedal edema; vital parameters were in the normal range. He received intravenous dexamethasone (8mg per day), loperamide (4mg orally three times per day), intra-venous sandostatin (100mg three times per day), intra-venous fluids (2.5 liters per day); diarrhea resolved completely within 2 days of therapy.

Blood tests showed elevation of serum alkaline phosphatase (ALP) (310 UI/ml – ULN, Upper Limit of Normality, 150 UI/ml), alanine aminotransferase (ALT) (41 UI/ml - ULN 35 UI/ml), direct bilirubin (0.61 mg/dl – ULN: 0.4 mg/dl), lactate dehydrogenase (LDH) (637 UI/L – ULN 450 UI/L); marked hypoalbuminemia (2.3mg/dL) and thrombocytopenia (platelets 62.500; G2 according to CTCAE). Laboratory tests for viral hepatitis A, B, C and E as well as cytomegalovirus and Epstein–Barr virus were negative. He underwent a whole-body CT scan using a first-generation 640-slice CT scanner (Aquilion One, Toshiba Medical Systems, Japan), that showed two hypoperfused, triangular, well-demarcated areas in the liver, extending toward the hepatic periphery, with normally enhancing, non-displaced vessels running through the otherwise low-attenuation lesions, without neither mass effect nor distortion of adjacent vessels; the lesions involved respectively V - VIII - I segments (11x6.5x10cm, LLxAPxCC) and II segment (3x3x3cm, LLxAPxCC) (Fig 2B). These lesions involved 35.7% of the liver parenchyma; widespread ascites and mild pleural effusion were also evident. CT-MIP (Maximum Intensity Projection) reconstructions help to demonstrate the patency of arterial (Fig 2C) and portal (Fig 2D) vessels. The patient underwent also a liver MRI using a 1.5T General Electric Medical System, that confirmed the presence of the liver lesions, showing homogeneously hypo-intense signal on SE T1-weighted images (repetition time [TR] 150ms; echo time [TE] 4.2ms), without signal intensity drop on the T1 opposed-Phase images (repetition time [TR] 110 ms; echo time [TE] 2.5 ms) compared to the In-Phase images (repetition time [TR] 110 ms; echo time [TE] 4.3 ms) (Figs. 2E, 2F), show slightly hyper-intense signal on TSE T2-weighted images (repetition time [TR] 2500 ms; echo time [TE] 88296 ms) (Fig 2G), hypoperfusion on 3D dynamic SE T1-weighted images (repetition time [TR] 4412 ms; echo time [TE] 1.6 ms) enhanced by gadolinium-diethylenetriaminepenta-acetic acid (16ml Multihance, 0.2 ml/kg) (Fig 2H).

These lesions were considered indicative of ischemic lesions because, according to the literature [2], proof of diagnosis of hepatic infarction is based on the coexistence of classic CT - MRI findings (geographic, low-

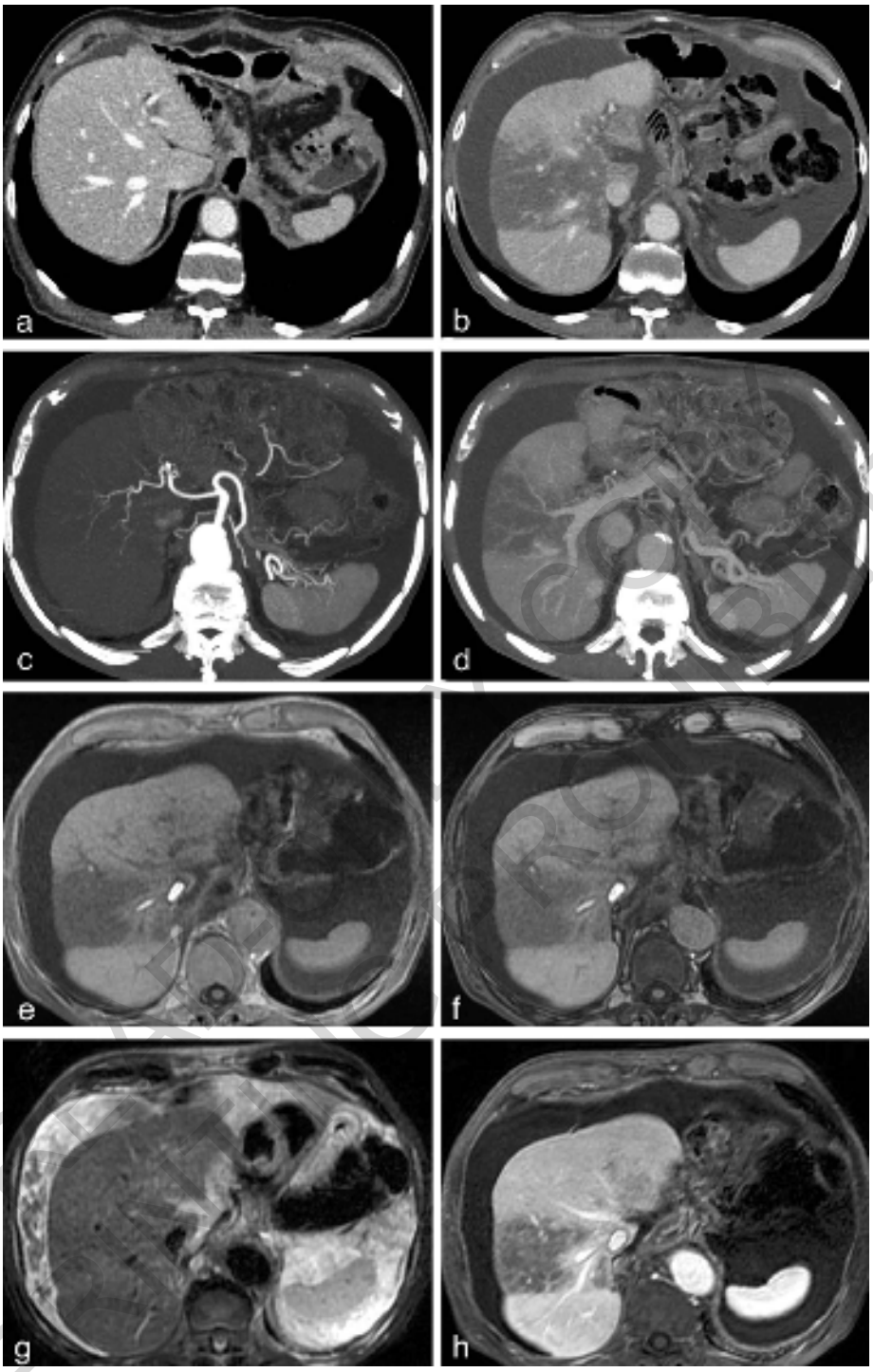

Fig. 2: Axial CT venous phase at 2 weeks after surgery (A); axial CT venous phase shows the appearance of wide hypoperfused areas involving respectively V – VIII - I and II hepatic segment after chemotherapy, with evidence of widespread perihepatic and abdominal effusion (B); axial CT-MIP reconstructions show regular patency of hepatic arterial (C) and portal (D) vessels; axial MRI images in-phase and out-phase showing no signal intensities drop (E, F); T2-weighted axial sequence shows slight, inhomogeneous hyperintensity in the affected areas (G); a wide, hypoperfused area is well evident in the venous-phase enhanced MR sequence (H).

attenuation perfusion defects without mass effect) seen in association with the following: acute increase in the serum alanine aminotransaminase level coinciding with the hepatic insult, normal CT or MR image of the liver before the hepatic injury, follow-up CT scan demonstrating the expected pattern of infarct evolution.

After ruling out all other possible causes of hepatic damage, the toxicity was more likely attributed to the

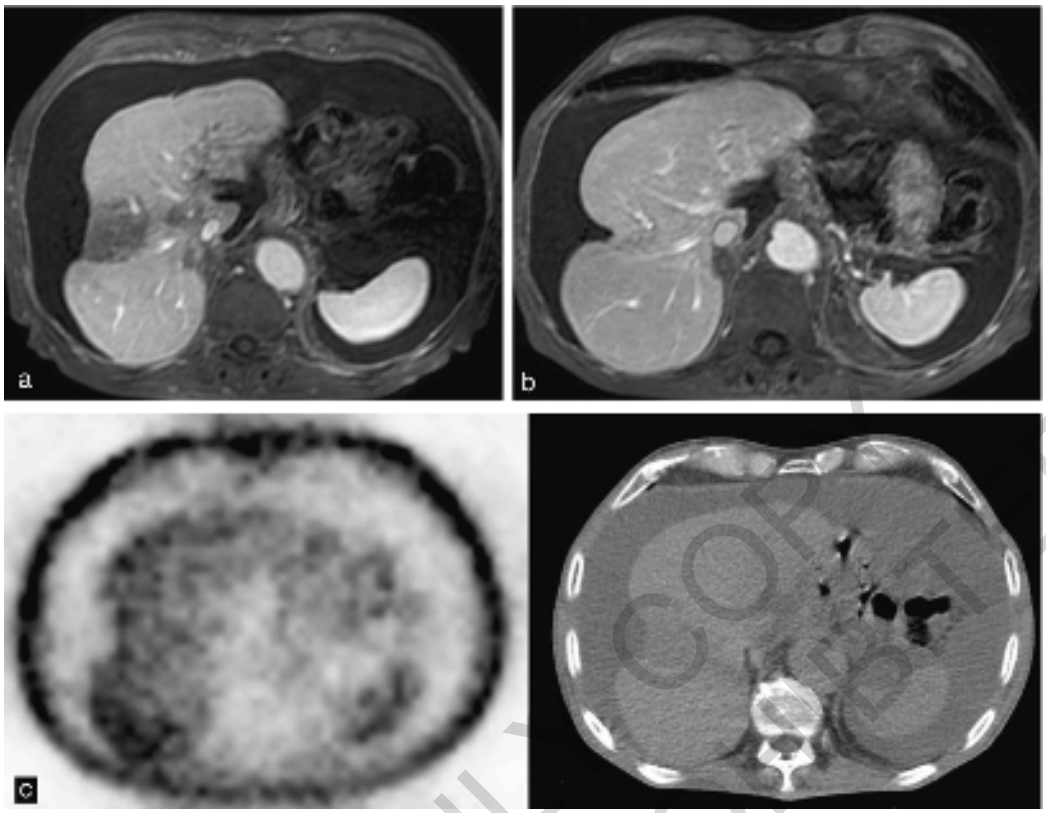

Fig. 3: Venous-phase enhanced follow-up MRI sequences show progressive reduction of the infarction size, with hepatic atrophy, capsular retraction and hypertrophy of the remaining parenchyma, on March 2019 (A) and November 2019 (B); CT-PET scan, on June 2019, did not show any pathological uptake (C)

chemotherapeutic regime and chemotherapy was discontinued; he received intra-venous albumin (10g albumin twice daily) and oral furosemide (20mg twice daily) from February 2019 to November 2019; since then, he has been receiving only oral furosemide (20mg twice daily). Elevated hepatic value and platelets count gradually improved and, on November 2019, they were in the normal range; mild hypoalbuminemia (3mg/dL) was still present.

He underwent repeated CT and MRI exams (on May 2019, Fig. 3A, and November 2019, Fig. 3B), that showed the expected evolution of the ischemic lesions: gradually decrease in lesions size with hepatic atrophy, capsular retraction and hypertrophy of the remaining parenchyma; ascites and pleural fluid gradually improved, and, on November 2019, only mild ascites is present. A FDG-CT-PET examination, performed on July 2019, did not show any pathological uptake (Fig. 3C). So far, in clinical and radiological follow-up, no local recurrence or metastases were observed.

Discussion

Gastric cancer ranks fifth among the most frequently diagnosed cancer and represents the third leading cause of cancer death, it is responsible for over 1.000.000 new cases in 2018 and an estimated 783.000 deaths (equating to 1 in every 12 deaths globally) [3]. Gastrectomy with regional lymphadenectomy (D2) is the curative-intent surgical treatment for all patients with gastric adenocarcinoma that fit to undergo surgery [3,7], as carried out on our patient. Even after a curative-intent surgical resection, relapse-related death remains a major problem [4]. In patients with stage II gastric cancer, as our patient, meta-analyses showed that post-operative adjuvant treatment is associated with a survival benefit [8], even if the systemic treatment is now increasingly moving to a pre-operative setting in locally advanced gastric cancer [4].

Hepatic infarction represents a relatively rare condition [2,9]; the prevalence in several series of consecutive autopsies is 1.1% [2]. Indeed, the liver's dual blood supply (furnished by the hepatic artery and, mainly, by the portal vein) and the extensive collateral pathways (from phrenic, intercostal and gastric arteries) is able to defend liver parenchyma from ischemic damage [2,9]. Liver infarction emerges from an insult either to the hepatic arterial supply or to both the hepatic arterial and portal venous systems, by events such as blunt abdominal trauma, thrombosis, embolism, surgical ligation, compression from tumor, hepatic arterial aneurysms o pseudoaneurysms, vasculitis such as polyarteritis nodosa [2, 9-14]. Nonocclusive

hepatic infarction can be observed in cases of systemic shock when blood flow to the hepatic artery is significantly reduced [9,14]. Liver infarction can be depicted as ischemic necrosis involving more than one hepatic lobule; these infarcts have gross and microscopic features similar to ischemic infarcts in other organs [15,16]. On CT, liver ischemia is defined as reduced or absent contrast enhancement during the portal phase with a severity of hypoperfusion, nonperfusion or necrosis [17].

Hypoperfusion is characterized by the reduction of contrast enhancement in the liver parenchyma and the presence of contrast enhancement in the intrahepatic vessels [17]. Nonperfusion is a complete absence of parenchymal and vascular contrast enhancement [17]. Necrosis encompasses all the criteria of nonperfusion together with the presence of air in the liver tissue [17]. The extension of ischemia is defined as segmental (involving an entire hepatic segment), partial (involving part of a segment) or marginal (ischemia limited to the resection margin) [17]. The lower attenuation is due to the fact that the infarcted area is not being perfused, since on pre-contrast scans the infarcted region is generally isodense with normal parenchyma [15]. CT and MRI diagnosis of liver infarction in our case was based on criteria previously employed [2]; indeed, our patient demonstrated the classic findings of a hypodense wedge-shaped non enhancing lesion extending to the capsule without mass effect and with enhancing non displaced vessels running through the otherwise low-attenuation lesions [18].

Oxaliplatin is a third-generation derivative of platinum (platinum compounds belong to a family of platinum, Pt) and belongs to the alkylating chemotherapy agents [19]. Oxaliplatin is one of the main chemotherapeutic agents currently used as a neoadjuvant/adjuvant treatment in gastric cancer, in combination with 5-fluorouracil (5-FU) (FOLFOX®) or capecitabine (XELOX®) [20,21]. It is mainly excreted through the kidney and does not undergo cyrochrome P450 hepatic metabolism [19].

Among the most frequent side effects related to oxaliplatin is peripheral neuropathy, isolated alteration of liver function tests, splenomegaly and thrombocytopenia [20, 22].

Chemotherapy is associated with different patterns of histopathological changes of the non-tumor-bearing liver [1.] The clinical presentation of chemotherapy-induced hepatotoxicity ranges from asymptomatic patients with increased liver laboratory tests, to overt hepatic injury and fulminant hepatic failure [23-26]. Diffuse chemotherapy-induced hepatopathy has been extensively evaluated in the radiological literature, and in the last two decades, the use of hepatobiliary contrast agents has helped to avoid misdiagnoses in the imaging of the tumor response after chemotherapy due to liver parenchymal changes [23]. On the other hand, focal chemotherapy-induced hepatopathy – which was earlier considered to be mainly a pathological diagnosis – is a relatively new challenge for radiologists because effective new chemotherapies have raised its occurrence on imaging and the focal features may simulate hepatic metastases [23]. A false-positive diagnosis of new hepatic metastases can lead to an inappropriate patient management with changes in the therapeutic strategy and unnecessary invasive procedures such as biopsies or surgery [23]. Hematogenous metastases from gastric carcinoma most commonly involve the liver because the stomach is drained by the portal vein [5]. On contrast-enhanced CT and MRI scans, liver metastases from gastric adenocarcinoma are hypovascular, show occasionally peripheral enhancement, demonstrate mass effect with distortion of adjacent vessels [5]. MRI imaging, especially with the use of hepatobiliary contrast agents and diffusion-weighted imaging, can be useful to properly evaluate these lesions thus preventing misdiagnoses [23]. FDG-CT-PET is the most sensitive non-invasive imaging modality for the diagnosis of liver metastases from gastro-intestinal cancers; FDG-CT-PET shows the hepatic metastases as areas with increased FDG uptake [26].

It is of paramount importance to be aware of chemotherapy-induced hepatotoxicity to prevent misinterpretations in the diagnosis of liver metastases and to select the most appropriated clinical management strategy [23]. Liver damage is defined as cholestatic when the ALP level is greater than 2 times the ULN or the ALT/ALP ratio is ≤ 2 [19]. Two major histopathological entities related to the use of chemotherapy can be defined: chemotherapy-associated steatohepatitis (CASH), with an incidence up to 85% of treated patients, and sinusoidal obstruction syndrome (SOS), with an incidence ranging from 19% to 52% of treated patients [1,19,27]. CT shows hepatic steatosis as reduced attenuation of the hepatic parenchyma and decreased tumor-to-liver attenuation during the portal venous phase; MRI shows fatty infiltration as areas with signal drop out on the opposed-phase image compared to the in-phase image [23]. Sinusoidal obstruction syndrome (SOS) appears on contrast-enhanced CT and MR imaging as patchy liver enhancement with a mosaic appearance, usually located in the peripheral parenchyma of the right lobe [23].

Segmental liver infarction has not been reported in previous articles neither with Oxaliplatin nor with Capecitabine. To the best of our knowledge, this is the first paper reporting a case of liver infarction following the chemotherapy with Oxaliplatin and Capecitabine.

Liver infarction is usually managed by conservative therapy; interventional procedures such as percutaneous imaging-guided drainage or surgical evacuation should be reserved in cases where septic complications occur, with development of a hepatic abscess from the necrotic area.

Conclusion

In the setting of a patient receiving chemotherapy with

Oxaliplatin and Capecitabine, the possibility of hepatic segmental necrosis should be considered and differentiated from metastatic disease and CT, MRI and FDG-CT-PET findings are useful in the differential diagnosis. It is important to avoid misdiagnoses with liver metastases in order to define the most appropriate clinical management strategy.

Riassunto

La chemioterapia è associata a diversi modelli di alterazioni istopatologiche del fegato non tumorale. L'infarto epatico rappresenta una condizione relativamente rara; la prevalenza in diverse serie di autopsie consecutive è dell'1,1%. Per quanto a nostra conoscenza, fino ad oggi non sono stati segnalati casi di infarto epatico secondario alla chemioterapia. Segnaliamo un caso di infarto epatico segmentario a seguito della chemioterapia adiuvante con oxaliplatino e capecitabina in un paziente che aveva subito gastrectomia totale ed esofagectomia distale per cancro gastrico. L'infarto del fegato è di solito gestito da terapia conservativa; procedure interventistiche come drenaggio guidato dall'imaging percutaneo o evacuazione chirurgica dovrebbero essere riservate nei casi in cui si verificano complicanze settiche, con sviluppo di un ascesso epatico dall'area necrotica. È importante evitare diagnosi errate delle metastasi epatiche al fine di definire la strategia di gestione clinica più appropriata.

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