

The clinical utility of normal range carbohydrate antigen 19-9 level as a surrogate marker in evaluating response to treatment in pancreatic cancer – a report of two cases

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Abstract: Carbohydrate antigen 19-9 (CA 19-9) is a tumor marker that is has been has been intensely studied and investigated as a surrogate marker in pancreatic cancer (PC). It is also commonly utilized in the clinical management of PC. We report two cases where normal range CA 19-9 level has been shown to be useful as a surrogate marker for following PC progression and response to treatment. Initially in our cases, both patients had a resectable tumor and their tumor markers were within normal range. In both cases the normal range CA 19-9 increase from the baseline was associated with corresponding progressive disease on imaging studies and CA 19-9 decline was in keeping with response to systemic and local therapy despite being within the normal range. To our knowledge, this is the first case report where we report the utility of serial normal values of CA 19-9 as a useful tool in following PC disease activity and in response to treatment. Clinicians should consider measuring serial normal values of CA 19-9 in patients with PC and normal range CA 19-9 which may help in assessing response to treatment in subset of this population.

Keywords: Pancreatic cancer (PC); tumor marker; carbohydrate antigen 19-9 (CA 19-9); CA 19-9 level; Lewis genotype; Secretor genotypes

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Introduction

Carbohydrate antigen 19-9 (CA 19-9) was isolated and reported by Koprowski *et al.* for the first time in 1979 (1). Even though it was not widely used clinically (2), it was the only available serum biomarker for pancreatic cancer (PC) (3). Previous report suggested the usefulness of serial monitoring of CA 19-9 levels in patients with resected PC post curative surgery (4). Serial monitoring of CA 19-9 levels is also useful for patients who receive chemotherapy for advanced disease (4). Several different groups have demonstrated a correlation between longevity of patients receiving chemotherapy for advanced disease and the level of CA 19-9 (5-10). These studies suggest a declining level of CA 19-9 in those patients receiving chemotherapy. In addition, it is also observed a prognostic impact of CA

19-9 in those patients (2). Considering this, the American Society of Clinical Oncology (ASCO) recommended Ca 19-9 measurement prior to any PC treatment. ASCO also recommended serial measurements of CA 19-9 during the therapy of advanced PC (once in every 1 to 3 months) (11).

After a decade from Koprowski and coworkers reporting the usefulness of CA 19-9, it has become the most widely used blood test among PC patients. It has a higher sensitivity (80% approx.) and specificity (90% approx.) with an upper limit of 37 U/mL cut-off value (12). CA 19-9 is also widely used in predicting unresectability of pancreatic adenocarcinoma (12). It has been reported that, at least 96% of tumors that result in blood levels greater than 1,000 U/mL have been found to be unresectable (3).

In it is widely accepted that CA 19-9 level is only

clinically useful if it was elevated above the normal range. In this report, we report two cases where normal range CA 19-9 level has been found to be a useful tool (surrogate marker) in following PC activity and in response to treatment in patients with PC.

Case presentation

Case 1

A 56-year-old Caucasian female with a localized PC confined to the neck of the pancreas, went under a pancreaticoduodenectomy with a positive margin. The surgical pathology was reported with concerning microscopic positive margin at the proximal and distal portal vein margins and had a pathological staging of pT3N1Mx adenocarcinoma of the pancreas according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh Edition [2010]. pT3 defined as tumor extends beyond the pancreas but without the involvement of the celiac axis or the superior mesenteric artery, pN1 defined as regional lymph nodes metastasis, the patient had 2 out of 30 lymph nodes involved, Mx distance metastasis can not be assessed, clinically the patient had M0 which is defined as no evidence of distant metastasis.

The patient preoperatively had a normal range of CA 19-9 with a level of 6.5 U/mL (normal range, 0.0–35.0). However, we observed a post-surgery marginal decline to 5 U/mL (*Table 1* and *Figure 1, A*). At 8 weeks post-operative period, CT imaging shows no interval development of metastatic disease. She underwent adjuvant systemic chemotherapy (gemcitabine 600 mg/m² for 3 weeks on and 1 week off schedule for 4 cycles) followed by radiation treatment with stable CA 19-9 value of 7.1 U/mL (*Table 1* and *Figure 1, B*). An increase in the CA 19-9 level to (9.8 U/mL) (*Table 1* and *Figure 1, C*) was noted during surveillance, this was consistent with the imaging studies in keeping with evidence of metastatic disease with peritoneal implant. The patient received 6 cycles of systemic palliative chemotherapy (6 cycles of GAX, each cycle is administered every 2 weeks, Gemcitabine at 400 mg/m², Abraxane (nab-paclitaxel) at 100 mg/m² and Xeloda (capecitabine) at 1,350 mg/m² which lead to marginal decline in the CA 19-9 level to 8.5 U/mL (*Table 1* and *Figure 1, D*).

The patient had a response to the treatment based on imaging studies which was associated with a decline in CA 19-9 level to 8 U/mL (*Table 1* and *Figure 1, E*). The CA 19-9 level plateaued (7.8 U/mL), without any sign of active disease on imaging studies surveillance continued (*Table 1* and *Figure 1, F-H*). Gradually CA 19-9 level

increased to 9.5 U/mL from the plateau level without any obvious clinical sign of progressive disease or as evidenced by imaging studies. Subsequently multifocal peritoneal implants was noted on imaging studies with a sharp increase in CA 19-9 value to 19.1 U/mL (*Table 1* and *Figure 1, J*). After re-introducing of the systemic chemotherapy (GAX) for 6 cycles (similar dosing and schedule as above) this was followed by a decline of CA 19-9, from 19.1 to 10.5 U/mL and there was a radiological response. After 6 months from the last chemotherapy treatment, the CA 19-9 level had increased up to 26.8 U/mL which is still within the normal range yet this was associated with evidence of relapsed disease in the peritoneum, systemic chemotherapy (GAX) was reintroduced for a total of 6 cycles (similar dosing and schedule as above) with subsequent decline in the level to 16.2 U/mL (*Table 1* and *Figure 1, M*) in keeping with response to the systemic treatment as confirmed by the imaging studies.

The serum CA 19-9 level declined for few months then peaked up to 16 U/mL without any sign of progression of disease as evidenced from the imaging studies (*Table 1* and *Figure 1, O*). However, the serum CA 19-9 level continued to rise and peaked to 30 U/mL with evidence of recurrent peritoneal disease on imaging CT (*Table 1* and *Figure 1, P*). Systemic chemotherapy (GAX) was reintroduced for a total of 2 cycles (similar dosing and schedule as above). After re-introducing the systemic chemotherapy the CA 19-9 level declined to 14 U/mL (*Table 1* and *Figure 1, Q*). Afterwards we noted a sharp peak in the CA 19-9 level which reached to 40 U/mL and which is above the upper limit of normal for CA 19-9 as per our institution (normal, 0.0–35.0). Imaging studies confirmed the progression of disease and patient currently receiving GAX systemic chemotherapy (similar dosing and schedule as above).

Case 2

The second case we are reporting a 68-year-old Caucasian female with borderline resectable pancreatic head adenocarcinoma. The preoperative CA 19-9 level of the patient was 12.5 U/mL (normal range, 0.0–35.0). The patient received neoadjuvant chemotherapy as part of a clinical trial with gemcitabine/erlotinib (gemcitabine 600 mg/m² for 3 weeks on and 1 week off schedule for 6 cycles and erlotinib orally at 100 mg daily for 6 months (*Table 2* and *Figure 2, A*).

A post-surgery decline of the CA 19-9 level to 10 U/mL was observed (*Table 2* and *Figure 2, B*) the patient underwent pancreaticoduodenectomy with negative margin—final

Table 1 CA 19-9 level variation over the treatment course in case 1

Point	Intervention	CA 19-9 level (normal, 0.0–35.0) (U/mL)
A	Surgery	6.5
B	Adjuvant chemotherapy therapy	7.1
C	Metastatic pancreatic cancer	9.8
D	Palliative chemotherapy (GAX for 6 cycles)	8.5
E	Treatment response on imaging	8.0
F + H	Surveillance—no active treatment	7.8
I	Surveillance—no active treatment	9.5
J	Relapsing metastatic disease with re introduction of palliative chemotherapy (GAX for 6 cycles)	19.1
K	Treatment holiday	10.5
L	Relapsing metastatic disease with re introduction of palliative chemotherapy (GAX for 6 cycles)	26.8
M	Treatment holiday	16.2
O	Relapsing metastatic disease	16.0
P	Re-introduction of palliative chemotherapy (GAX for 2 cycles)	30.0
Q	Treatment holiday	14.0
R	Relapsing metastatic disease	40.0

CA 19-9, carbohydrate antigen 19-9.

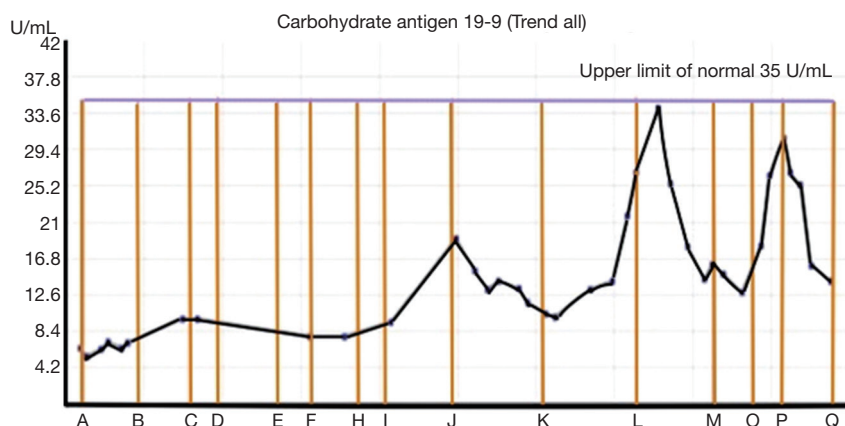


Figure 1 CA 19-9 level variation over the treatment course in case 1, horizontal line represents time in months, where A represents CA 19-9 level at diagnosis. CA 19-9, carbohydrate antigen 19-9.

pathological staging pT3N1MX adenocarcinoma of the pancreas according to the AJCC Cancer Staging Manual, Seventh Edition [2010]. pT3 defined as tumor extends beyond the pancreas but without the involvement of the celiac axis or the superior mesenteric artery, pN1 defined as regional lymph nodes metastasis, the patient had 5 out of 34 lymph nodes involved, Mx distant metastasis cannot be assessed, clinically the patient had M0 which is defined as no evidence of distant metastasis.

After the surgery the patient underwent adjuvant gemcitabine chemotherapy and had a marginal decline in the CA 19-9 to 9 U/mL (Table 2 and Figure 2, C).

On subsequent surveillance, the patient was noted to have an increase in the CA 19-9 level to 16 U/mL (Table 2 and Figure 2, D) imaging studies did not demonstrate any evidence of disease, patient continued surveillance, CA 19-9 level further increased to 22 U/mL (Table 2 and Figure 2, E). This was associated with peritoneal metastasis in the

Table 2 CA 19-9 level variation over the treatment course in case 2

Point	Intervention	CA 19-9 level (U/mL)
A	CA 19-9 level at diagnosis	12.5 (normal, 0.0–47.0)
B	Surgery (pancreaticoduodenectomy)	10.0 (normal, 0.0–47.0)
C	Adjuvant chemotherapy (gemcitabine)	9.0 (normal, 0.0–47.0)
D	Recurrent disease with peritoneal metastasis	16.0 (normal, 0.0–35.0)
E	Systemic chemotherapy for metastatic disease (GAX)	22.0 (normal, 0.0–35.0)
F	Systemic chemotherapy for metastatic disease (GAX)	16.2 (normal, 0.0–35.0)
G	Vaginal local recurrence treated with concurrent chemoradiation with capecitabine	13.0 (normal, 0.0–35.0)

CA 19-9, carbohydrate antigen 19-9.

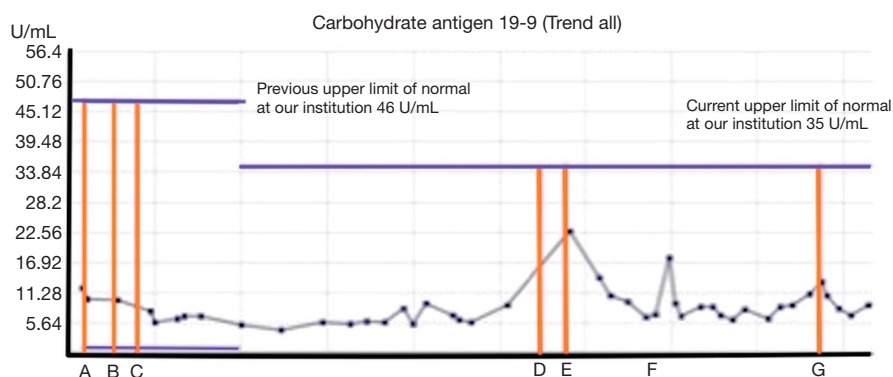


Figure 2 CA 19-9 level variation over the treatment course in case 2, horizontal line represents time in months, where A represents CA 19-9 level at diagnosis. *, upper limit of normal at our institution was 46 U/mL, this was later changed to 35 U/mL to reflect more accurate cut off point for normal range. CA 19-9, carbohydrate antigen 19-9.

imaging studies; palliative systemic chemotherapy (GAX) was introduced for metastatic disease at similar dosing and schedule as case 1. Subsequently the CA 19-9 level decreased in keeping with response to systemic treatment which was confirmed on imaging studies. Recurrent peritoneal metastasis disease responded to re-introduction of palliative chemotherapy (4 cycles of GAX).

Unfortunately the patient experienced vaginal local recurrence with the CA 19-9 level increase to 13 U/mL, this was treated with concurrent chemoradiation with capecitabine and CA 19-9 declined to 6.5 U/mL from an initial value of (Table 2 and Figure 2, G). The patient is currently under surveillance without any evidence of active disease.

Discussion

Patients with PC mostly require multimodalities treatment including surgery, radiation and chemotherapy either in the neoadjuvant, adjuvant or metastatic settings (5). Multiple studies have demonstrated that a treatment related decline in

CA 19-9 serum levels is associated with prolonged survival and is an independent predictor of overall survival (5,10,13,14). CA 19-9 has been used extensively in the clinical settings to assess response to treatment for PC (10). In clinical research, CA 19-9 has also been used as a surrogate marker in neoadjuvant, adjuvant and also metastatic disease (15,16).

Several previously reported studies have explored the utility and sensitivity of CA 19-9 serum levels as a screening tool for PC (12,17-19). Previous reporters suggested an optimal value of CA 19-9 in serum as >37 U/mL (20), although the sensitivity and specificity were in a range of 96% to 99% respectively. CA 19-9 levels also have low specificity (20). CA 19-9 is frequently elevated in patients with cancers other than PC and various benign pancreaticobiliary disorders (12,21-24). One study found that serum concentrations above 37 U/mL represented the most accurate cut-off value for discriminating PC from benign pancreatic disease, but the sensitivity and specificity for PC at this level were only 77 and 87 percent, respectively (25). Furthermore, the positive predictive value (PPV) is low,

Table 3 Genotype-specific reference values for CA 19-9 in serum[#]

Variables	Lewis gene	Secretor gene	n	Median, kilounits/L	Range, kilounits/L	Upper reference limit*, kilounits/L	CVG, %
All individuals			497*	4.1	<2.5–66.5	28.7	102.2
Women			118	5.2	<2.5–47.2	30.2	94.2
Men			379 [#]	3.6	<2.5–66.5	23.0	106.9
Genotype groups							
1	Le/Le	se/se	51	14.4	2.9–61.2	50.6	69.4
2	Le/le	se/se	39	12.2	2.6–30.0	30.0	45.9
3	Le/Le	Se/se	113	4.7	<2.5–27.2	17.7	68.8
4	Le/le	Se/se	91	3.7	<2.5–12.1	11.0	48.2
5	Le/Le	Se/Se	86	3.7	<2.5–28.7	27.6	93.1
6	Le/le	Se/Se	77	3.0	<2.5–10.2	7.9	42.9

[#], in three individuals, no serum was available; *, *Clinical Chemistry* 1999;45:54-61. Adapted from Vestergaard EM *et al.*, 1999, used with the permission from the *Journal of Clinical Chemistry*. CA 19-9, carbohydrate antigen 19-9.

particularly among asymptomatic individuals. In a large series of over 70,000 asymptomatic individuals, the PPV of a serum CA 19-9 level >37 U/mL was only 0.9% (26). Because of this, expert guidelines recommend against the use of CA 19-9 as a screening test for PC (11). Even among symptomatic individuals (epigastric pain, weight loss, jaundice), the sensitivity, specificity, and PPV of an elevated CA 19-9 >37 U/mL level are only approximately 80%, 85%, and 72% (3,12).

Clinically CA 19-9 level has only been serially measured if the initial level has been elevated on presentation. Most clinicians usually stop measuring the CA 19-9 serum level if the level is within normal range. The CA 19-9 level in previously reported cases have been within the normal range. Despite that, the CA 19-9 level has been a useful surrogate marker to follow the patients' progression and response to treatment in neoadjuvant, adjuvant and metastatic settings. Both patients had a resectable PC, an indolent course of disease and sensitivity to systemic chemotherapy treatment with decline in the CA 19-9 associated with imaging response and clinical improvement.

In one report at least 76.9% of stage III PC patients with a CA 19-9 serum level of <37 U/mL survived more than 5 years (27). In another retrospective study concluded that an elevated preoperative CA 19-9 serum levels of >200 U/mL, a high-grade tumor, an R2 resection independently predicted early death (20). In another study, 129 subjects with surgically resected PC were grouped based on their pre-operative CA 19-9 level [undetectable, normal (<37 U/mL), 38–200 U/mL, and >200 U/mL]. It was found that patients

with undetectable pre-operative CA 19-9 serum levels and serum levels of <37 U/mL had an improved survival rate compared to patients with CA 19-9 serum levels between 37–200 U/mL (28). These studies give an insight into various cut-off levels for pre-operative CA 19-9 serum levels in an effort to predict survival among PC patients.

CA 19-9 requires the presence of the Lewis blood group antigen (a glycosyltransferase) to be expressed. Among individuals with a Lewis-negative phenotype (an estimated 5 to 10 percent of the population) the CA 19-9 is normal (16,29). The concentration of the tumor marker CA 19-9 is influenced by the patient's secretor status and Lewis genotype, which is determined by the immunological reactivities with Lewis carbohydrate antigens on blood cells (29). It is also known that genetic background of the patient influence the overall Lewis structures on the cell membrane (16). The structure A1 Lewis b is more complex than the structure Lewis b, which creates a discrepancy between Lewis positive and Lewis negative individuals (29). In addition to the Lewis genotype, CA 19-9 concentrations in secretor individuals normally depend on the Secretor genotypes (*Se/Se* or *Se/se*) (29). Patients with heterozygous mutated in the Secretor gene shows higher concentrations of CA 19-9 in serum than individuals who are homozygous wild type (29).

As mentioned above, a study by Vestergaard *et al.*, Reported the mean level of CA 19-9 for subgroups with different secretor and Lewis genotypes were found to be 28.7 kilounits/L (29). However, for secretors and nonsecretors groups, the upper limits were detected as 12.4 and 61.2 kilounits/L, respectively (29) (Table 3). This

partitioning of the data was originally described by another group (30), where it was reported that a statistical difference between the different subgroups represents one possible way to increase the clinical utility of CA 19-9 tumor marker.

In our two patients, we were unable to determine the secretory and Lewis genotype as the test was not available in our institution, we suspect the secretory status of the patients was contributing to the low level of CA 19-9, as evident in the first patient, The CA 19-9 level has increased above the upper limit of normal as the tumor became more aggressive (based on imaging studies) and more resistant to chemotherapy which indicates likely the patient has positive Lewis genotype.

Conclusions

CA 19-9 is the most extensively studied and widely used biomarkers for treating PC. CA 19-9 is usually not serially measured if the initial value is within normal range. However, from our two reported cases we suggest that measuring and following serum CA 19-9 in patient with normal range values may be helpful in monitoring a subset of this population who may be undersecretors, this may help in following PC disease activity in response to various treatment modalities specially in patients with low volume of disease which can be difficult to assess response on imaging studies only.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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