

CA 19-9 in the Presence of Obstructive Jaundice due to Mirizzi Syndrome

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CA 19-9 is a carbohydrate antigen, originally identified by a murine monoclonal antibody produced against a human colorectal cell line. This glycoprotein is expressed by several epithelial cancers, as well as normal pancreatic and biliary ductal epithelial cells, and is also detectable in salivary mucous and meconium [1,2]. Assessment of the levels of this antigen is used in the diagnosis and prognosis of upper gastrointestinal malignancies, especially pancreato-biliary [3]. However, its levels can be elevated in many benign conditions, including liver diseases such as primary sclerosing cholangitis, primary biliary cirrhosis and chronic hepatitis, biliary conditions, pancreatitis, and even respiratory, renal and rheumatologic disorders [2,3]. In interpreting the results, there is no clear cutoff to distinguish between benign and malignant disease [3], and there seems to be an overlap of values between cancer and non-cancer causes [1]. Thus, patients with benign biliary tract disease may have levels up to 400 U/ml, with 87% having concentrations higher than 70 U/ml. A significant number of patients with pancreatitis, acute or chronic, also have elevated levels. In addition to pancreatic cancer, CA 19-9 levels are also elevated in patients with other cancers, including those of the biliary tree (95%), stomach (5%), colon (15%), liver (hepatocellular carcinoma 7%) and lung (13%).

CA 19-9 is not useful as a screening modality because of its low sensitivity in early-stage disease. With increasing levels of CA 19-9 the diagnosis of pancreatic cancer becomes more accurate. When a cutoff level of 100 U/ml is used, a number of studies have demonstrated that although sensitivity ranges from 60% to 84%, specificity for pancreatic cancer is 95% or higher. Levels higher than 1000 U/ml are almost diagnostic of pancreatic cancer.

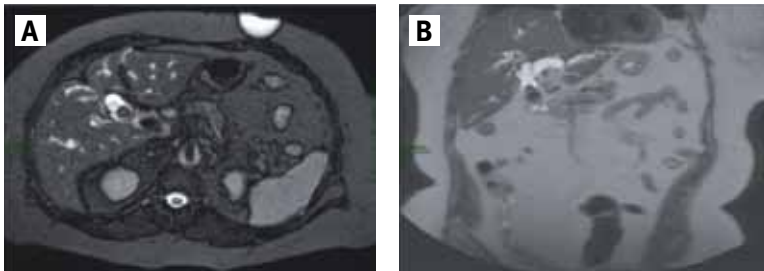
Hyperbilirubinemia seems to be a confounding factor in the interpretation of CA 19-9 since it is associated with an increased CA 19-9 level in cases of both benign and malignant obstruction, and its interpretation requires great caution in this setting [1,3]. This report describes the case of a 68 year old woman with suspected cholangiocarcinoma or a pancreatic carcinoma based on a high CA 19-9 level and painless obstructive jaundice. The patient was eventually found to suffer from Mirizzi syndrome.

PATIENT DESCRIPTION

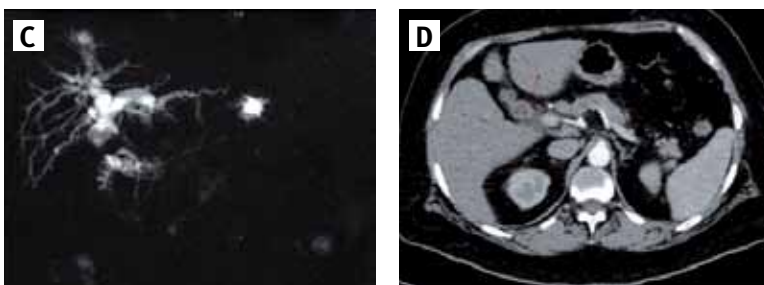
A 68 year old woman was referred to our emergency room (ER) with a history of progressive jaundice, dark urine and light-colored stools. She denied fever, chills, pain, nausea, vomiting or pruritus. On physical examination the patient was afebrile, blood pressure was 117/82 and pulse 100/min. The patient was icteric, and the rest of the exam was unremarkable. An ultrasound performed in the ER showed dilated intra- and extrahepatic bile ducts; the common bile duct (CBD) measured 1.1 cm. Blood tests showed a total bilirubin level of 11.7 mg/dl (direct 6.3 mg/dl), alkaline phosphatase 354 U/L, aspartate aminotransferase

174 U/L, alanine aminotransferase 249 U/L, and white blood cell count 7000 μ l. The patient was admitted with the diagnosis of obstructive jaundice and a suspected cholangiocarcinoma. Computed tomography scan performed the next day showed dilated intra- and extrahepatic bile ducts without a discernible cause [Figure 1C]. The gall bladder contained a stone. Serum CA 19-9 was 23,996 U/ml (normal 0–37 U/ml). A magnetic resonance cholangiopancreatogram (MRCP) showed a significant dilatation of intrahepatic bile ducts and hepatic duct, CBD was not dilated [Figure 1 A & B]. Gallbladder was small and contained a large stone (> 1.5 cm). The anatomic variation of a very short cystic duct that inserts into the CBD in a higher-than-normal position was noted [Figure 1D].

Endoscopic retrograde cholangiopancreatography (ERCP) revealed a stricture 1–2 cm in length in the upper third of CBD. In the gallbladder a stone > 2 cm in diameter was apparent. No tumor was seen and no biopsy was taken. An Amsterdam stent was inserted. Serum CA 19-9 was repeated approximately 2 weeks after the procedure and was 3145 U/ml. The ERCP was repeated 2 weeks later with stent extraction and subsequent cholecystectomy. During the surgery, a small gallbladder with many adhesions to the duodenum and omentum was seen, with its wall fused to that of the CBD. The stent inserted during ERCP was recognized, and CBD exploration with extraction of a number of large stones that were blocking the common duct and T-tube insertion was performed. A biopsy taken at surgery revealed evidence of marked chronic inflammation with areas of acute inflammation, but no tumor was seen.



[A and B] Axial and coronal T2W sequence showing a filling defect ovoid signal in gallbladder neck adjacent to common hepatic duct. Intrahepatic ducts are distended



[C and D] Contrast-enhanced axial CT **[C]** and MRI **[D]** show a hypodense small round lesion with calcified rim adjacent (posterior) to gallbladder

Three weeks after the surgery the CA 19-9 returned to normal: 28.63 U/ml.

COMMENT

Mirizzi syndrome is a rare and benign cause of obstructive jaundice occurring in about 1% of patients undergoing cholecystectomy in the western world. It occurs when the common hepatic duct becomes obstructed due to extrinsic compression from an impacted gallstone in the cystic duct or the neck of the gallbladder. Currently, it is divided into four subtypes depending on the degree of compression of hepatic duct or presence of a fistula, although other classifications have been proposed [4]. The differential diagnosis of Mirizzi syndrome includes conditions that can cause obstructive jaundice, such as choledocholithiasis, gallbladder cancer, pancreatic cancer, sclerosing cholangitis and others [4].

The association between elevated bilirubin level and increased CA 19-9 levels is not completely understood. Since CA 19-9 is synthesized by both normal epithelial cells of biliary tract and tumor cells and is excreted in the bile, it is suggested that

in the presence of an obstruction from any cause, this product refluxes into the bloodstream due to the increased permeability between bile and blood, secondary to bile stasis [1,2,5]. This process can be reversed by removing the obstruction in benign cases, but not necessarily in malignant cases where CA 19-9 levels may decrease, stay the same or even increase [2]. For example, in one series [5] CA 19-9 positivity in pancreatic carcinoma without jaundice was 73.5% for the recommended cutoff (29–37 U/ml) and 64.7% for the high cutoff (four times the recommended cutoff value, about 120–160 U/ml); these ratios were 7.3% and 2.4%, respectively, for the benign pancreatic disease without jaundice.

On the other hand, CA 19-9 positivity in benign pancreatic diseases with jaundice was as high as 64.7% for the recommended cutoff and 41.2% for the high cutoff levels. When the obstruction was removed CA 19-9 returned to normal in the group with benign conditions; however, it mostly remained high in those with pancreatic carcinoma. This was largely the case in other series [1,2].

Thus, interpreting these results calls for extreme caution, even more so when conveying them to the patient or his/her family who generally are not familiar with medical jargon and would be unnecessarily alarmed by elevated CA19-9 in the presence of hyperbilirubinemia. We recommend that CA19-9 levels be measured upon admission but should be used solely for surveillance and not as a diagnostic tool, even if the levels are markedly elevated.

CONCLUSIONS

The tumor marker CA 19-9 cannot be used to diagnose malignancy alone, and caution must be exercised when interpreting its result in accordance with medical history, physical examination and laboratory tests, especially bilirubin level and imaging studies.

When interpreting the results of this marker, if bilirubin level is high, CA 19-9 level is not significant since it can be elevated beyond the malignancy cutoff, in the presence of obstructing jaundice, as our case has demonstrated.

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