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REVIEW

TUMOR MARKERS IN BILIARY MALIGNANCIES

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Summary

Although biliary tract malignancies are very rare tumors, they are associated with very high rates of mortality due to the fact that they remain clinically asymptomatic for a long period of time. In order to improve the outcomes of these patients', serum tumor markers measurements were proposed as part of the diagnostic and follow up protocol of these cases. This is a literature review regarding the role of tumor markers determination (CEA, CA 125, CA 19-9 and AFP) in cases with biliary tract cancer
Key words: biliary tract, malignancy, CEA, CA 125, CA 19-9

Résumé

Marqueurs tumoraux dans le biliaires malignités

Bien que les tumeurs malignes des voies biliaires sont des tumeurs très rares, elles sont associées à des taux très élevés de mortalité lié au fait qu'elles restent cliniquement asymptomatique pendant une longue période de temps. Afin d'améliorer les résultats de ces patients, le dosage des marqueurs tumoraux sériques a été proposées dans le cadre du diagnostic et le suivi de protocole de ces cas. Ceci est une revue de la littérature concernant le rôle du dosage des marqueurs tumoraux (CEA, CA 125, CA 19-9 et AFP) dans les cas d'un cancer des voies biliaires
Mots clés: voiesbiliaries, malign, CEA, CA 125, CA 19-9

Introduction

From all the biliary tumors, 5%-10% develop from the intrahepatic ducts, 20%-30% are localized in the distal common bile duct and 60-70% develops at the bifurcation of the hepatic ducts and are named Klatskin tumors (1).

Although biliary tract carcinomas are very rare (they represent less than 1% of all the malignancies), their early detection is very necessary in order to reduce the high mortality rate which characterizes the patients and which is due to the late detection of the disease. One of the solutions which can improve the outcome is the use of the tumor markers. Until now, the most frequently studied tumor markers were: CA 125, CA 19-9, CEA (carcino-embryonic antigen), chromogranin A, mucin 1, mucin 5, alpha-fetoprotein, claudins and cytokeratins (1).

CEA

Numerous studies have been done in order to find out the sensitivity and the specificity of CEA in the diagnosis of cholangiocarcinoma. Qin et al found the following results: 68.57% and 81.52%, respectively, while Ramage et al found the values: 63.3% and 78.4% (2,3).

Since literature data showed that the sensitivity of CA 19-9 is higher than that of CEA in the detection of biliary malignancy, research has been done in order to find the sensitivity and specificity of the association of the two markers. The formula CA 19-9 + (CEA× 40) can be used for the screening of patients diagnosed with primary sclerosing cholangitis. The positive predictive value, the specificity and the sensitivity of this index for a cut-off value of 400 U/mL were 100%, 100% and 67%, respectively. Another cut-off value that can be used is that proposed by Chalasani et al (100 U/ mL)(1,4).

A study realized in 2003 took into account 132 patients and studied them prospectively. They were diagnosed with bile duct cancer (32 patients), pancreatic cancer (32 patients), and benign biliary diseases (84 patients). On the next day of the biliary drainage procedures, the authors obtained bile samples and measured the concentration of

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CEA. The mean value obtained in patients with bile duct cancer was 120.6 ng/ml, while the mean value obtained in patients with pancreatic cancer was 32.0 ng/ml and the mean value obtained in benign biliary diseases was 29.3 ng/ml. The normal values of the biliary fluid CEA was not known, but for a cut-off level of 20 ng/ml, the sensitivity and specificity of the bile CEA in detecting the bile duct cancer was 65.6% and 66.7%. The results showed that the levels of bile CEA and serum total bilirubin can be considered as independent markers used in patients with bile duct cancer and the conclusion was that the bile CEA concentrations can be used in the diagnosis of bile duct cancer, but as a supplementary test, given the low sensitivity and specificity (5).

CA 125

Literature data show that the sensitivities of CA 125 in the detection of gallbladder cancer and cholangiocarcinomais of 58% and 40-50%, respectively. The low specificity is explained by the presence of elevated CA 125 levels in many other benign, physiological and malignant conditions (6).

CA 125 is very useful in differentiating various benign and malignant causes of the bile duct obstruction. This is important because CA 19-9 is frequently increased in patients diagnosed with cholangitis and hepatolithiasis (1).

CA 19-9

The use of CA 19-9 as a tumor marker is limited by the fact that about 10% of the general population, who is Lewis negative, has undetectable CA 19-9 concentrations. Thus, the use of CA 19-9 depends on the Lewis phenotype (7,8).

CA 19-9 is used successfully in the detection of cholangiocarcinoma in patients with primary sclerosing cholangitis (1). Literature data show different sensitivities of this tumor marker in the detection of biliary malignancies: 97% (Torzilli et al), 76% (Hultcrantz et al) and 68% (Caturelli et al). For an established cut-off of this marker of 100 U/ml, Nichols et al found a sensitivity and a specificity of 89% and of 86%, respectively (9-12).

Literature data showed that for a cut-off of 129 U/mL, the CA 19-9 sensitivity and specificity in the detection of biliary cancer are 78.6% and 98.5%, respectively, while for a cut-off of 67.3 U/ml, the sensitivity and specificity were 90% and 98%, respectively (13).

Increased CA 19-9 concentrations are found in some benign conditions like: Mirizzi syndrome, autoimmune pancreatitis, primary sclerosing cholangitis associated with biliary stenosis and pancreatic exocrine dysfunction. The presence of biliary obstruction leads to increased concentrations of CA 19-9 and bilirubin, which normalize after the removal of the obstacle (14-17).

CA 19-9 can be also used to predict the resectability of a biliary cancer, since some advanced biliary cancers are unresectable and associated with very increased CA 19-9 values, poor prognosis and poor survival (18,19, 20, 21).

A study realized in 2010 by B. Juntermanns et al included 136 patients diagnosed with hilar cholangiocarcinoma and the authors measured the serum preoperative concentrations of CEA and CA 19-9. The patients diagnosed with stage UICC I of disease had the mean concentration of CA 19-9 of 253 U/ml and the mean concentration of CEA of 2.9 U/ml, the patients diagnosed with stage II of disease had the mean concentration of CA 19-9 of 742 U/ml and the mean concentration of CEA of 4.6 U/ml. For the stage III of the disease, the mean values were 906 U/ml for CA 19-9 and 18.1 U/ml for CEA. For stage IV of the disease, the mean values were 1707 U/ml and 22.7 U/ml, respectively. The results proved the relation between tumor marker values and the stage of the disease and also proved that tumors characterized by a CA 19-9 level of >1000 U/ml and a CEA level of >14.4 ng/ml were characterized by a poorer respectability rate and survival (22).

AFP

There is an AFP subfraction, named AFP-L3 (lectin-reactive AFP), which proved its utility in the diagnosis of the intrahepatic cholangiocarcinoma. Unlike those with elevated CA 19-9 values, the patients diagnosed with cholangiocarcinoma and increased AFP values have features which resemble those of hepatocarcinoma and are different from those of the classical intrahepatic cholangiocarcinoma (1,23).

CLAUDINE

Claudins are tumor markers expressed by many tissues. Different types have also different expressions in different segments of the biliary tract. For example, the expression of claudin-2 was found to be higher in gallbladder cancer, that of claudin-4 is higher in extrahepatic bile duct cancers. Claudin-4 is can be successfully used for the differentiation of the biliary tract malignancies from hepatocellular cancers. Claudin-1 and claudin-10 have an expression that is higher in intrahepatic bile duct malignancies than in extrahepatic bile duct and gallbladder malignancies (1, 24-26).

Conclusions

Although a specific marker for biliary tract malignancies has not been discovered yet, association between various markers (such as CEA, CA 125, CA 19-9) seem to provide a better orientation of the diagnosis.

References

1. Malaguarnera G, Giordano M, Paladina I, Rando A, Uccello M, Basile F, Biondi A, Carnazzo S, Alessandria I, Mazzarino C. Markers of bile duct tumors. World J GastrointestOncol 2011; 3(4):49-59.
2. Qin XL, Wang ZR, Shi JS, Lu M, Wang L, He QR. Utility of serum CA19-9 in diagnosis of cholangiocarcinoma: in comparison with CEA. World J Gastroenterol 2004; 10(3):427-432.
3. Ramage JK, Donaghy A, Farrant JM, Iorns R, Williams R. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 1995; 108(3):865-869.
4. Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, McCashland TM, Reddy KR, Zervos X, Anbari MA, Hoen H. Cholangiocarcinoma in patients with primary sclerosing

cholangitis: a multicenter case-control study. Hepatology 2000; 31(1):7-11.
5. Joo KR, Kim DH, Park JH, Bang SJ, Shin JW, Park NH, Park JH. The role of bile carcinoembryonic antigen in diagnosing bile duct cancer. J Korean Med Sci 2003; 18(6):855-858.
6. Chaube A, Tewari M, Singh U, Shukla HS. CA 125: a potential tumor marker for gallbladder cancer. J SurgOncol 2006; 93(8):665-669.
7. Narimatsu H, Iwasaki H, Nakayama F, Ikehara Y, Kudo T, Nishihara S, Sugano K, Okura H, Fujita S, Hirohashi S. Lewis and secretor gene dosages affect CA19-9 and DU-PAN-2 serum levels in normal individuals and colorectal cancer patients. Cancer Res 1998; 58(3):512-518.
8. Vestergaard EM, Hein HO, Meyer H, Grunnet N, Jorgensen J, Wolf H, Orntoft TF. Reference values and biological variation for tumor marker CA 19-9 in serum for different Lewis and secretor genotypes and evaluation of secretor and Lewis genotyping in a Caucasian population. ClinChem 1999; 45(1):54-61.
9. Torzilli G, Makuuchi M, Ferrero A, Takayama T, Hui AM, Abe H, Inoue K, Nakahara K. Accuracy of the preoperative determination of tumor markers in the differentiation of liver mass lesions in surgical patients. Hepatogastroenterology 2002; 49(45):740-745.
10. Hultcrantz R, Olsson R, Danielsson A, Jarnerot G, Loof L, Ryden BO, Wahren B, Broome U. A 3-year prospective study on serum tumor markers used for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 1999; 30(4):669-673.
11. Caturelli E, Bisceglia M, Villani MR, de Maio G, Siena DA. CA 19-9 production by a cystadenoma with mesenchymalstroma of the common hepatic duct: a case report. Liver 1998; 18(3):221-224.
12. Nichols JC, Gores GJ, LaRusso NF, Wiesner RH, Nagorney DM, Ritts RE, Jr. Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. Mayo ClinProc 1993; 68(9):874-879.
13. Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci 2005; 50(9):1734-1740.
14. Robertson AG, Davidson BR. Mirizzi syndrome complicating an anomalous biliary tract: a novel cause of a hugely elevated CA19-9. Eur J GastroenterolHepatol 2007; 19(2):167-169.
15. Toomey DP, Swan N, Torreggiani W, Conlon KC. Autoimmune pancreatitis. Br J Surg 2007; 94(9):1067-1074.
16. Murray MD, Burton FR, Di Bisceglie AM. Markedly elevated serum CA 19-9 levels in association with a benign biliary stricture due to primary sclerosing cholangitis. J ClinGastroenterol 2007; 41(1):115-117.
17. Uygur-Bayramicli O, Dabak R, Orbay E, Dolapcioglu C, Sargin M, Kilicoglu G, Guleryuzlu Y, Mayadagli A. Type 2 diabetes mellitus and CA 19-9 levels. World J Gastroenterol 2007; 13(40):5357-5359.
18. Dorandeu A, Raoul JL, Siriser F, Leclercq-Rioux N, Gosselin M, Martin ED, Ramee MP, Launois B. Carcinoma of the ampulla of Vater: prognostic factors after curative surgery: a series of 45 cases. Gut 1997; 40(3):350-355.
19. Nakamura S, Suzuki S, Sakaguchi T, Serizawa A, Konno H, Baba S, Baba S, Muro H. Surgical treatment of patients with mixed hepatocellular carcinoma and cholangiocarcinoma. Cancer 1996; 78(8):1671-1676.
20. Ionel Z, Dumitrascu T, Brasoveanu V, Lupescu I, Anghel R, Herlea V, Ionescu M, Popescu I. Intrahepatic cholangiocarcinoma – the impact of pathological characteristics on the long-term outcome after resection. Modern Medicine 2014; 21(4): 241-245
21. Turculet C, Popescu B. Obstructive jaundice of malignant origin. Modern Medicine 2015; 22(4):390-392
22. Juntermanns B, Radunz S, Heuer M, Hertel S, Reis H, Neuhaus JP, Vernadakis S, Trarbach T, Paul A, Kaiser GM. Tumor markers as a diagnostic key for hilarcholangiocarcinoma. Eur J Med Res 2010; 15(8):357-361.
23. Okuda H, Shiratori K, Yamamoto M, Takasaki K, Nakano M. Clinicopathologic features of patients with intrahepatic cholangiocarcinoma who are seropositive for alpha-fetoprotein-L3 and those with combined hepatocellular and cholangiocarcinoma. J GastroenterolHepatol 2006; 21(5):869-873.
24. Nemeth Z, Szasz AM, Tatrai P, Nemeth J, Gyorffy H, Somoracz A, Szijarto A, Kupcsulik P, Kiss A, Schaff Z. Claudin-1, -2, -3, -4, -7, -8, and -10 protein expression in biliary tract cancers. J HistochemCytochem 2009; 57(2):113-121.
25. Lodi C, Szabo E, Holczbauer A, Batmunkh E, Szijarto A, Kupcsulik P, Kovalszky I, Paku S, Illyes G, Kiss A, Schaff Z. Claudin-4 differentiates biliary tract cancers from hepatocellular carcinomas. Mod Pathol 2006; 19(3):460-469.
26. Nishino R, Honda M, Yamashita T, Takatori H, Minato H, Zen Y, Sasaki M, Takamura H, Horimoto K, Ohta T, Nakanuma Y, Kaneko S. Identification of novel candidate tumour marker genes for intrahepatic cholangiocarcinoma. J Hepatol 2008; 49(2):207-216.