ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 136 SECTIO D 2004

2nd Department of General Surgery, Skubiszewski Medical University of Lublin

GRZEGORZ ĆWIK, GRZEGORZ WALLNER, TOMASZ SKOCZYLAS, MACIEJ KRZYŻANOWSKI, ALEKSANDER CIECHAŃSKI, PRZEMYSŁAW MĄDRO

Elevated tumor marker CA 19-9 in the differential diagnosis of pancreatic mass lesions

The diagnostic work-up of pancreatic tumors can be expensive and invasive. An accurate and efficient diagnosis continues to be a difficult clinical challenge. Adenocarcinoma is the most frequent form of all mass lesions in pancreatic pathology (6, 9, 10).

Clinical research conducted around the world is supposed to set relatively simple and reliable noninvasive diagnostic technique that would be able to differentiate malignant from benign tumor quickly and cost-effectively. Ductal pancreatic cancer reveals expression of mucin-related carbohydrate antigens, such as CEA, CA 19-9, DU-PAN-2, Span 1, the mucin MUC 1, and cytokeratins 7, 8, 18, 19 (5, 10). The CA 19-9 marker is an antigen determinant, defined by murine monoclonal antibody 1116-NS-19-9, resulting from the immunization by cancer cells, and is specific for the colon-carcinoma-derived cell-lines. Despite that, the elevated CA 19-9 serum level in pancreatic adenocarcinoma has been also demonstrated (3, 4, 5, 9). CA 19-9 is described as the most useful serologic marker in diagnosing of pancreatic cancer with sensitivity of 63–93% and specificity of 78–98% (1, 6, 7, 8, 9, 11, 14, 15). It is reported that the elevated Ca 19-9 level can also be evident in the extrapancreatic tumors and in benign lesions, particularly with concomitant high bilirubin level (2, 3, 6, 9, 11). Because of that, sensitivity and specificity of the test will never reach 100%. The CA 19-9 marker is a reliable diagnostic test when is evaluated in consistency with US, EUS or CT (6, 14).

In the preoperative staging of pancreatic cancer the tumor marker level correlates with a large tumor size as well as with a high stage of tumor advancement. It allows to use the CA 19-9 marker as an indicator of some boundary beyond which the tumor is highly likely to be unresectable (1, 4, 5, 11, 15). The CA 19-9 level may also be considered as a prognostic factor (7, 15).

The aim of the present study was to evaluate efficacy of the elevated serum CA 19-9 level in the differential diagnosis of pancreatic tumors.

MATERIAL AND METHODS

One hundred and fifty patients with heterogenic pancreatic lesion were diagnosed and treated between June 1998 and December 2003 at 2nd Department of General Surgery of the Medical University of Lublin. Their age ranged between 26 and 78 years. Percutaneous ultrasound (US) was performed in all the patients at our own ultrasound unit. For more precise evaluation of the lesion 97 patients underwent a computed tomography (CT) in 5-mm scans at the Radiology Department of the Medical University (Head – prof. J. Złomaniec). Following detailed analysis of US and CT presentation of the

lesion, the patients were preliminarily qualified for US-guided fine-needle aspiration biopsy. The biopsy samples were taken twice from two distant areas (central and peripheral). In 16 patients, an additional biopsy was taken due to difficulty in cytological evaluation, or due to taking of the samples in inappropriate manner (cell-less samples), or due to a discrepancy between the microscopic and the preliminary US and/or CT evaluation. The cytological evaluation was carried out immediately following receiving of the samples and hematoxylin/eosin staining. Eventually, the results of cytological evaluation were verified during open resection surgery, bypass surgery or explorative laparotomy. All patients with cholestasis, in whom the tumor was regarded inoperable, underwent endoscopic stent placement or percutaneous biliary drainage when necessary.

The CA 19-9 marker assaying. VIDAS CA 19-9 assay utilizes murine 1116-NS-19-9 antibody. This antibody binds reactive antigen determinants, 1116-NS-19-9, fixed to tumor glycoproteins of the high molecular weight. The test is based on immunoenzymatic, sandwich, dual-phase reaction with ending fluorescence recording (ELFA). The test results are expressed in units per milliliter (U/ml). The basic value range was 0–500 U/ml with the possibility of further dilutions and determination of the maximal marker level of up to 100,000 U/ml.

Statistical methods. The diagnostic accuracy of the CA 19-9 assay was determined using standard statistical definitions. Sensitivity of the assay was defined as the number of true positive assay results divided by the total number of patients with confirmed pancreatic cancer. Specificity of the assay was defined as the number of true negative assay results divided by the total number of patients without pancreatic cancer. Predictive value of a positive assay was defined as the number of true positive assay results divided by the total number of positive assay results. Predictive value of a negative assay was defined as the number of true negative assay results divided by the total number of negative assay results.

RESULTS

In 150 patients with pancreatic tumor, the lesion was confined to the head of the pancreas in 116 patients, to the body and tail of the pancreas in 29 patients and to the tail of the pancreas in the remaining 5 patients. Among 116 patients with the tumor of the head of the pancreas, an elevated bilirubin level (> 2 mg%) was found in 79 patients (68.1%).

Overall 372 US-guided fine-needle aspiration biopsies were carried out in all 150 patients. In 15 patients the procedure was repeated due to an equivocal result. The cytological evaluation revealed cancerous cells or cell atypia indicating malignant nature of the lesion in 84 patients. Finally, after clinical and histopathological evaluation the malignant pancreatic tumor was diagnosed in 98 of 150 patients and the benign pancreatic tumor was diagnosed in the remaining 52 patients.

Serum level of the CA 19-9 marker. In all 150 patients with pancreatic tumor the CA 19-9 marker was assayed. The values ranged from < 3 to 56,000 U/ml. In patients with confirmed pancreatic cancer CA 19-9 level exceeded the reference cut-off level of 37 U/ml in the majority of cases (80 patients). However, in 16 patients the CA 19-9 level was lower than 37 U/ml or around the reference value. The CA 19-9 level over 500 U/ml was found in 40 patients and in 32 of them (80%) advanced neoplastic process in a form of distant metastases, neoplastic dissemination, wide lymph node involvement or wide local infiltration was demonstrated. In this group of patients no false positive result (benign lesion) was found. In patients with benign pancreatic tumor the CA 19-9 level ranged from 0 to 300 U/ml. Most of CA 19-9 values were low and ranged between 0 and 37 U/ml in 47 patients, which constituted 87% of patients with benign tumor. The marker level exceeded the reference value in 5 patients. In these patients the mass lesion over 50 cm^3 and the significantly elevated bilirubin level indicating a high degree of cholestasis were demonstrated on individual case analysis. A detailed distribution of the CA 19-9 level in both groups is demonstrated on Figure 1.

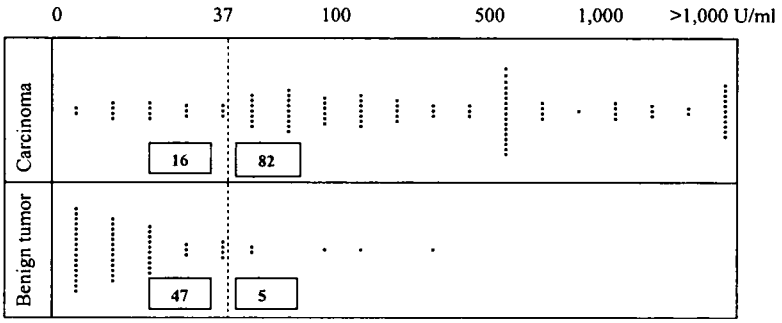

Fig. 1. The CA 19-9 marker levels in patients with pancreatic tumor. The groups of malignant and benign pancreatic tumor following verification are demonstrated separately. The cut-off level of the marker was 37 U/ml

Based on cytological, histopathological and clinical evaluation patients were assigned to the group of malignant or benign pancreatic lesion. Correlation of tumor nature to the serum CA 19-9 level revealed true positive assay results in 82 (54.7%) of cases and false positive assay results in 5 (3.3%) of cases. The detailed results are listed in Table 1.

Table 1. Evaluation of the CA 19-9 marker assay correlated to confirmed malignant lesion in the differential diagnosis of pancreatic cancer

True positive results	82
False positive results	5
True negative results	47
False negative results	16

Specificity of the CA 19-9 marker assay in the evaluation of the nature of pancreatic mass lesions was determined to be 90.4% and its sensitivity 83.7%. The complete statistical analysis is demonstrated in Table 2.

Table 2. Statistical evaluation of the utility of the CA 19-9 marker in the differential diagnosis of pancreatic tumors

Specificity	47/ 47+5 x 100% = 90.4%
Sensitivity	82/ 82+16 x 100% = 83.7%
Positive predictive value	82/ 82+5 x 100% = 94.25%
Negative predictive value	47/ 47+16 x 100% = 74.6%

DISCUSSION

The clinical picture of pancreatic cancer can mimic a number of other non-malignant gastrointestinal diseases. Differential diagnosis of pancreatic tumors poses a difficult task due to the similarity of clinical presentation. It concerns imaging techniques as well as signs and symptoms of the disease (6, 10, 11). Confirmation of the benign nature of the lesion can totally change indications for determined management. In the majority of cases it allows to avoid highly extensive resection surgery (3, 6).

Although, various diagnostic imaging techniques are useful to a lesser or greater extent, there are some real limitations regarding their sensitivity, specificity and cost-effectiveness. The serum CA 19-9 marker test is relatively inexpensive and accurate. Among variety of serum markers used in pancreatic cancer diagnostics the CA 19-9 assay is considered the most sensitive neoplastic marker (1, 7, 8, 9, 11). The CA 19-9 assay, despite some limitations regarding its sensitivity, may be applied in the diagnosis of pancreatic cancer due to its high specificity. A diagnostic accuracy of the CA 19-9 marker may be further augmented by a simultaneous evaluation with imaging techniques, such as US and CT. It allows to increase a sensitivity of the test over 90% (5, 6, 9, 14). In our series sensitivity and specificity of the CA 19-9 assay was 83.7% and 90.4%, respectively. These results are similar to results reported by others, where sensitivity and specificity of the CA 19-9 assay ranged from 69 to 93% and from 78 to 98% (1, 7, 8, 9, 11, 14, 15).

The high marker level is usually associated with the large tumor size. This observation supports a concept that the marker level reflects a total tumor-cell burden (11, 12). The marker level may not strictly predict a tumor volume because a tumor mass constitution varies individually, depending upon the amount of nontumor marker-expressing cells, the volume of tumor stroma and the association of coexistent inflammatory, degenerative or necrotic lesions secondary to the tumor (2, 4, 7, 8, 11). Our results confirm that a high CA19-9 level reflects a large tumor size in 88.9% of patients. Moreover, it may suggest distant metastases or peritoneal dissemination of the disease. Although tumor size is an important component in decision making process about surgery, its application as a prognostic factor may appear misleading in the case of unresectable tumors. In addition, it appears that there are significant difficulties in the assessment of a size of neoplastic tumor, mainly due to a large inflammatory component (7, 11, 12). Under these circumstances, the CA 19-9 marker level instead of the tumor size may appear a more valuable prognostic factor in the evaluation of the patients with stage III of pancreatic cancer (1, 4, 11).

The CA 19-9 assay is valuable in the assessment of resectability of pancreatic cancer. T o m a z i c et al. (14) reported that unresectable lesion was confirmed in 96% of patients with the marker level exceeding 1000 U/ml. Much better prognostic value of the CA 19-9 level in terms of operability of the lesion and survival longer than 10 months was found in patients with the marker level lower than 370 U/ml (14). The CA 19-9 level tends to increase from tumor stage I to stage IV (UICC TNM classification) and is also higher in those with resectable than in patients with unresectable tumor. It allows to use the CA 19-9 marker as an indicator of some boundary beyond which the tumor is highly likely to be unresectable. This boundary is considered to be in the wide range between 370 and 1000 U/ml (3, 11, 14). To precisely analyze the advancement and course of the disease, the imaging examinations allowing for adequate assessment of the tumor growth and for detecting some findings indicating dissemination of the disease should be performed (7, 8, 10). In our present series, unresectable pancreatic tumor was diagnosed in 58 patients with the CA 19-9 level higher than 100 U/ml. In all patients with the CA 19-9 level between 3 and 98 U/ml pancreatic tumor was found to be resectable.

Moderately elevated levels of CA 19-9 have been shown in serum of patients with a variety of benign diseases, such as pancreatitis, renal failure, jaundice and cholangitis (1, 7, 15). It is important to determine the limit level of the CA 19-9 marker that would allow to differentiate malignant from benign lesion. In most available studies this value has been set as 37 U/ml that was also characteristic of intestinal-derived adenocarcinomas (6, 7, 10, 13, 15). This reference level has resulted in relatively low specificity and sensitivity of the test reported to be 71–90% and 68–87%, respectively. When we increase the cut-off level for instance to 100 U/ml, we are also able to increase specificity of the test even to more than 90%. Nevertheless, this results in decrease of sensitivity of the test to 33–62%, as well (3, 4, 8, 13). In our series the reference value has been established as 37 U/ml. Following cytological and histological evaluation the results of the CA 19-9 assay have been regarded as true positive in 80 of 150 patients as compared to all 96 patients with finally confirmed pancreatic cancer.

False negative results characteristic of patients with confirmed pancreatic cancer and the CA 19-9 level lower than 37 U/ml, were demonstrated in 16 patients. In the majority of cases there were small, stage II tumors, but also large volume tumors without evidence of metastasis or high local expansion potential in their presentation on imaging examinations. The most frequently occurring explanation of this phenomenon is low dynamics of tumor growth, coexistent inflammation surrounding the tumor and weak marker expression by cancer cells (2, 4, 7, 8, 11). In 5 patients of this group we confirmed after operation other than adenocarcinoma neoplastic tumor.

The next 5 patients without malignancy had a positive CA 19-9 level (false positive results). In this group, the elevated bilirubin level was found in all the patients, which could be a direct cause of a positive test result, as it has been reported in many papers (2, 3, 6, 9, 11).

In summary, the CA 19-9 marker is a useful test in a preoperative differential diagnosis of malignant and benign tumors. The major limitations of the method are false negative and false positive results affecting a diagnostic reliability of the test. It results in the necessity of further clinical investigation to define more reliable markers or to conduct the evaluation of several markers simultaneously with modern imaging techniques and fine-needle aspiration biopsy.

CONCLUSIONS

1. An increased level of the CA 19-9 marker in patients with pancreatic pathology usually indicates malignant nature of the lesion.
2. A high CA 19-9 level suggests advanced, inoperable pancreatic cancer.
3. Sensitivity and specificity of the CA 19-9 assay was demonstrated to be 83.7% and 90.4%, respectively.

REFERENCES

1. van den Bosch R. P. et al.: Serum CA 19-9 determination in the management of pancreatic cancer. Hepato-Gastroenterology, 43, 710, 1996.
2. Cerwenka H. et al.: Preoperative differential diagnosis of benign and malignant pancreatic lesion – the value of Pancreatic Secretory Tripsin Inhibitor, Procarboxypeptidase B, Ca 19-9 and CEA. Hepato-Gastroenterology, 44, 1117, 1997.
3. Chi-Hsiao Y. et al.: Clinical analysis of inflammatory masses of the pancreatic head region. Hepato-Gastroenterology, 45, 2392, 1998.
4. Gattani A. M. et al.: Tumor markers in patients with pancreatic carcinoma. Cancer, 78, 57, 1996.
5. Hayakawa T. et al.: A prospective multicenter trial evaluating diagnostic validity of multivariate analysis and individual serum marker in differential diagnosis of pancreatic cancer from benign pancreatic diseases. International J. Pancreatol., 25, 23, 1999.
6. DelMaschio A. et al.: Pancreatic cancer versus chronic pancreatitis: Diagnosis with CA 19-9 assessment, US, CT, and CT-guided Fine-Needle Biopsy. Radiology, 178, 95, 1991.
7. Ohara K. et al.: Utility of serum CA 19-9 monitoring in preoperative radiotherapy for pancreatic cancer. Hepato-Gastroenterology, 48, 859, 2001.
8. Okusaka T. et al.: Tumor markers in evaluating the response to radiotherapy in unresectable pancreatic cancer. Hepato-Gastroenterology, 45, 867, 1998.
9. Pleskow D. K. et al.: Evaluation of serologic marker, CA 19-9, in the diagnosis of pancreatic cancer. Ann. Intern. Med., 110, 704, 1989.

10. Rosewicz S., Wiedenmann B.: Pancreatic carcinoma. Lancet, 349, 485, 1997.
11. Safi F. et al.: Prognostic value of CA 19-9 serum course in pancreatic cancer. Hepato-Gastroenterology, 45, 253, 1998.
12. Sellner F., Machacek E.: The importance of tumour volume in the prognosis of radically treated periampullary carcinomas: Eur. J. Surg., 159, 95, 1993.
13. Slesak B. et al.: Tissue polypeptide specific antigen (TPS), a marker for differentiation between pancreatic carcinoma and chronic pancreatitis. Cancer, 89, 83, 2000.
14. Tomazic A., Pegan V.: Preoperative staging of periampullar cancer with US, CT, EUS and CA 19-9. Hepato-Gastroenterology, 47, 1135, 2000.
15. Willett C. G. et al.: CA 19-9 is an index of response to neoadjunctive chemoradiation therapy in pancreatic cancer. Am. J. Surg., 172, 350, 1996.

SUMMARY

Inflammatory and neoplastic tumors of the pancreas still remain a diagnostic dilemma for a surgeon mainly due to subtle differences between these two sorts of tumors. The aim of the study was to assess the utility of the serum marker, CA 19-9, in the differential diagnosis of pancreatic tumors. 150 patients with heterogenic pancreatic lesion were diagnosed and treated at 2nd Department of General Surgery, Medical University of Lublin between June 1998 and Dec. 2003. Their age ranged between 26 and 78 years. Based upon cytology and histology, patients were assigned to malignant or benign group. The serum from all the patients was assayed for the CA 19-9 test and sensitivity and specificity of the CA 19-9 test was determined. Finally pancreatic cancer was diagnosed in 98 patients, benign pancreatic lesion in 52 patients. Based upon the serum level of the CA 19-9 true positive results were found in 82 patients, true negative results in 47 patients, false negative results in 16 patients and false positive results in 5 patients. Sensitivity of the CA 19-9 assay was 83.7% and specificity was 90.4%. An elevated serum level of the CA 19-9 in the presence of pancreatic lesions usually suggests malignant nature of the lesion. A high CA 19-9 level is typical of advanced inoperable pancreatic cancer. Taking into account a limited sensitivity and specificity of the CA 19-9 assay, its results should be interpreted in consistency with an analysis of imaging examinations such as US and CT.

Podwyższony poziom markera CA 19-9 w diagnostyce różnicowej zmian guzowatych w trzustce

Guzy zapalne i nowotworowe trzustki są nadal dylematem dla chirurga, szczególnie wtedy, gdy różnice pomiędzy nimi nie są wyraźnie zaznaczone. Celem analizy klinicznej było oznaczenie skuteczności zastosowania markera surowiczego CA 19-9 przy ocenie patologicznych guzów trzustki. W okresie od czerwca 1998 do grudnia 2003 diagnozowano i leczono w klinice 150 chorych z heterogeniczną zmianą w obrębie trzustki, wiek chorych 26–78 lat. Surowicę na badanie markera CA 19-9 pobierano we wstępnej fazie diagnostyki. Ostateczna weryfikacja następowała na podstawie badań cytologicznych i histopatologicznych. Obecność raka trzustki potwierdzono u 98 chorych, a zmiany łagodnej u 52. Na podstawie oceny poziomu markera CA 19-9 wynik prawdziwie dodatni stwierdzono u 82 badanych, prawdziwie ujemny u 47, fałszywie ujemny u 16 oraz wynik fałszywie dodatni u kolejnych 5 badanych. W analizie statystycznej czułość metody określono na 83,7%, swoistość na 90,4%. Podwyższone miano markera CA 19-9 w obecności patologii trzustkowej wskazuje zwykle na występowanie choroby nowotworowej. Wysokie miano markera jest charakterystyczne dla zaawansowanych, nieoperacyjnych postaci raka trzustki. Z uwagi na ograniczoną czułość i swoistość testu jego wyniki należy interpretować wspólnie z analizą badań obrazujących, jak USG oraz KT.