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A Case of Cholangiocarcinoma with Markedly Elevated Serum CA199 as the Initial Symptom

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Abstract: This report presents a case of intrahepatic cholangiocarcinoma (ICC) initially manifested by a significant elevation of serum CA199. The patient, a middle-aged male with a history of hypertension, renal disease, and renal transplantation, exhibited no typical clinical symptoms but was found to have a persistently elevated CA199 level during follow-up (from 218.6 U/mL to 4000 U/mL). Early imaging studies showed no obvious signs of tumor, but subsequent MRI revealed a nodule in the left lobe of the liver. Postoperative pathology confirmed moderately differentiated cholangiocarcinoma (pathological stage IA). The CA199 level significantly decreased after surgery and gradually returned to normal. This case suggests that persistent isolated elevation of CA199 may be an important indicator of early cholangiocarcinoma, and malignancy should be highly suspected, especially after excluding false positives. Combining imaging and pathological examinations is crucial for the early detection of cholangiocarcinoma, which can effectively improve patient prognosis.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from the secondary bile ducts within the liver and is the second most common primary malignant tumor of the liver. In recent years, its incidence has been increasing annually, accounting for about 10-15% of all primary malignant tumors of the liver [1]. Biliary cancer often shows no obvious symptoms in the early stages, and clinical manifestations are generally non-specific; most patients are diagnosed at an advanced stage. Currently, the diagnosis of biliary cancer is primarily based on a combination of clinical, radiological, biochemical, and histological analyses for final confirmation [2]. This study retrospectively analyzed the clinical data of one patient with biliary cell carcinoma who had significantly elevated serum carbohydrate antigen 199 (CA199).

2. Analysis of Data

The patient's past physical condition was average. There is a history of hypertension and kidney disease; two years ago, the left eye surgery was performed due to "hyperthyroidism," and one year ago, "left upper limb arteriovenous fistula reconstruction surgery" was performed. Six years ago, the patient underwent kidney transplantation surgery, with postoperative urine output being normal and renal function recovered well. One year ago, the patient found that CA19-9 was elevated, with

the carbohydrate antigen CA19-9:218.6↑U/mL. After completing gastrointestinal endoscopy and abdominal enhanced CT scans, no obvious tumor was found, and the patient was discharged, advised to recheck tumor markers within one month, and to undergo a full-body PET-CT if necessary. One month ago, during a follow-up at a local hospital, the patient found that CA19-9 had risen to 4000U/mL, with no abdominal distension, abdominal pain, or other discomforts. The patient has no history of diabetes, heart disease, stroke, or acute myocardial infarction; no history of tuberculosis, viral hepatitis, or other infectious diseases; has a habit of drinking alcohol for 20 years, but has quit for 2 years. The patient has a smoking habit, smoking 20 cigarettes per day for 20 years, but has quit for 2 years. The patient has no history of exposure to toxins or radioactive substances. The patient now seeks further treatment at our hospital and is admitted for "follow-up examination after transplant surgery."

Table 1 Preoperative tumor marker test results of the patient.

Test Items	Test Results	Reference range
Carbohydrate Antigen 72-4(CA72-4)	4.5	<7.0 IU/ml
Carbohydrate Antigen 19-9(CA19-9)	3112.7	≤43.0 U/ml
Carbohydrate Antigen 125(CA125)	8.6	≤24.0 U/ml
Total Prostate Specific Antigen(TPSA)	0.787	<4.0 ng/ml
Cytokeratin 19 fragment 21-1(CYFRA21-1)	1.6	<3.3 ng/ml
Neuron-specific enolase(NSE)	13.4	<30.0 ng/ml
Carcinoembryonic Antigen(CEA)	2.5	≤5.0 ng/ml
Alpha-Fetoprotein(AFP)	1.1	≤7.0 ng/ml
Ferritin(Fer)	109.7	27.0-375.0 ng/ml
Free Prostate Specific Antigen(fPSA)	0.23	<1.0 ng/ml
Carbohydrate Antigen 242(CA242)	65.9	<20 U/ml
Carbohydrate Antigen 50(CA50)	141.62	≤25 U/ml

The patient was found to have elevated carbohydrate antigen CA19-9 on May 18,2023, and there was a trend of continuous elevation during subsequent monitoring (see Table 1). On May 18,2023, the male patient's 10 tumor markers (AFP + CEA + CA19-9 + CA125 + TPSA + FPSA + CA724 + NSE + FERR + CY21-1) showed: carbohydrate antigen CA19-9218.6U/mL. An abdominal enhanced CT scan revealed no significant tumor, and the patient was advised to recheck tumor markers within one month, with a full-body PET-CT if necessary. On August 7, 2023, a PET scan detected slightly hypermetabolic small nodules in the medial segment of the left lobe of the liver, but no clear abnormal density changes were seen on the corresponding CT. Please combine with an enhanced MR scan to rule out lesions. On August 20,2023, a liver and gallbladder MR scan without contrast (using Praxair) followed by enhancement (1.5T): a small nodule near the hepatic fissure in S3 of the liver, suspected inflammatory granuloma or hepatic hemangioma? Follow-up is recommended; slight abnormal perfusion in the liver. On August 21,2023, liver, gallbladder, spleen, and pancreas: multiple polyps in the gallbladder and a suspicious small nodule in the left lobe of the liver. On March 19,2024, after admission, tumor marker tests showed: carbohydrate antigen CA19-93112.7U/mL, significantly higher than before. The laboratory used 25% PEG precipitation, resulting in a final value of 3135.75 with a recovery rate of 100.7%, preliminarily ruling out heterophilic antibody interference. Further tests included carbohydrate antigen CA242:65.9U/mL,CA50:141.62U/mL (see Figure 1). 2024-03-22 Liver and Gallbladder MR Plain Scan with Contrast (Prismavid) Enhancement (3.0T): 1. Nodules near the hepatic fissure in S3, larger compared to August 2023, suspected to be a tumor, possibly cholangiocarcinoma. Further biopsy is recommended to confirm the nature of the lesion. 2. Minor abnormal perfusion within the liver. 2024-03-21 CT Full Abdomen Plain Scan with Enhancement: Nodules in S3, combined with

the increase in the lesion on August 2023 MR image, suggesting a possible tumor. Abnormal perfusion in the left lobe of the liver during arterial phase.

The patient underwent partial hepatectomy and laparoscopic cholecystectomy. Postoperative pathology (see Figure 2) revealed: tumor size: 2.0cm*2.0cm*1.5cm, solitary: 2.0 cm; primary diagnosis: moderately differentiated cholangiocarcinoma. Histological type of tumor: intrahepatic cholangiocarcinoma: small bile duct type, differentiation grade: moderately differentiated; pathological stage: IA, T1aN0M0. Special staining: 2024003291-3: D-PAS (-), PAS (-), trichrome (masson) (+), iron stain (-), copper stain (-), reticulum stain (+). Immunohistochemistry: CA199 (+), CEA (slightly +), CK19 (+), CK20 (-), CK7 (+), Her-2 (1+), KI67 (30%+), MLH1 (+), MOC31 (+), MSH2 (+), MSH6 (+), P53 (no significant mutation), PD-1 (-), PMS2 (+), CDX2 (partially +). The patient was discharged one week postoperatively and had a follow-up serum CA199:944.9U/mL test. One month postoperatively, serum CA199:216.4U/mL was significantly reduced compared to preoperative levels, and CA199 concentration returned to normal more than two months postoperatively; CA242:11.17U/mL,CA50:24.41U/mL has returned to normal levels.

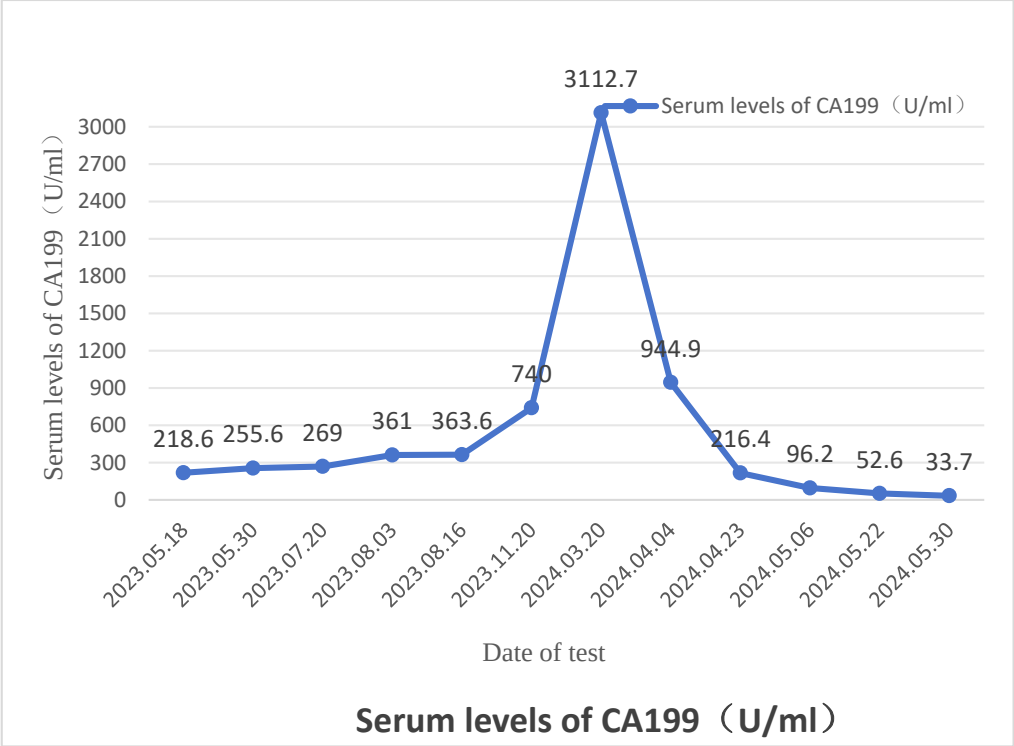
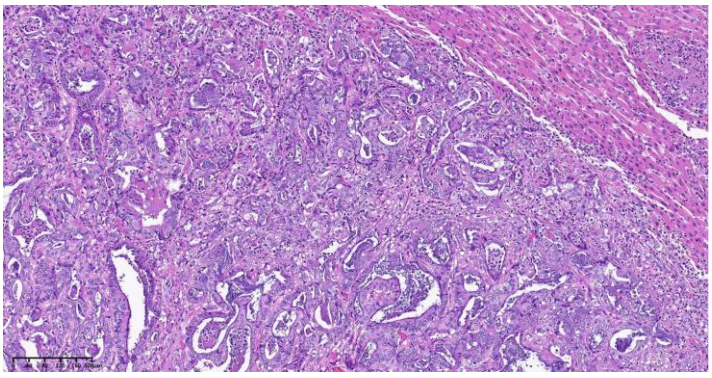
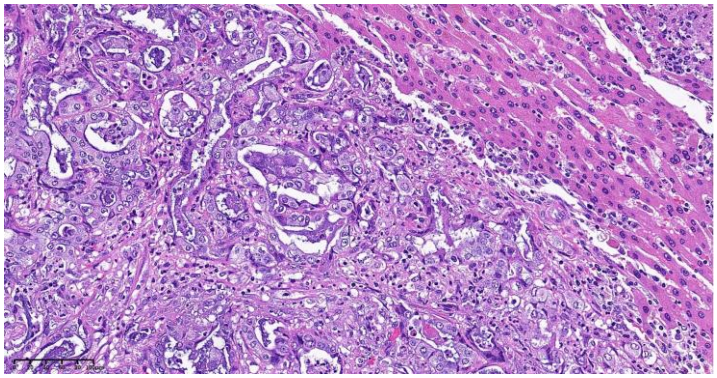


Figure 1: Preoperative tumor marker results and CA199 level changes during treatment



A: HE staining x 100



B: HE staining x 200

Figure 2: Postoperative liver tissue HE staining pathology report of the patient

3. Discuss

Cholangiocarcinoma (CCA) is a highly lethal malignant tumor that occurs in the epithelial cells of extrahepatic bile ducts, including those from the porta hepatis to the lower end of the common bile duct. Depending on its anatomical subtype, CCA can be classified into intrahepatic cholangiocarcinoma (ICC), periportal cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA). Cholangiocarcinoma (CCA) is the second most common primary liver tumor after hepatocellular carcinoma (HCC), with an increasing incidence and significant epidemiological variations worldwide. Due to its high heterogeneity, common symptoms of intrahepatic cholangiocarcinoma include abdominal discomfort, vomiting, night sweats, and fatigue. In the early stages, these symptoms are often asymptomatic or mild and easily overlooked by patients. Additionally, due to a lack of disease knowledge, patients may confuse it with other liver diseases, leading to delayed diagnosis and treatment. By the time the disease is diagnosed, it is often in an advanced stage, missing the optimal surgical window or losing the opportunity for surgery, resulting in reduced treatment outcomes and poor prognosis. Therefore, early diagnosis and differentiation of intrahepatic cholangiocarcinoma are crucial, playing a key role in disease control, treatment, and prognosis[3-4]. As a type of cholangiocarcinoma, ICC is characterized by rapid progression, poor differentiation, high malignancy, easy recurrence and metastasis, and insensitivity to drug therapy, with an increasing incidence trend[5]. There are many diagnostic methods for cholangiocarcinoma, including imaging examination, laboratory examination, cholangiography, biopsy and so on. However, to some extent, a single examination may have certain limitations. At present, in clinical practice, imaging and biopsy are mainly combined to better confirm the diagnosis of cholangiocarcinoma [6].

CA199 antigen is formed by the precursor of Lewis antigen under the combined action of sialidase and fucosyltransferase, constituting a high-molecular-weight glycoprotein complex. In normal human bodies, CA199 is primarily synthesized by pancreatic and biliary cells, as well as bronchial epithelial cells, stomach, colon, endometrium, and salivary epithelial cells. It is present in small amounts in the serum of healthy individuals. When these cells or organs undergo carcinogenesis, tumor cells increase the synthesis of CA199, which is then released into the bloodstream along with cell necrosis and the infiltration of new blood vessels, leading to an abnormal elevation in serum CA199 levels. The increase in CA199 is associated with various malignant tumors, particularly closely linked to pancreatic cancer. Other malignant tumors originating from the colon, rectum, gastrointestinal system, lung, breast, and liver may also show elevated CA199 levels. Generally speaking, elevated CA199 levels correlate with increased probability of malignant disease[7-9]. Clinically, carcinoembryonic antigen (CEA), carbohydrate

antigen 19-9 (CA19-9), and carbohydrate antigen 125 (CA125) are commonly used as serum markers for cholangiocarcinoma, but their sensitivity and specificity are low, making them insufficient for early detection. Other serum biomarkers, such as cytokeratin-19 fragment (CYFRA21-1) and CA-242, have been reported to exhibit higher specificity for iCCA compared to CA19-9 [10].

In this case, the patient's CA199 initially increased at 218.6U/mL, while no other tumor markers showed an increase. About three months later, there was a trend of elevation upon re-examination. However, further imaging did not reveal any significant signs of systemic tumors, and the patient had no obvious discomfort, so follow-up observation continued. Seven months later, the patient's CA199 significantly increased again, with 3112.7U/mL results. At this point, sialoadenoid antigen CA242:65.9U/mL, CA50:141.62U/mL was tested, and no abnormalities were found in other tumor markers. MR suggested possible cholangiocarcinoma. The patient underwent laparoscopic partial hepatectomy + laparoscopic cholecystectomy. Postoperative pathology: moderately differentiated cholangiocarcinoma, pathological stage: IA, T1aN0M0. One week after surgery, the patient's CA199 level dropped significantly and continued to decrease during subsequent follow-ups. Some literature states that serum CA199 levels may be significantly elevated in all patients with malignant biliary tract tumors, but typically, high levels of CA19-9 are associated with cholangiocarcinoma metastasis, and [11-12] is usually not elevated in early-stage cholangiocarcinoma. However, in this patient, only CA199 increased in the early stage of the disease, and no significant abnormalities were found in other tumor markers or imaging studies. As the disease progressed, CA199 showed an upward trend, and imaging suggested the presence of a tumor. Postoperative pathology ultimately diagnosed cholangiocarcinoma, and after treatment of the primary lesion, CA199 continued to decline. As one of the important tumor markers for diagnosing cholangiocarcinoma, CA199 has relatively low sensitivity and specificity when tested alone compared with other tumor markers [13]. However, this case suggests that if CA199 is elevated alone and persistently, the patient may have malignant tumors under the premise of excluding false positives.

4. Conclusion

In summary, cholangiocarcinoma has a high degree of malignancy and rapid tumor progression. The likelihood of surgery in patients with advanced disease is low, and treatment outcomes are poor. Early diagnosis is crucial for patient prognosis. Therefore, when tumor markers show abnormalities, multiple examinations including imaging and cholangiography should be conducted comprehensively. If feasible, puncture biopsy and immunohistochemical tests should be performed if necessary, to facilitate early diagnosis and treatment.

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