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CA 19-9 and Pancreatic Cancer

Erxi Wu, PhD[1], **Shuang Zhou, BS**[1], **Kruttika Bhat, PhD**[1], and **Qingyong Ma, MD, PhD**[2]
[1]Department of Pharmaceutical Sciences, North Dakota State University, Fargo, North Dakota

[2]Department of Hepatobiliary Surgery, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Discussion

Wu and colleagues describe an interesting case of a 58-year-old white man with stage I pancreatic head adenocarcinoma whose fluctuating carbohydrate antigen 19-9 (CA 19-9) levels did not reflect recurrent pancreatic malignancy.[1] The CA 19-9 level of the patient decreased from 120 U/mL pre-operation to 89 U/mL after resection. Upon receiving chemotherapy, his CA 19-9 level was fluctuating without significant clinical symptoms. He was later diagnosed with melena and anemia associated with elevated CA 19-9 levels, which were reduced by treatment with a proton pump inhibitor. The authors suggest that physicians must be cautious when using CA 19-9 as a diagnostic aid for pancreatic cancer, and that making treatment decisions based solely on a rising CA 19-9 is not recommended.

Indeed, the case of Wu and colleagues is another example that CA 19-9 should not be the only indicator for diagnosing pancreatic cancer.[2,3] Pancreatic cancer is one of the leading causes of cancer-related death, with a 5-year survival rate of only 4–6%.[4,5] This poor prognosis is attributable to late stage presentation, lack of effective treatments, early recurrence, and the absence of clinically useful biomarkers that can detect precursor forms or the earliest stages of disease. Thus, revisiting CA 19-9 to further study its value as a marker for pancreatic cancer is worthwhile.

CA 19-9 is also known to be a sialylated Lewis^a blood group antigen with the sequence NeuNAcα2-3Ga1β1-3Glc [4-Fucα1] NAcβl-3Galβl-4Glc.[6–8] It was originally isolated from the colorectal carcinoma cell line SW1116 using the mouse monoclonal antibody 1116-NS-19-9 in 1979.[6,9,10] This molecule was first identified as a component of a ganglioside[6,11] and was later found to also be a component of glycoproteins[12] and mucins.[13] The concentration of CA 19-9 can be quantitatively determined by a CA 19-9 enzyme-linked immunosorbent assay (ELISA), which measures the CA 19-9 antigen on many different carrier proteins.[14–16] Elevated levels (>37 U/mL) of CA 19-9 have been associated with gastrointestinal carcinomas, particularly in pancreatic cancer,[17–20] and is considered to be one of the most favorable biomarkers for the management of pancreatic cancer.[21–25] It is the only biomarker related to pancreatic cancer for which US Food and Drug Administration (FDA)-cleared diagnostics exist.

An ideal tumor marker should be specific to a given tumor type and highly sensitive in order to refrain from a false positive diagnosis.[26,27] However, CA 19-9 does not appear to fit these criteria due to its inadequate sensitivity,[3,28,29] false negative results in the Lewis blood type negative (Le^{a-b-}) population,[7,30] and high false-positive results induced by obstructive

Address correspondence to: Erxi Wu, PhD, Department of Pharmaceutical Sciences, North Dakota State University, 203 Sudro Hall, Fargo, ND 58108-6050; Phone: 701-231-7250; Fax: 701-231-8333; erxi.wu@ndsu.edu.

jaundice (10–60%).[21,31] The major limitation of CA 19-9 is that it may be markedly elevated in patients with other malignancies such as colorectal, liver, breast, and lung cancers, as well as nonmalignant diseases such as obstructive jaundice, pancreatitis, cirrhosis, and lung disorders.[2,3,18,29,32–34] Previous reports have detected as much as 1,000–6,000 U/mL of CA 19-9 in cholangitis patients.[35,36] Since CA 19-9 serum levels alone cannot distinguish between benign, precursor lesions, and malignant pancreatic and biliary tract conditions, the American Society of Clinical Oncology (ASCO) claimed the specificity and sensitivity of CA 19-9 alone is inadequate for a reliable diagnosis in pancreatic cancer.[37] Interestingly, it has been reported by Howaizi and coworkers[38] that markedly elevated CA 19-9 levels can also be associated with heavy tea consumption, which is another factor to be taken into account when using CA 19-9. Due to the aforementioned limitations, the National Academy of Clinical Biochemistry (NACB) highly recommended that the diagnosis of pancreatic cancer by elevated CA 19-9 be applied in conjunction with combined examination approaches, such as computed tomography (CT) or endoscopic ultrasound (EUS).[39]

Our recent review[2] and other literature have indicated that it is necessary to perform in-depth investigations of CA 19-9 and to make use of its value as a marker for pathological conditions, especially for pancreatic cancer. The current case reported by Wu and colleagues supports the notion that possible false positive/negative results limit the universal application of CA 19-9 in the prognosis of pancreatic cancer. Future efforts should focus on establishing genotype-based reference intervals of CA 19-9 measurement[40] and on the simultaneous detection of CA 19-9 and its specific carriers in order to improve the clinical performance of CA 19-9. As previously mentioned, the CA 19-9 epitope sialylated lacto-N-fucopentaose II can be linked to different carriers, including ganglioside, glycoproteins, and mucins. It has been shown that mucins carry CA 19-9 in patients with pancreatic or gastrointestinal tumors.[15] CA 19-9–bearing mucins are physiological exocrine pancreatic secretion products that accumulate in the blood of pancreatic cancer patients.[15,41] The currently used CA 19-9 clinical assay measures the CA 19-9 antigen without distinguishing its potentially different carriers.[29,42] However, it is possible that the carrier proteins of the CA 19-9 antigen are different between disease states, as suggested by several recently published studies.[43–46] In this case, the detection of the CA 19-9 antigen on particular carrier proteins may yield improved discrimination of the disease states, in comparison to measurements of total CA 19-9. Using such an approach, Yue and colleagues demonstrated enhanced discrimination of malignant versus benign pancreatic disease.[43,45] In order to optimize the CA 19-9 assay and to develop approaches to further improve cancer detection, it is important to understand the specificity differences between CA 19-9 antibodies and the consequential effect on biomarker performance. In addition to CA 19-9, combining other tumor markers (eg, PAM4,[47] DU-PAN-2,[48,49] and *K-ras*[50–53]) with CT or EUS may increase sensitivity and specificity,[29,48,49] although more research efforts are needed. The combination of CA 19-9 with *K-ras* mutational analysis remains controversial.[50–55]

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