

## Gallstone with abnormally high serum values of CA19-9

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### Abstract

Jaundice was recognized in a 73-year-old man examined because of right hypochondralgia, and he was then admitted. Preliminary examination revealed yellowish bulbar conjunctivae and hypochondriac tenderness. Abdominal ultrasonography and computed tomography (CT) examinations revealed hypertrophy of the cholecystic wall and gallstones, as well as dilation of the common bile duct and the hepatic bile ducts. Biochemical studies on admission revealed unusually high serum CA19-9 values of 36,021 U/ml. Laparotomy was performed after percutaneous transhepatic gallbladder drainage had been carried out to relieve the jaundice. Preoperative endoscopy of the biliary system was conducted, but no neoplastic lesions were observed. Ultrasonography examination of the head of the pancreas indicated only inflammation. Following cholecystectomy pathological studies showed chronic cholecystitis, and some areas of the pancreas were severely indurated. After surgery, serum CA19-9 values declined rapidly, and returned to normal levels. The authors report this case together with a review of the literature.

### Introduction

CA19-9 is widely used clinically as a tumor-associated antigen indicator related to malignant tumors of the pancreas and biliary system. Cases of benign tumors, inflammation, and obstructive jaundice showing high values for CA19-9 are occasionally encountered. CA19-9 values are usually 10,000 U/ml or less. The present case was gallstone, and serum CA19-9 values were extremely high (36,021 U/ml), but declined rapidly following cholecystectomy.

### Case Report

A 73-year-old man without a contributory history had jaundice and examination right hypochondriac pain. On admission, the patient was 162 cm in height and afebrile. Bulbar conjunctivae were yellowish. The right hypochondriac area was tender, and tumors

were found upon palpation at the same area. Biochemical tests indicated slight inflammation, with a leukocyte count of  $7,400/\mu\text{l}$  and CRP of 1.53 mg/dl. Slight anemia was confirmed, with a red blood count of  $3.6 \times 10^6/\mu\text{l}$  and an Hb of 11.7 g/dl. Total blood bilirubin was 15.3 mg/dl. Liver function was slightly impaired, with AST 65 U/L and ALT 124 U/L. The level of the tumor marker CA19-9 was high: 36,021 U/ml.

A clear debris echo within the gallbladder was found by abdominal ultrasonography. In addition, strong echo images accompanying acoustic shadows were suspected to be images of a large calculus 7 mm in diameter. Abdominal CT images revealed dilation of hepatic bile ducts, and a suspected 10 mm calculus in the gallbladder. The cholecystic inner mucosal surface was smooth, and no findings suggested the presence of malignant tumor. Moreover, no signs of neoplastic lesions were observed in the gallbladder or pancreas (Fig. 1).

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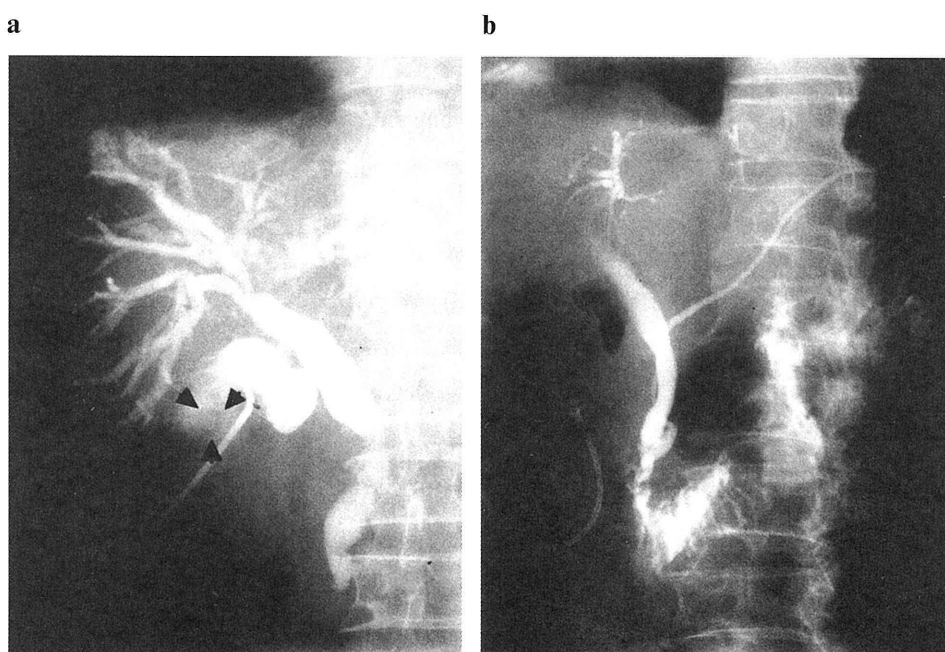


**Fig. 1** Images are observed on abdominal CT showing dilation of hepatic bile ducts (white arrow), and calcification that is suspected to be a large calculus of 10 mm in the gallbladder (black arrow). The cholecystic inner membrane surface is smooth, and there are no findings suggesting the presence of a malignant tumor.

Percutaneous transhepatic gallbladder drainage was performed to ameliorate the jaundice, and bile duct contrast was carried out at the same time. A calculus-like filling defect in the gallbladder and dilation of the common bile duct were observed (Fig. 2a). Endoscopic retrograde cholangiopancreatography (ERCP)

was carried out afterward, but contrast medium did not enter the gallbladder. No irregularity of the mucosa of the bile and pancreatic ducts was noted, and there were no biliary or pancreatic tumors or stones, excluding those in the pancreatic duct (Fig. 2b).

Accordingly, gallstone and cholecystitis were



**Fig. 2** a) A calculus-like filling defect (▼) in the gallbladder and dilation of the common bile duct are observed by percutaneous transhepatic gallbladder drainage. b) The gallbladder was not shown by contrast medium on ERCP. No irregularities of the mucosa in the bile and pancreatic ducts are noted.

diagnosed, and the gallbladder was resected. Pronounced hypertrophy of the gallbladder wall and one large compound stone measuring 7×6 mm were noted in the resected gallbladder (Fig. 3). The portion of the gallbladder wall with pronounced hypertrophy was submitted for pathological diagnosis during surgery, but the report from the pathologists was that only inflammation, and no malignancies, had been found ; therefore no surgery other than gallbladder resection was performed. Following surgery, CA19-9 levels rapidly declined to the normal range.

In postoperative pathological examinations, permeation of inflammatory cells extending to all layers of the gallbladder wall, and fibrogenesis, were observed by

means of hematoxylin and eosin (HE) staining, but there were no findings suggesting malignancy (Fig. 4). Immunostaining was performed using CA19-9 monoclonal antibodies (Clone 1116NS19-9, Japan Tanner Co., Osaka, Japan). It was confirmed that CA19-9 was clearly present when the cytoplasm of the mucosal epithelium of the gallbladder wall was stained brown at the same position (Fig. 5).

From the foregoing it may be surmised that the unusually high preoperative CA19-9 values were due to unusual secretion of CA19-9 by the gallbladder wall resulting from gallstone and cholecystitis.

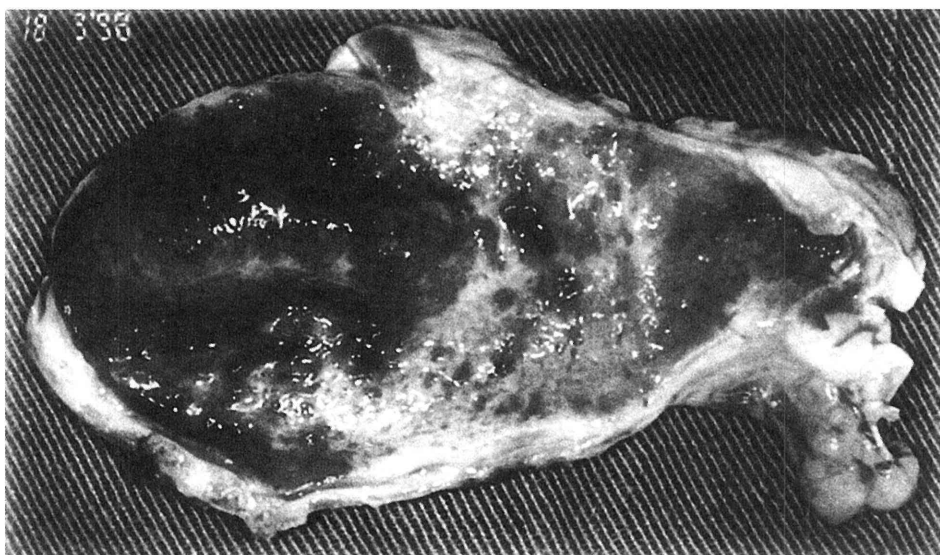


Fig. 3 Macroscopic view of resected gallbladder.



Fig. 4 In postoperative pathological examinations, HE staining, ×200.

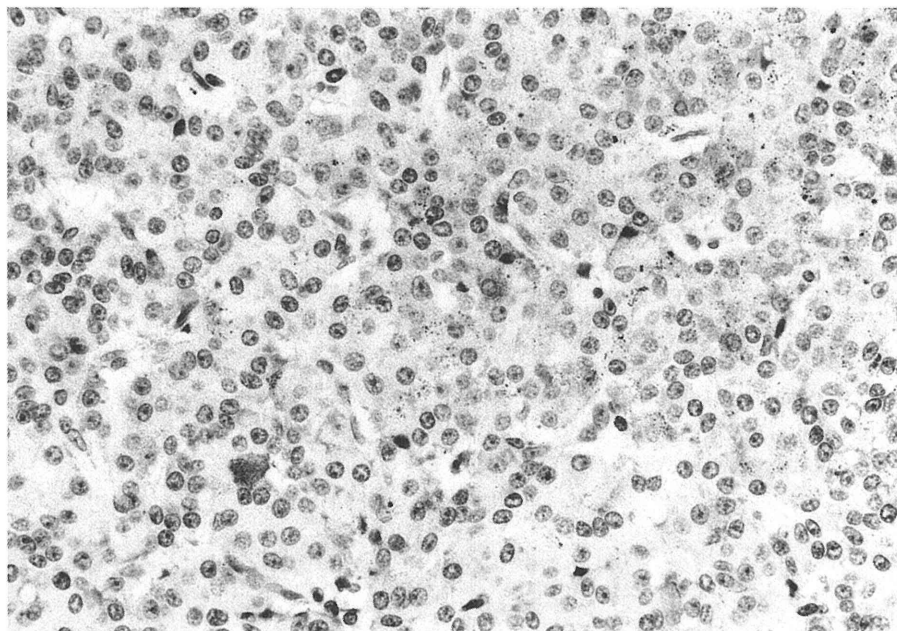


Fig. 5 Immunostaining used CA19-9 monoclonal antibodies,  $\times 200$ .

### Discussion

CA19-9 is an I type sugar chain antigen, with sialyl Lewis a. It has been reported that sialyl Lewis a is concerned with blood-borne metastasis by causing adhesion of cancer cell with vascular endothelial cells<sup>1,2)</sup>. CA19-9 was first observed by Koprowski et al in 1979 as a sugar chain antigen that was specific to cancer of the large intestine, and that was recognized by the monoclonal antibody NS19-9 prepared by immunizing mice with cells cultured from cancer of the large intestine (SW1116)<sup>3)</sup>. Recently, it has become clear that the positive rates are, if anything, higher in cases of malignant tumors of the pancreas and the biliary system, and it is used as an effective marker in diagnoses of these tumors. Reports of increases in serum CA19-9 values have also been made in cases of, for example, benign tumors, acute and chronic hepatitis, obstructive jaundice due to gallstone, acute and chronic pancreatitis, endometriosis, bronchogenic cyst. In addition to its presence in tumor cells of pancreatic carcinoma, cholangiocarcinoma, and gallbladder cancer, traces of CA19-9 are present in normal tissues of the gastrointestinal tract mucosa, pancreatic duct, gallbladder, bronchial glands, and the epithelial cells of the salivary glands<sup>4)</sup>. It may be that increased serum CA19-9 is due to the antigen straying into the bloodstream. Increase in serum CA19-9 in cases of jaundice due to occlusion of the gallbladder by choledocholiths are not uncommon, and there are also reports indicating high CA19-9 values associated with obstructive jaundice<sup>5)</sup>. There are, however, reports of cases in which jaundice was not associated from CA19-9 values<sup>6)</sup>, and others suggesting that

there is no significant correlation between CA19-9 and bilirubin values<sup>7)</sup>. Moreover, in cases of fever, CA19-9 values decline with decreasing body temperature, and inflammation is present in cases in which there are high CA19-9 values<sup>5)</sup>; therefore, the possibility has been suggested that, in addition to increased internal pressure in the biliary system due to occlusion, infection and inflammation are also concerned in increased CA19-9 values<sup>6,8)</sup>.

In spite of the lack of inflammation in the findings at the time of admission in this case, examination of the wall of the resected gallbladder clearly showed cholecystitis accompanied by pronounced hypertrophy of the cholecystic wall. Moreover, total blood bilirubin was 15.3 mg/dl, and pronounced jaundice was apparent. Thus, it may be that the unusually high CA19-9 values appeared due to obstruction in the biliary system as a result of cholecystitis brought on by a gallstone impacted in the neck of the gallbladder, causing increased internal pressure in the biliary system, and that the CA19-9 present in the normal epithelium of the gallbladder emanated into the bloodstream from the epithelial cells, following the destruction of the epithelium. Following surgery, serum CA19-9 values rapidly returned to normal levels, and no malignant tumor was found on pathological examination of the resected gallbladder.

The normal CA19-9 value is  $8.4 \pm 7.4$  U/ml, and the cut off value is 37 U/ml<sup>9)</sup>. However, some cases we encounter routinely, may have high CA19-9 values because of the same mechanism. These values are usually all 10,000 U/ml or less<sup>10,11,12)</sup>, and cases such as the one in the present study, with values up to 36,021 U/ml, are extremely rare. When high values of this antigen

appear, the question arises as to whether there is malignant tumor present. At present, however, it is difficult to preoperatively determine whether or not a malignant tumor is present solely on the basis of CA19-9 values, and a final determination must be made postoperatively, based on pathological examination of the resected gallbladder. Therefore, postoperative pathological monitoring of trends in CA19-9 is important in cases of high preoperative serum CA19-9 values. If the mechanism by which CA19-9 enters the bloodstream can be clarified, it may become possible to interpret cases in which high serum CA19-9 values appear in patients with benign tumors.

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## 血中 CA19-9 が異常高値を示した胆石・胆嚢炎の一例

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【要旨】血性 CA19-9 は膵・胆道系の悪性腫瘍で高率に陽性を示す腫瘍関連抗原として広く臨床の場で使われている。一方、良性疾患でも時に高値を示す症例を経験することがあり、その評価は慎重になされなければならないが多くの場合は 10,000 U/ml 以下である。今回、我々は血中 CA19-9 値が著明に高値を示したが胆嚢摘出術を施行し、速やかに血中 CA19-9 が低下した症例を経験したので、若干の文献的考察を加えて報告する。

症例は 73 歳、男性。右季肋部痛の為に近医受診したところ黄疸が認められ、当院当科紹介となった。初診時、眼球結膜の黄染と右季肋部の圧痛を認めた。腹部エコー、CT で胆嚢壁の肥厚と胆石の存在、さらに総胆管、肝内胆管の拡張を認めた。入院時の生化学検査で血中 CA19-9 値が 36,021 U/ml と異常高値を示した。減黄を目的に PTGBD を施行後、開腹手術施行。術中胆道内視鏡検査を施行したが、腫瘍性病変は観察されず、また、膵頭部をエコーで観察したが炎症所見のみであった。そこで、胆嚢摘出術を行った。術後の病理学的検索では、胆嚢は慢性胆嚢炎の所見であり、膵臓硬結部も悪性所見は認めなかった。また、胆嚢粘膜の CA19-9 モノクローナル抗体による免疫染色では陽性所見が得られた。血中 CA19-9 値は、術後急速に低下し正常値に復した。

術後 16 ヶ月を経た現在外来経過観察中であるが、再発、または悪性腫瘍を疑わせる所見は得ていない。

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〈Key words〉 CA19-9, 胆石症, 腫瘍マーカー

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