Measurement of Serum CA 19-9 in Biliary Diseases Requires Great Caution

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In 1983 Del Villano et al. developed a simple radioimmunometric assay for the quantification of serum CA 19-9 which proved useful in the management of patients with pancreatic cancer (1). According to the authors, a sensitivity of 79% and a specificity of 98.5% were obtained at the chosen cut-off value of 37 KU/L. It then became apparent that the originally proposed (and commonly used) cut-off yielded a specificity of not higher than 90%, the cut-off of 100 KU/L yielded a 98% specificity, and serum CA 19-9 levels higher than 1000 KU/L, which decreased after decompression of the common duct, were found in patients with acute cholangitis (2).

Significant elevations in serum CA 19-9 have been frequently reported in many other non-malignant disorders (primary sclerosing cholangitis, primary biliary cirrhosis, chronic hepatitis B and C, autoimmune hepatitis, alcoholic liver disease, extra-hepatic cholestasis) (3, 4).

We present here two cases demonstrating that cholangitis and biliary system obstruction can induce virtually any serum concentration of CA 19-9.

Patient 'A', a 58-year-old man, was referred to our Department on January 22 1997 because of progressive jaundice. The blood tests on admission were: total bilirubin = 75 μmol/L (n.v. 2–21 μmol/L), conjugated bilirubin = 41 μmol/L (n.v. 0–7 μmol/L), AST = 116 U/L (n.v. 5–40 U/L), ALT = 177 U/L (n.v. 5–50 U/L), GGT = 790 U/L (n.v. 5–60 U/L), ALP = 226 U/L (n.v. 30–115 U/L), CA 19-9 = 250 KU/L (n.v. < 100 KU/L); CEA = 1.5 μg/L (n.v. < 10 μg/L). Ultrasonography (US) and computed tomography (CT) showed an initial dilatation of the intra- and extra-hepatic biliary system, without abnormal findings in the pancreas. The endoscopic retrograde cholangio-pancreatography (ERCP) demonstrated a prominent papilla of Vater suggestive of ampulloma. On February 2 1997 the patient underwent the resection of the papilla with insertion of a T-tube in the bile tract. The intraoperative examination and US of the head of the pancreas were normal. The pathologic examination demonstrated eterotopic pancreatic tissue around the papilla, without neoplastic cells. The postoperative course was uneventful and the cholangiogram was normal; the patient was discharged on the 24th postoperative day and the T-tube was removed on the 30th postoperative day.

After 6 months of good health, the patient was readmitted suffering from severe cholangitis with right upper quadrant pain, jaundice and high fever (39.6°C). The blood tests included: total bilirubin = 68 μmol/L, conjugated bilirubin = 39 μmol/L, AST = 46 U/L, ALT = 85 U/L, GGT = 334 U/L, ALP = 179 U/L, urea = 8.7 mmol/L (n.v. 2.8–7.8 mmol/L), creatinine = 139 μmol/L (n.v. 44–100 μmol/L), CA 19-9 = 104 500 KU/L, CEA = 1 μg/L, ESR = 127 mm/h (n.v. 1–20 mm/h). US and CT demonstrated a dilatation of the intrahepatic biliary system, without abnormal findings in the common bile duct and pancreas. Obstruction of the hepatic duct was confirmed by ERCP, with no evidence of residual stones in the bile duct and percutaneous transhepatic cholangiography (PTC) documented a severe stenosis of the hepatic duct close to the first-order bifurcation. After 2 weeks of medical therapy, the patient's general condition improved and he was operated on. The laparatomic exploration of the bile duct bifurcation and the hepatic duct revealed severe stenosis. Intraoperative biopsies of the fibrous tissue around the hepatic duct and retropancreatic lymph node investigation of neoplastic cells were negative. The common hepatic duct was completely resected, and hepatic-jejuno-anastomosis was performed. The postoperative course was uneventful and the patient was discharged on the 11th postoperative day. Thirty days after surgery, serum CA 19-9 concentration was 24 KU/L and 13 months later 12 KU/L.

Patient 'B', a 74-year-old woman, was referred to us in November 1999 with epigastrium and right upper abdominal pain, fever, progressive jaundice, nausea and vomiting. Eleven years earlier, the patient had undergone a gastrectomy for early gastric cancer (T1smN0M0). The patient had been monitored every 6 months by clinical examination, blood testing (including CEA and CA19-9), abdominal US, chest x-ray and annual digestive endoscopy; none of the tests had shown any signs of recurrence. Initial laboratory evaluation of her blood revealed: total bilirubin = 70 μmol/L, conjugated bilirubin = 60, AST = 537 U/L, ALT = 365 U/L (n.v. 5–40 U/L), GGT = 978 U/L (n.v. 5–45 U/L), ALP = 1.002 U/L, amylase = 285 U/L (n.v. 15–60 U/L), CA 19-9 = 405 000 KU/L, CEA = 1.6 μg/L.

Since the US demonstrated gallbladder distension, multiple stones within its lumen, thickening of the wall hypoecholic layer, pericholecystic liquid collection and a little stone within the cystic

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duct, a percutaneous cholecystostomy was urgently performed (5). After 48 h, the transcholecystic cholangiogram showed choledocholithiasis with initial dilatation of the intra- and extra-hepatic biliary system. Two days later the patient underwent a cholecystectomy with open choledocholithotomy and insertion of a T-tube in the bile duct. The surgical exploration of the abdomen excluded a recurrence. The postoperative course was uneventful and the patient was discharged on the 10th postoperative day. Serum CA19-9 concentration decreased to 689 KU/L after 5 days and to 57 KU/L after 12 days.

Several recent reports of high serum CA 19-9 concentration in benign diseases led Maestranzi et al. to conclude that caution should be exercised in the interpretation of carbohydrate antigen tumour marker results in the presence of a significantly abnormal liver function (3). Another study reported marked elevation of serum CA 19-9 concentration (range 190–32000 KU/L) in all seven investigated patients with acute cholangitis (6). Also Basso et al. showed results higher than 10000 KU/L (and one higher than 100000) in 4 out of 30 patients with benign stenosis of the main bile duct (7). However, as far as we know, this paper reports the highest ever reported serum CA 19-9 concentration (405000 KU/L) in a benign condition. It has been stated that CA 19-9 is not a true 'tumour marker' since it is present in the bile of patients without cancer and can be found in extremely high amounts in the serum of patients with many benign biliary tract disorders (6).

CA 19-9 antigen appears to leak from the biliary system into the blood at any level of the biliary system but the mechanisms behind the increases in CA 19-9 blood concentrations are not clear, although cholestasis seems to be an important factor. It must be remembered that neither bilirubin nor bile acids interfere with serum CA 19-9 measurement (8). Note that we used an up-to-date, completely automated immuno-chemiluminometric analyser based on the monoclonal antibody 1116 NS 19-9 (Liaison, Byk Sangtec Diagnostica, Germany).

The detection of cancer by a blood test is an emotive and ethically charged issue since markers such as CA 19-9 are linked to particular tumours and may be requested by physicians unaware of their limitations both in diagnosing the presence of a cancer and in defining its nature. These two reported cases and the discussion we (researchers and surgeons) had about them persuade us that hardly any CA 19-9 concentration exists which assures, when taken alone, a firm diagnosis of pancreatic cancer.

In conclusion, while CA 19-9 continues to be the 'gold standard' against which present and future markers for pancreatic cancer are and will be evaluated (2), the serum CA 19-9 concentration even 10000 times higher than the classical 37 KU/L upper reference limit should not be considered as definitely consistent with the diagnosis of pancreatic cancer.

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