

# CA 19-9 Tumor Marker: Is It Reliable?

## A Case Report in a Patient With Pancreatic Cancer

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### Introduction

Pancreatic cancer is one of the most lethal malignancies affecting mankind. At the time of diagnosis, only 20% of patients are considered eligible for surgery and approximately one half of these patients undergo successful resection. For patients with locally advanced or metastatic disease, the median survival time is less than 1 year.<sup>1-4</sup> Thus, it is crucial to diagnose or detect the recurrence of pancreatic cancer at its early stage. Serum or tissue tumor markers have been proposed for use in clinical practice in order to predict prognosis, monitor response to treatment, and help detect recurrence. Among such markers, carbohydrate antigen 19-9 (CA 19-9) is the most widely investigated. However, because CA 19-9 may be an imprecise or insufficient indicator of disease progression, treatment decisions should not be based solely on an increase of CA 19-9 levels. Here we present a case of a patient whose fluctuating levels of CA 19-9 did not reflect recurrent pancreatic malignancy.

### Case Report

A 58-year-old white man was admitted for evaluation of painless jaundice and weight loss. Although no obvious mass was detected on computed tomography (CT) scan, endoscopic retrograde cholangiopancreatography (ERCP) brush cytology revealed malignant pancreatic ductal cells. Pathology results following a Whipple procedure confirmed a stage I pancreatic head adenocarcinoma in a tumor less than 2 cm in diameter. Preoperative CA 19-9 of 120 U/mL decreased to 89 U/mL postoperatively.

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The patient received adjuvant concurrent 5-fluorouracil (5-FU)-based chemoradiation followed by sequential maintenance capecitabine (Xeloda, Hoffmann-La Roche). CA 19-9 levels initially decreased to 40 U/mL, but gradually rose to 100 U/mL. Treatment with gemcitabine (Gemzar, Eli Lilly) was initiated, which resulted in normalized levels of CA 19-9. Since the original diagnosis, the patient had fluctuating CA 19-9 levels with no significant clinical symptoms and negative staging positron emission tomography (PET) and CT scans. Aggressive chemotherapy with erlotinib (Tarceva, Genentech/Roche) was administered to prevent biochemical relapse of CA 19-9 and the development of metastasis. The patient was recently admitted for melena and anemia. Upper endoscopy showed a bleeding peptic ulcer at the anastomotic site and elevated CA 19-9 levels at 100 U/mL. He was started on a proton pump inhibitor for the treatment of the peptic ulcer, which resulted in a dramatic reduction of his CA 19-9 levels.

### Discussion

#### *Clinical Significance and Limitations of CA 19-9*

CA 19-9 is a tumor-associated antigen that was first described in the early 1980s.<sup>5,6</sup> A large literature review of 24 pancreatic cancer studies in 1990 by Steinberg and associates showed that when using 37 kU/L as a cutoff point, CA 19-9 was reported to have a median sensitivity of 81% and specificity of 90%, whereas increasing the cutoff point to 100 kU/L improved specificity to 98% but reduced sensitivity to 68%.<sup>7</sup>

Physicians must be careful when using CA 19-9 as a diagnostic aid for pancreatic cancer. CA 19-9 exists as an epitope of sialylated Lewis A blood group antigen and it is not expressed in subjects with Lewis  $\alpha$ - $\beta$ - genotype, which accounts for approximately 5–10% of the Caucasian population.<sup>8,9</sup> CA 19-9 is increased in multiple

gastrointestinal cancers, but elevated levels are also found in benign diseases, including peptic ulcers, chronic and acute pancreatitis, cirrhosis, cholangitis, and obstructive jaundice.<sup>10-13</sup> In patients with cholangitis and obstructive jaundice, it is recommended to recheck CA 19-9 levels after treatment, as levels usually decline after biliary decompression.<sup>12</sup> CA 19-9 lacks the sensitivity for detecting early pancreatic cancer and is elevated in only 50% of pancreatic adenocarcinomas less than 3 cm in size. Poorly-differentiated pancreatic cancer also appears to produce less CA 19-9 than moderately- or well-differentiated cancers.<sup>7</sup>

### ***Predictive and Prognostic Value of CA 19-9***

CA 19-9 is not accurate enough to be used in screening asymptomatic patients for pancreatic cancer. Large studies have been performed in Japan and Korea that assessed the usefulness of CA 19-9 in diagnosing pancreatic cancers. A mass screening carried out in Japan in the 1980s of 10,162 asymptomatic subjects resulted in detection of only 4 cases of pancreatic cancer.<sup>14</sup> Screening of 4,506 symptomatic patients found 85 cases (2%), of which 28 were resected (32%).<sup>15</sup> A similar study in Korea involving the screening of 70,940 asymptomatic subjects detected only 4 patients with pancreatic cancer.<sup>16</sup> Therefore, CA 19-9 is not recommended to be used as a screening test for pancreatic cancer, particularly in asymptomatic patients.

CA 19-9 levels were assessed for potential use in determining the antitumor activity of treatment. In a study by Micke and colleagues that sought to determine the predictive value of CA 19-9 in locally advanced pancreatic cancer patients treated with the combination of radiation and 5-FU, CA 19-9 was measured before and during therapy.<sup>17</sup> Patients who had a treatment-related decline in CA 19-9 levels exhibited prolonged median survival. In a multivariate analysis, a decrease of CA 19-9 during chemotherapy was found to be an independent prognostic factor regarding survival.<sup>17</sup> Multiple studies have reported that responders whose CA 19-9 levels were reduced by more than 50% of pretreatment baseline levels have a longer median survival when compared to CA 19-9 nonresponders.<sup>18</sup> Okusaka and coworkers found that in patients receiving chemotherapy and radiotherapy for locally advanced pancreatic cancer, the CA 19-9 responders had a longer median survival of 10.6 months compared to 4.1 months in nonresponders.<sup>19</sup> In metastatic pancreatic cancer patients, Ishii and associates reported longer median survival times in CA 19-9 responders than in nonresponders (141 days vs 88 days). The relative risk of cancer death in CA 19-9 responders versus nonresponders was 0.47 (95% confidence interval [CI], 0.21–1.05).<sup>20</sup> A study of 87 patients in 2003 by Stemmler and colleagues showed that among patients who received combination chemotherapy with gemcitabine and cispla-

tin, CA 19-9 responders survived significantly longer than CA 19-9 nonresponders (295 days vs 174 days;  $P=.022$ ).<sup>21</sup>

Postoperative surveillance studies have shown that serial determination of CA 19-9 can detect recurrence or metastasis of pancreatic cancer several months before finding clinical or radiologic evidence of disease.<sup>22</sup> In a phase II trial evaluating the efficacy of combined irinotecan and gemcitabine in the treatment of advanced pancreatic cancer, a significant correlation ( $P<.001$ ) was found between the proportional changes in CA 19-9 and radiologic changes of the tumor with regard to extent of change ( $r=.67$ ), and also a strong correlation ( $P<.001$ ) between CA 19-9 progression and time to disease progression ( $r=0.89$ ), with CA 19-9 progression preceding radiographic progression in most of the patients.<sup>23</sup> In a subsequent phase III study, although the overall diagnostic accuracy of CA 19-9 values in the predication of tumor response and tumor progression from radiologic evaluation was low (57.6% and 59%, respectively), a less than 50% decline in CA 19-9 values was predictive of a lack of response as determined by Response Evaluation Criteria In Solid Tumors (RECIST) criteria, with a negative predictive value of 94.8%. In addition, progression of CA 19-9 values was predictive of disease progression, with a positive predicted value of 82.8%.<sup>24</sup>

### ***Current Recommendations For the Use of CA 19-9 in Pancreatic Cancer***

Although multiple studies have demonstrated the prognostic value of CA 19-9 in monitoring response to treatment, changing treatment based solely on rising CA 19-9 levels is not recommended. According to the American Society of Clinical Oncology (ASCO) guidelines for the use of CA 19-9 as a marker for pancreatic cancer,<sup>25</sup> CA 19-9 measurements by themselves cannot provide definite evidence of disease recurrence without confirmation by imaging for clinical findings and/or biopsy. CA 19-9, however, can be measured every 1–3 months during active treatment. A rise in serial CA 19-9 levels may indicate disease progression, and confirmation of progression should be established with additional testing.

### **Conclusions**

CA 19-9 has been the most widely used tumor marker in pancreatic cancer. Certain limitations of CA 19-9, such as elevated levels in benign jaundice, pancreatitis, ovarian cancer, or other gastrointestinal malignancies, have made it unfavorable as a screening test. The rising CA 19-9 levels in patients under observation or in those receiving active therapy could be an indicator of disease recurrence, progression, and ineffectiveness of the current regimen, and may be correlated with shorter sur-

vival time. However, the value of initiating therapy based on rising CA 19-9 levels remains to be demonstrated. Decisions to initiate or change chemotherapy should not be made before seeking additional confirmative tests.

Our patient, who presented with serial rising of CA 19-9 but had no clinical symptoms or positive image findings, was treated aggressively with different chemotherapy regimens. This is not recommended based on current guidelines, which state that CA 19-9 alone is not sufficient to indicate progression of disease. In addition, the magnitude of change in CA 19-9 levels that is considered clinically significant has not yet been determined. Interestingly, when our patient received adequate treatment for peptic ulcers, his CA 19-9 levels decreased dramatically. Thus, clinicians should always be mindful of the limitations when interpreting the significance of a rising CA 19-9. Chemotherapy should not be initiated without definitive evidence of disease recurrence.

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# Review

## CA 19-9 and Pancreatic Cancer

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### 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.<sup>1</sup> 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.<sup>2,3</sup> Pancreatic cancer is one of the leading causes of cancer-related death, with a 5-year survival rate of only 4–6%.<sup>4,5</sup> 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<sup>x</sup> blood group antigen with the sequence NeuNAc $\alpha$ 2-3Gal $\beta$ 1-3Glc [4-Fuc $\alpha$ 1] NAcb $\beta$ 1-3Gal $\beta$ 1-4Glc.<sup>6-8</sup> It was originally isolated from the colorectal carcinoma cell line

SW1116 using the mouse monoclonal antibody 1116-NS-19-9 in 1979.<sup>6,9,10</sup> This molecule was first identified as a component of a ganglioside<sup>6,11</sup> and was later found to also be a component of glycoproteins<sup>12</sup> and mucins.<sup>13</sup> 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.<sup>14-16</sup> Elevated levels (>37 U/mL) of CA 19-9 have been associated with gastrointestinal carcinomas, particularly in pancreatic cancer,<sup>17-20</sup> and is considered to be one of the most favorable biomarkers for the management of pancreatic cancer.<sup>21-25</sup> 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.<sup>26,27</sup> However, CA 19-9 does not appear to fit these criteria due to its inadequate sensitivity,<sup>3,28,29</sup> false negative results in the Lewis blood type negative (Le<sup>a-b-</sup>) population,<sup>7,30</sup> and high false-positive results induced by obstructive jaundice (10–60%).<sup>21,31</sup> 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.<sup>2,3,18,29,32-34</sup> Previous reports have detected as much as 1,000–6,000 U/mL of CA 19-9 in cholangitis patients.<sup>35,36</sup> 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.<sup>37</sup> Interestingly, it has been reported by Howaizi and coworkers<sup>38</sup> 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).<sup>39</sup>

Our recent review<sup>2</sup> 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<sup>40</sup> and on the simultaneous detection of CA

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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.<sup>15</sup> CA 19-9-bearing mucins are physiological exocrine pancreatic secretion products that accumulate in the blood of pancreatic cancer patients.<sup>15,41</sup> The currently used CA 19-9 clinical assay measures the CA 19-9 antigen without distinguishing its potentially different carriers.<sup>29,42</sup> 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.<sup>43-46</sup> 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.<sup>43,45</sup> 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,<sup>47</sup> DU-PAN-2,<sup>48,49</sup> and *K-ras*<sup>50-53</sup>) with CT or EUS may increase sensitivity and specificity,<sup>29,48,49</sup> although more research efforts are needed. The combination of CA 19-9 with *K-ras* mutational analysis remains controversial.<sup>50-55</sup>

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