

# CA 19-9 to Rule Out Pancreatic or Biliary Cancer Among Patients with Cholestasis: An Unsuitable Test?

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## Introduction

Carbohydrate antigen CA 19-9 was initially proposed as a serologic marker for colorectal cancer [1]. Nowadays its use is not recommended for this purpose [1] and CA 19-9 serum concentration is mostly evaluated in patients with suspected pancreatic or biliary cancer, because of its presumed higher specificity in this setting [2–5].

Unfortunately, CA 19-9 levels have also been reported in other malignancies such as gastric and ovarian cancer and in different benign conditions like cystic fibrosis, hydronephrosis, and Hashimoto thyroiditis [5–7]. Furthermore, elevated CA 19-9 serum concentration can be associated with several conditions producing reduced biliary drainage [8–10], especially in the presence of cholangitis [11]. It is generally be-

lieved that benign conditions cause mostly slight elevations, while very high levels are mainly related to malignancies. This goes along with the results of some papers [2, 4].

We describe here three cases showing extremely elevated CA 19-9 serum concentration secondary to benign biliary obstruction, rapidly normalizing after recovery of biliary patency. CA 19-9 was evaluated by immunochemoluminescence test (DiaSorin, Saluggia, Italy; normal range, 0–19 IU/ml).

## Case reports

### Case 1

A 78-year-old white man suffering from hypertension, diabetes, and chronic obstructive pulmonary disease was admitted to our department because of recent jaundice and very high levels of CA 19-9 (187000 IU/ml). He had no recent history of fever or abdominal pain. At admission AST and ALT were  $2 \times$  and  $3 \times$  the upper limit of normal (ULN), respectively, with alkaline phosphatase  $4 \times$  ULN,  $\gamma$ -glutamyltransferase ( $\gamma$ -GT)  $8 \times$  ULN, and total/conjugated bilirubin 22/14 mg/dl. Ultrasound showed gallbladder stones and dilated biliary ducts with multiple choledocolithiasis. The diagnosis was confirmed by cholangiopancreatography, and calculi were extracted after endoscopic sphincterotomy. Neither ultrasound nor cholangiography showed biliary or pancreatic neoplasms. Because of the very high levels of CA 19-9, the patient underwent CT scan that did not show any malignancy.

One and two months later CA 19-9 was 1403 and 105 IU/ml, respectively. After a further 30-day period it was reduced to within the normal range.

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## Case 2

A 79-year-old white man was admitted to our department because of right upper abdominal pain and fever for 3 days, dilated bile ducts and choledocholithiasis at ultrasound, and serum CA 19-9 of 14000 IU/ml. He had undergone cholecystectomy in 1958. In 1993 he had his first episode of cholangitis with evidence of choledocholithiasis, successfully treated by endoscopic sphincterotomy.

At admission, body temperature was 37.9°C and blood tests showed AST  $3 \times$  ULN, ALT  $4 \times$  ULN,  $12250 \text{ WBC/mm}^3$ , slightly elevated values of alkaline phosphatase and  $\gamma$ -GT, and normal values of bilirubin. Endoscopic retrograde cholangiopancreatography showed multiple small intracholedocic stones, which were extracted by a balloon catheter after Dormia basket lithotripsy. Ultrasound and cholangiopancreatography showed no evidence of pancreatic or biliary neoplasm.

Two weeks later alkaline phosphatase and  $\gamma$ -GT were normalized and CA 19-9 was reduced to 94 UI/ml. After a further 2 weeks, CA 19-9 had returned to normal.

About 2 months later the patient had a new slight and self-limiting episode of cholangitis, with CA 19-9 increasing again, to 350 IU/ml. Values of CA 19-9 normalized rapidly after spontaneous cholangitis resolution.

## Case 3

An 82-year-old white man with diabetes and hypertension was admitted to our department for jaundice for 1 week, with no fever or abdominal pain. At admission he was slightly jaundiced but asymptomatic. Blood tests showed bilirubin of 4.7 mg/dl, AST  $2 \times$  ULN, ALT  $4 \times$  ULN, alkaline phosphatase  $2 \times$  ULN,  $\gamma$ -GT  $6 \times$  ULN, and CA 19-9 of 1306 IU/ml. Ultrasound showed gallbladder stones and dilated biliary ducts. CT scan confirmed these findings and showed an intracholedocic stone. The patient underwent endoscopic retrograde cholangiopancreatography, showing evidence of choledocic calculi, which were extracted by balloon catheter.

Within 7 days, fever and jaundice recovered, blood tests, including CA 19-9, normalized, and at ultrasound bile ducts were back to normal size. Neither ultrasound, CT scan, nor cholangiopancreatography showed biliary or pancreatic neoplasms.

All patients were followed up for 12 months after initial admission, undergoing clinical evaluation, abdominal ultrasound, and CA 19-9 dosage every 3 months. CA 19-9 serum concentration remained normal, and no patient showed evidence of biliary or pancreatic cancer.

## Discussion

Different papers have shown CA 19-9 to be a reasonable test for detecting cholangiocarcinoma among patients with primary sclerosing cholangitis [12, 13]. Out of this setting its use seems not to be as promising, especially because of its low specificity. Very high levels have been described in different benign conditions [8, 14]. Nevertheless, CA 19-9 is still frequently used to rule out pancreatic or biliary cancer in patients with biliary obstruction, and detecting very high serum concentrations generally induces doctors to perform further investigations. Some published papers seem to justify this approach. One study including 164 patients with high CA 19-9 showed a correlation between the degree of CA 19-9 elevation and the underlying disease, with benign conditions being associated with significantly lower levels than pancreatobiliary tumors and metastatic liver disease [4]. Similar findings have been reported by another study that compared 36 patients with cholangiocarcinoma with 67 patients with benign bile duct stricture [2]. Furthermore, one study reported a positive correlation between bilirubin concentration and serum CA 19-9 level among patients with jaundice caused by benign conditions, while this correlation did not apply to malignant jaundice [4].

In patients with benign biliary disease, acute cholangitis can cause marked elevation of CA 19-9 serum levels. In one study including 40 patients with benign disease of the biliary tract, all 7 patients with acute cholangitis had marked elevations of serum CA 19-9, whereas levels were normal in all patients without cholangitis [11].

The three patients described here reached extremely high CA 19-9 levels despite benign disease in all of them, normal or only slightly elevated bilirubin in two, and absence of cholangitis in two. CA 19-9 quickly normalized in all patients after biliary stone removal. Is the rapid restoration of normal values after recovery of biliary patency crucial in distinguishing between benign obstruction and malignancies? In benign conditions, after resolution of biliary obstruction, CA 19-9 generally returns within the normal range. In malignancies different responses have been described: the majority of patients show a decline, while in some instances further elevations have been observed [4]. Thus, even a rapid fall of serum CA 19-9 after resolution of biliary obstruction does not discriminate between benign obstruction and malignancies.

The cases described show that in the presence of cholestasis caused by choledocholithiasis, CA 19-9 can rise to extremely elevated levels even without jaundice or cholangitis. Thus, the degree of CA 19-9 elevation seems not to be helpful in discriminating between benign conditions and malignancies, as is its rapid decline after recovery of biliary patency.

Considering these data, in the presence of biliary obstruction, dosing CA19-9 serum concentration to rule out pancreatic or biliary cancer seems to be unsuitable and potentially misleading. CA 19-9 should not be taken into account in this context.

## References

1. Bast RC, Ravdin P, Hayes DF, *et al.* (2001) 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19:1865–1878
2. Patel AH, Harnois DM, Klee GG, La Russo NF, Gores GJ (2000) The utility of CA 19-9 in the diagnosis of cholangiocarcinoma in patients without primary cholangitis. *Am J Gastroenterol* 95:204–207
3. Kim HJ, Kim MH, Myung SG, Lim BC, Park ET, Yoo KS, Seo DW, Lee SK, Min YI (1999) A new strategy for the application of CA 19-9 in the differentiation of pancreatobiliary cancer: analysis using a receiver operating characteristics curve. *Am J Gastroenterol* 94:1941–1946
4. Mann DV, Edwards R, Ho S, Lau WY, Glazer G (2000) Elevated tumor marker CA 19-9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg Oncol* 26:474–479
5. Parra JL, Kaplan S, Barkin JS (2005) Elevated CA 19-9 caused by Hashimoto thyroiditis: review of the benign causes of increased CA 19-9 levels. *Dig Dis Sci* 50:694–695
6. Meyer A, Kausch I, Kruger S, Fetscher S, Bohle AD (2004) Elevation of CA 19-9 in giant hydronephrosis by a renal calculus. *Urology* 63:381–382
7. Suzuki K, Muraishi O, Tokue A (2002) The correlation of serum carbohydrate antigen CA 19-9 with benign hydronephrosis. *J Urol* 167:16–20
8. Katsanos KH, Kitsanou M, Christodoulou DK, *et al.* (2002) High CA 19-9 levels in benign biliary tract diseases. Report of four cases and review of the literature. *Eur J Intern Med* 13:132–135
9. Osswald BR, Klee FE, Wysocki S (1993) The reliability of highly elevated CA 19-9 levels. *Dis Markers* 11:275–278
10. Collazos J, Genolla J, Ruibal A (1992) CA 19-9 in non neoplastic liver disease. A clinical and laboratory study. *Clin Chim Acta* 210:145–151
11. Albert MB, Steinberg WM, Henry GP (1988) Elevated serum levels of tumor marker CA19-9 in acute cholangitis. *Dig Dis Sci* 33:1223–1225
12. Siqueira E, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, Abu-Elmagd K, Madariaga JR, Slivka A (2002) Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. *Gastrointest Endosc* 56:40–47
13. Nichols JC, Gores GJ, LaRusso NF, Wiesner RH, Nagorney DM, Ritts RE Jr (1993) Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Mayo Clin Proc* 68:874–879
14. Akdogan M, Sasmaz N, Kayhan B, Biyikoglu I, Disibeyaz S, Sahin B (2001) Extraordinarily elevated CA19-9 in benign conditions: a case report and review of the literature. *Tumori* 87:337–339