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Elevation of CA 19-9 in Mirizzi Syndrome in the Absence of Malignancy: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 71-year-old
Final Diagnosis: Mirizzi syndrome
Symptoms: Epigastric pain • fatigue • jaundice
Medication: —
Clinical Procedure: Laparoscopic cholecystectomy
Specialty: Surgery

Objective: Unusual clinical course

Background: Mirizzi syndrome (MS) is relatively a rare condition; incidence rates may increment with age. It is characterized as an obstruction of the common hepatic duct (CHD) auxiliary to outward compression of an infected stone in the cystic duct.

Carbohydrate antigen (CA) 19-9 is a tumor marker that is usually related to upper-gastrointestinal malignancies. However, a few case reports have shown high levels of CA19-9 in the absence of malignancy. In this case, we report a case of a patient with MS, elevated CA19-9, and radiological findings suggesting gallbladder cancer, which shows the challenges of diagnosis and therapeutic procedures.

Case Report: We report the case of a 71-year-old Saudi man who presented to the emergency department with signs of obstructive jaundice. Magnetic resonance cholangiopancreatography (MRCP) revealed cholelithiasis, with a huge cystic duct stone compressing the CHD, resulting in mild intra-/extrahepatic biliary dilatation and positive MRCP pearl necklace sign for adenomyomatosis of the gallbladder. Serum tumor markers revealed raised levels of CA19-9 to 21 068 u/ml. The patient underwent laparoscopic cholecystectomy. Biopsy results confirmed the diagnosis of acute calcular cholecystitis and adenomyosis with no malignancy.

Conclusions: We report what can be considered a rare case of Mirizzi syndrome with a very high CA19-9 marker, in an elderly patient, in the absence of malignancy. This illustrates that Mirizzi syndrome and cholangiocarcinoma are difficult to distinguish, and the diagnosis is considered challenging. Thus, a high index of suspension must be kept in mind, especially in elderly patients, to rule out the cause of malignancy and thus to create an appropriate management plan.

Keywords: Carbohydrate Antigen 199, Human • Gallbladder Neoplasms • Mirizzi Syndrome

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/931819

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Background

Mirizzi syndrome (MS) is a generally uncommon condition with an incidence rate of less than 1% a year [1], it occurs in 0.1% of patients with gallbladder stones and in up to one-quarter of patients who undergo cholecystectomies. The incidence of MS increases with age, but its incidence appears to be roughly equal in males and females with gallstones [1]. MS is characterized as an obstruction of the common hepatic duct auxiliary to outward compression of an infected stone in the cystic duct [2]. MS is known for typical symptoms of abdominal pain in the right upper quadrant, associated with fever, and with or without jaundice. Hence, a few patients may exhibit atypical symptoms [3]. The most common clinical presentation is obstructive jaundice (60-100%), related with right upper-quadrant abdominal pain in from one-half to nearly all of patients and fever, whether the patient is known or suspected to have gallstone disease [1]. Gallstone ileus has been reported in Mirizzi syndrome [1]. Less common presentations can range from totally asymptomatic to acute pancreatitis, gallbladder perforation and weight loss, and malignancy [2].

The diagnostic assessment of MS is affirmed by either computed tomography (CT) scan or magnetic resonance imaging (MRI), as well as by surgery with tissue examination [4]. Endoscopic retrograde cholangiopancreatography (ERCP) may be considered in patients who cannot tolerate surgery. It has been proposed that using one or more biliary plastic stents utilizing ERCP can clarify the method by acting protecting the CBD [4]. ERCP has value in determining the presence of a fistula [4], and it helps relieve jaundice and obstruction and permits elective procedures [4].

Carbohydrate antigen 19-9 (CA19-9) is a tumor marker [5] commonly found on pancreatic and biliary duct cells [6]. It is typically related to pancreatic cancer [5] but can relate to other tumors, such as biliary and gastric carcinoma [6]. Our literature review uncovered several studies in which patients were diagnosed with MS complicated with malignancy [7,8]. However, few cases have been reported of patients who presented with high levels of CA19-9 in the absence of malignancy [5,9]. Little is known about it. Here, we report a case of a patient who presented with obstructive jaundice, elevated CA19-9, and radiological findings suggesting gallbladder cancer, which outlines the challenges of diagnosis and therapeutic procedures.

Case Report

History

A 71-year-old Saudi man presented to the emergency department in October 2020 reporting epigastric pain and discomfort, heartburn, nausea, and fatigability for 4 days. He reported signs of obstructive jaundice. He had a history of fever for 2 weeks, with weight loss and loss of appetite for 1 month. At the time of examination, the patient was asymptomatic. His medical history was unremarkable apart from benign prostatic hyperplasia and pulmonary embolism 6 years ago, and had not been on anticoagulants.

Physical Examination (PE)

The patient was vitally stable, conscious, alert, and oriented. He was ambulatory. The examination was unremarkable, other than the presence of jaundice.

Investigations and Imaging

The patient was admitted under the medical team first to manage his obstructive jaundice. Laboratory workup on admission revealed C-reactive protein (CRP) of 38.35 mg/L (normal range 0-3.0 mg/L), alkaline phosphatase (ALP) of 210 U/L (normal range 40-129 U/L), direct bilirubin of 8.57 mg/dL (normal range 0-0.2 mg/dL), total bilirubin of 11.12 mg/dL (normal range 0.146-1.4 mg/dL), aspartate aminotransferase (AST) of 65.1 U/L (normal range 0-40 U/L), and alanine aminotransferase (ALT) of 94.1 U/L (normal range 0-40 U/L). Complete blood count, creatinine, and serum electrolytes were within normal range. Serology results of hepatitis B and C and HIV were negative.

Tumor markers revealed a markedly elevated level of CA19-9, reaching 21 068 u/mL. The diagnosis of gallbladder cancer and Mirizzi syndrome were kept in mind. Thus, imaging was ordered.

Regarding radiology imaging, a CT scan of the abdomen and pelvis was done and showed a common bile duct (CBD) stone compressing the common hepatic duct (CHD) and causing dilatation of the intra- and extrahepatic ducts (**Figure 1**). MR pancreas (**Figure 2**) and MRCP (**Figure 3**) both showed a segmental gallbladder adenomyomatosis with cholelithiasis. There was positive MRCP pearl necklace sign for adenomyomatosis of the gallbladder with (Okitansky-Aschoff sinuses. A large cystic duct stone was compressing the CHD, resulting in mild intra-/extrahepatic biliary dilatation (Mirizzi syndrome). Gastric endoscopy was done, and it was unremarkable.

Timeline of Therapeutic Intervention

In November 2020, ERCP was done for the patient to examine CBD, showing a slightly dilated cystic duct, with hugely dilated intrahepatic ducts and intrahepatic radicles. In addition, a 9-cm plastic stent was placed to relieve the cholestasis (**Figure 4**). After ERCP, he was started on antibiotics for 1 week and he was scheduled for elective surgery.

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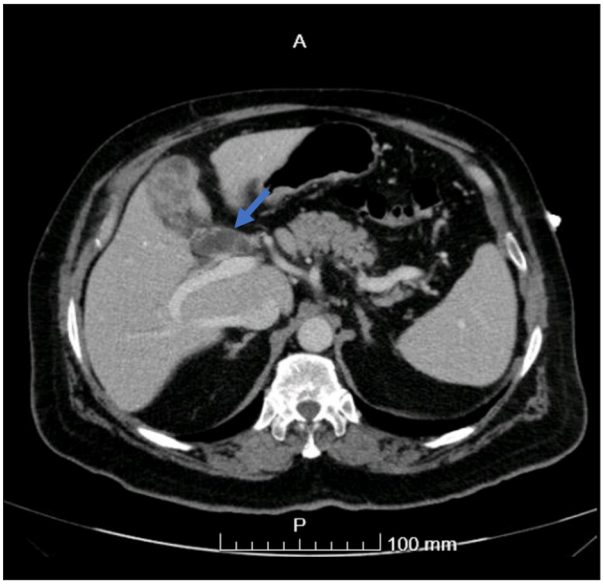

Figure 1. CT scan of the abdomen and pelvis showed CBD stone (arrow) compressing the CHD.

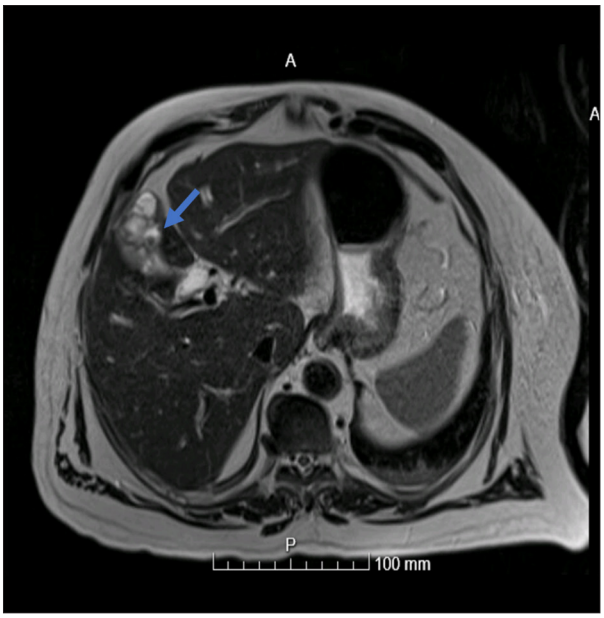

Figure 2. MR pancreas showed positive pearl necklace sign (arrow) for adenomyomatosis of the gallbladder.

An abdominal ultrasound after ERCP revealed chronic acalculous cholecystitis (a known case of gallbladder adenomyomatosis), with in situ biliary stent and dilated CBD.

The patient was seen 3 times preoperatively by the surgical team. His cholestatic parameters were falling, especially direct bilirubin levels (normal range 0-0.2 mg/dL) (20.23→0.67 mg/dL), total bilirubin levels (normal range 0.146-1.4 mg/dL) (21.17→0.94), ALP (normal range 40-129 U/L) (184.2→77.8 U/L), and GGT (normal range 10-71 U/L) (95→89 U/L) after CBD stent insertion

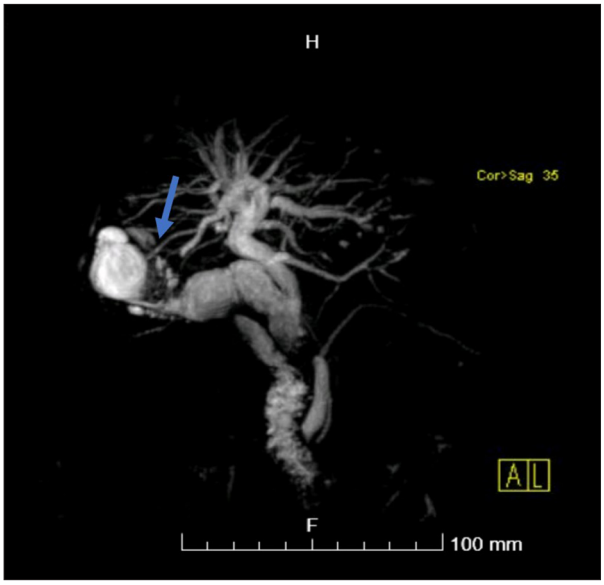

Figure 3. MRCP imaging showed positive pearl necklace sign (arrow) for adenomyomatosis of the gallbladder.

via ERCP. In addition, the CA19-9 level declined significantly from 21 068 u/ml to 52 u/ml after stent insertion.

Operation

The patient underwent laparoscopic cholecystectomy in January 2021. He was given cefuroxime as a prophylactic dose preoperatively. The patient put was under general anesthesia. Ports and insufflation of gas were done in the usual manner. The diagnostic laparoscopy showed a strongly inflamed gallbladder with omental adhesions and inflammation of the whole hepatoduodenal ligament.

Then, the gallbladder was retracted in cephalic direction toward the right shoulder and exposure of the Calot triangle, which was dissected meticulously. After gaining a window laterally and medially, we started with the fundus' first approach and mobilized the bladder. Then, we performed retraction of gallbladder laterally and made an incision of the infundibulum. A Fogarty catheter was inserted, and an impacted stone was removed.

We used an EndoGIA purple 45-mm load. Hemostasis was checked and ensured. Retrieval of specimens was performed with an Endobag. Closure of the fascia and skin was done in a similar manner.

The patient was transferred to a post-anesthesia care unit (PACU) in stable condition. Then, he was shifted to a standard surgical ward in a stable condition. A collection of patient gallbladder tissues was taken for histopathology. He was placed postoperatively on enoxaparin 40 mg SC once daily, fluids,

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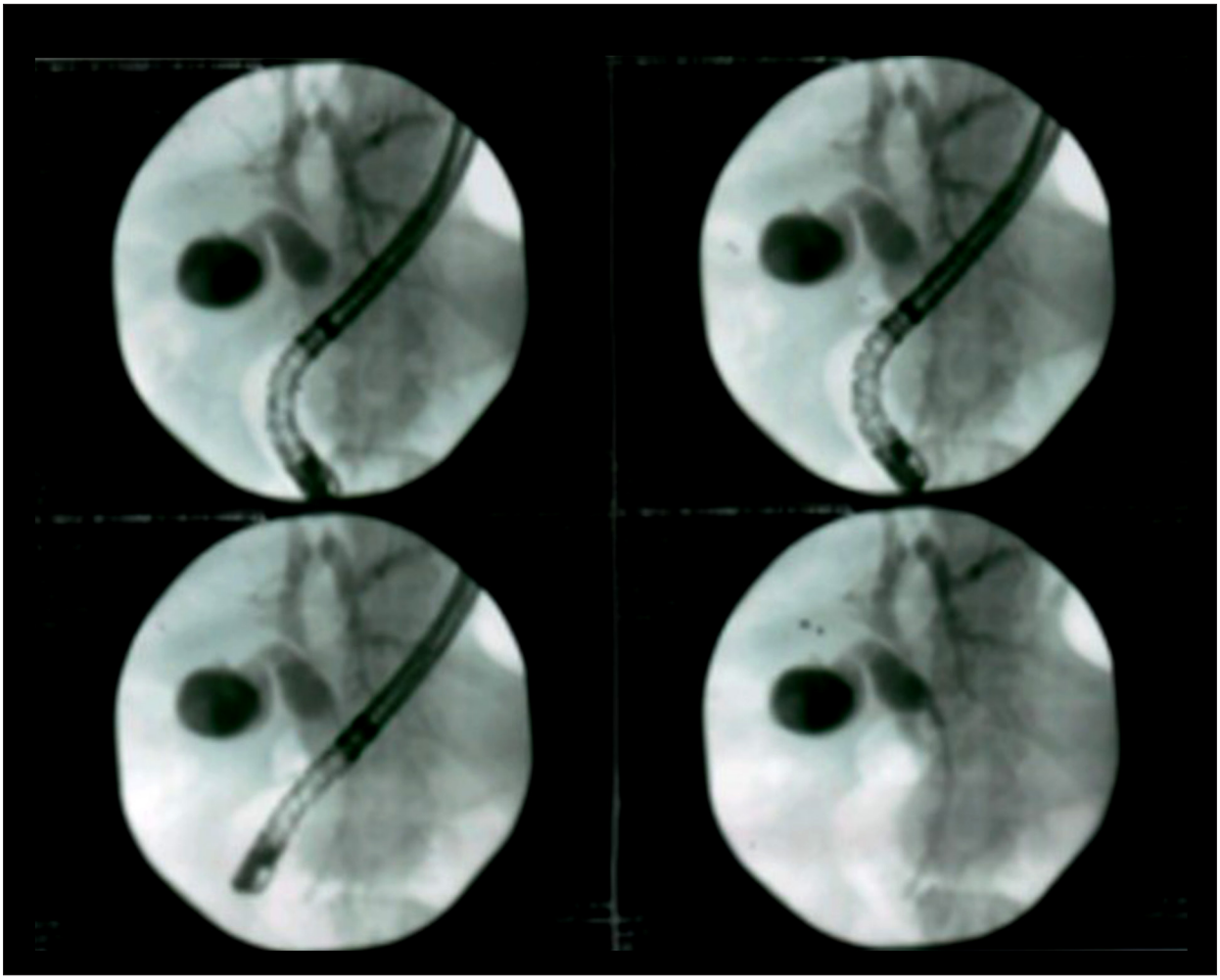

Figure 4. ERCP imaging showing a stent in CBD.

analgesia (paracetamol, pethidine), omeprazole, and cefuroxime 1500 mg BID. Antibiotics were given for 2 days in the hospital due to the presence of severe inflammation and adhesion intraoperatively and antibiotics.

Post-laparoscopic cholecystectomy laboratory investigations revealed a CRP of 47.05 mg/L (normal range 0-3.0 mg/L), WBC of 13×10^3/uL (normal range 4.5-11×10^3/uL), hemoglobin of 13.4 g/dL (normal range 12.6-17.4 g/dL), ALT of 70.6 U/L (normal range 0-40 U/L), AST of 72.2 U/L (normal range 0-40 U/L), ALP of 59 U/L (normal range 40-129 U/L), total bilirubin of 0.99 mg/dL (normal range 0.146-1.4 mg/dL), and direct bilirubin of 0.42 mg/dL (normal range 0-0.2 mg/dL). The patient was discharged on the second day postoperatively in a stable condition.

Biopsy results showed the intact gallbladder measured 5.2×2.6×1.6 cm, the serosa was reddish-brown, serial cut sections showed the mucosa was reddish-brown and rough, the wall thickness ranged from 0.3 cm to 0.7 cm, and the gallbladder contained 3 black stones.

Microscopically, it showed that the gallbladder wall was thickened, with transmural chronic inflammation, hemorrhage, fibroblast proliferation, partial mucosal ulceration, and adenomyosis. It was negative for malignancy. Thus, the diagnosis was acute calcular cholecystitis, and adenomyosis was performed.

Follow-up and Outcomes

At the last follow-up, the patient was doing well, tolerating oral intake, and resuming normal bowel habits. He was not jaundiced. Physical examination revealed a soft and lax abdomen, with clean wounds. He underwent ERCP and removal of the CBD stent 6 weeks postoperatively, where multiple stones were removed; a large one in the CBD could not be removed, and another stent was inserted. He was placed on ursodeoxycholic acid 250 mg once daily and is scheduled for removal of the stent after 2 months.

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Discussion

As mentioned above, (MS) is a benign, rare complication of cholelithiasis. Mirizzi syndrome affects the cystic duct or neck of the gallbladder and is defined as the impaction of gallstones in the common bile duct or common hepatic duct. It can cause hindrance, inflammation, and fistula formation [6].

There are different classifications of Mirizzi syndrome. The most recent one was by Csendes et al [10] who included a further type to the classification, which was approved by Beltran in 2012 [11]. It is partitioned into 5 types [11]. Type 1 is external compression of the bile duct by a stone found in the cystic duct of the infundibulum of the gallbladder. Types 2 and 3 are cholecystobiliary fistula including less than 1/3 and up to 2/3 of the circumference of the bile duct, respectively. Type 4 is a fistula with complete bile duct obstruction. Type 5 is any type of Mirizzi with cholecystoenteric fistula.

Interestingly, few studies have explored the association between aggressively high CA19-9 levels and MS [6]. Carbohydrate antigen 19-9 (CA19-9) is a tumor marker that is a mucinous glycoprotein used in the diagnosis of upper gastrointestinal malignancies, generally pancreatic, biliary, gastric colorectal, and lung carcinoma, and is utilized as a prognostic factor for follow-up. Other non-cancerous conditions that can cause high CA19-9 levels include gallstones, cholangitis, and jaundice. The higher acceptable typical level of CA19-9 is 37 U/mL [5,6]. High levels of CA19-9 greater than 1000 U/ml are a very specific and considered a marker for malignancy [8,12]. A previous study suggested that a significantly higher level of CA19-9 among patients with MS can be associated with gallbladder malignancies [8], but it may occur in rare benign conditions with a level of more than 1000. Moreover, MS can mimic gallbladder cancer and vice versa [13].

There are few cases reported of high levels of CA19-9 due to MS with no evidence of malignancy. In this case, a high level of CA19-9 up to 21 068 U/mL was noticed secondary to MS. Important discoveries were reported in 2015, when a 68-year-old woman with a level of CA19-9=23996 U/mL was reported [14]. In addition, in Brazil in 2012, an 83-year-old woman had a level of CA19-9=24 480 U/mL [12]. An extremely high level was reported by Principe el at in a case of MS with serum CA19-9 coming up to 35 000 U/mL [7]. Lower values also have been noticed in the United State in 2017 in a 51-year-old man with MS and a history of alcohol abuse with serum CA 19-9 level of 4618 U/L [6]. Furthermore, in 2014, a 51-year-old man presented with a CA 19-9 level was elevated at 4258 U/ml [15]. All these cases shared the same outcome, in which the level of CA19-9 improved after relieving the obstruction and there was no malignancy.

High levels of CA19-9 cannot be applied alone to detect the presence of malignancy mostly in benign complex conditions of the biliary tract [12]. By understanding this information, we can avoid unnecessary invasive diagnostic workup [6]. CA19-9 levels need to be interpreted carefully as they can be raised beyond the malignancy cut-off level, contributing to false readings and prediction [14].

As explained previously, the diagnosis of MS is affirmed by CT or MRI followed by tissue examination [4]. CT scans can assess the gallbladder and measure the wall thickness and bile duct dilatation. Periductal inflammation can be mistaken for gallbladder cancer. The primary advantage of CT is the exclusion of malignancy in the porta hepatis region or in the liver [1]. MRCP is a valuable instrument for illustrating bile duct extrinsic compression and for evaluating whether a fistula is present. Furthermore, it is advantageous to rule out choledocholithiasis and certain other causes of obstruction of the bile duct. MRCP may describe some typical characteristics of MS, such as the extrinsic narrowing of the common hepatic duct, gallstones in the cystic duct, intrahepatic and common hepatic duct dilatation, and normal choledochus. In addition, MRI can demonstrate the degree of the inflammatory process surrounding the gallbladder. MRCP can diagnose Mirizzi syndrome with an accuracy reaching 50% [1].

ERCP is an invasive procedure, both diagnostic and therapeutic. It validates the occurrence of MS with or without cholecystobiliary or cholecystoenteric fistulas. Moreover, it permits stone extraction, stent placement, and sphincterotomy. Utilizing ERCP, the diagnostic accuracy of MS reaches 55% to 90%, with a failure rate varying from 5% to 10% [1]. It is recommended to perform an ERCP in conjugation with placement of a biliary plastic stent to ease the surgical operation by ensuring the CBD. Additionally, the direct ERCP cholangiography contributes to making the correct diagnosis, which was obvious in our case as well as in other reported cases [4]. In respect to the intraoperative diagnosis, more than half of patients with MS are diagnosed during surgery [1].

Conclusions

CA19-9 can aid in the diagnosis of digestive malignancy, such as in pancreatic, biliary, and gastric carcinoma. It is also noted to be elevated in cases of inflammation, particularly in obstructive jaundice cases, because it can occur without proven malignancy, as illustrated in this case of Mirizzi syndrome. Hence, it must be interpreted cautiously, alongside the patient's medical history, physical examination, additional labs, and imaging studies. Biliary disease improvement will decrease CA19-9 levels as soon as the offensive agent is ceased, as in this case of obstruction by a stone.

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This elderly patient had what can be considered a rare case of MS in which the biliary obstruction was found to be associated with a very high CA19-9 marker in the absence of malignancy, similar to a few published cases. Being mindful that high CA19-9 levels can be present without the presence of malignancy can prevent unnecessary invasive diagnostic workups.

Acknowledgment

We would like to thank the patient, who approved for his case to be published for medical advancement.

Conflicts of interest

None.

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