

Immunological and histopathological correlations in exocrine pancreatic cancer

ADRIANA TURCULEANU¹⁾, CARMEN AVRĂMESCU¹⁾, MARIA BĂLĂȘOIU¹⁾, EM. PLEȘEA²⁾,
CRISTIANA SIMIONESCU²⁾, CARMEN FLORINA POPESCU³⁾

¹⁾Department of Microbiology-Immunology, University of Medicine and Pharmacy of Craiova

²⁾Department of Morphopathology, University of Medicine and Pharmacy of Craiova

³⁾Department of Cytology, Emergency County Hospital Craiova

Abstract

The CA19-9 antigen is a tumoral marker that can be found in high concentration within a malignant digestive pathology. *Objective.* Study of CA19-9 antigen from the immunological point of view, at the patients with pancreatic cancer, and his relation with the histopathological aspects. *Material and method.* The determinations have been done at the time of the diagnosis and after the treatment of the patients with pancreatic cancer (25). Method: indirect ELISA. *Results.* The values of the CA19-9 marker have been increased at the time of the diagnosis either in pancreatic cancer of the head and mid. At the moment of the diagnosis the CA19-9 marker has higher values (150–400 U/ml) in cancer of the pancreatic body than in cancer of the head of the pancreas (40–200 U/ml). Correlating the size of the tumor with the value of the CA19-9 marker in the case of pancreatic cancer we have been shown the highest serum values (300–400 U/ml) at patients whose tumor was 3 cm bigger. Four weeks post-surgery the CA19-9 values decreased (37–100 U/ml) or reached normal levels (<37 U/ml). At patients with local recurrence or metastasis, especially hepatic, CA19-9 values have increased (100–400 U/ml in case of recurrence and 800 U/ml in case of metastasis). The highest values of the CA 19-9 marker were found in cases of mid pancreas adenocarcinoma. *Conclusion.* CA19-9 marker values higher than normal cause problems to digestive cancer (especially pancreatic). CA19-9 is a good marker for monitoring of these cancers after treatment; the favorable development is associated with lower values in comparison to the determinations before treatment, or with normal values, unfavorable evolution (local recurrence or metastasis) being associated with very high values. The high values of CA 19-9 suggest an adenocarcinoma.

Keywords: tumoral marker CA19-9, pancreatic cancer, adenocarcinoma.

Introduction

The study of tumors in general and of malignant ones especially, important for both morbidity and mortality, is one of the main problems of today's health, preoccupying equally epidemiological specialists or of similar management, oncologists, interns, surgeons, pharmacologists, biologists and geneticists, making them collaborate in one common human effort to control this serious illness, at least in what the seriousness of the illness is concerned.

The idea of discovering a factor that would confirm the presence of a malignant tumor formation at the level of the human body dates since the moment when doctors realized that, for now, the only way to obtain better results in treating the cancerous illness is to discover it in its early curable stage.

The notion "tumor marker" was introduced in medical language with the meaning of substances or molecules, the appearance and accumulation of which was associated with the appearance and the development of malignant tumors [3].

After becoming malignant, the cytoplasmic membrane is the most modified cellular structure. Regulating signals of growth and multiplication control, that act primarily through membrane receivers, cannot find their structural target.

The cellular incapacity of receiving regulating signals of growth and division or of adequately answering those signals is the main cause of the invasive behavior of malignant cells.

Losing the contact inhibition reflects the changes of the cellular surface. Often, this modification is accompanied by synthesis of certain new molecules, located in each compartment of the cell and who act as tumor antigens.

Any chemical structure of the malignant cell, absent in or on normal cells of the originating tissue of the tumor, susceptible of inducing an immune reaction in the first host or, after injecting, in a new host, can be considered a tumor antigen [21].

The tumor marker is a suspicion indicator of the presence of tumoral formations and within a characteristic context, next to other clinical and paraclinical elements, can contribute to the diagnosis of malignant tumors, to evaluating the prognosis, monitoring the evolution of the illness and treatment control [3, 21].

I. CA 19-9 marker

Carbohydrate antigen 19-9 is a tumoral marker. CA 19-9 is a synthesis tumor product obtained through hybridization (like other markers: CA 15-3 in breast cancer, CA 125 in ovarian cancer, PSA in prostate cancer) [2, 5, 11, 12].

CA 19-9 or GIGA was identified in 1979 by Koprowski due to monoclonal antibody 111 6-NS 19-9 obtained through immunizing the mouse with a cell line SW 1116 derived from an adenocarcinoma of the human colon. Tumor antigen 19-9 is a glycolipid that can be detected at the level of the fetal epithelia of the

stomach, lower and upper intestines, liver and pancreas. In adults very like concentrations is spread between gastro-intestinal organs and lung tissue; it can be found in higher concentrations in secretions of the mucus cells like saliva, seminal liquid, gastric liquid, amniotic liquid, and at the cystic formations as well.

High concentrations can appear within benign diseases like acute hepatitis, active chronic hepatitis, biliary illnesses, cystic fibrosis, and rheumatism illnesses. Concentrations levels in healthy donor's serum are generally inferior to 37 KU/L [3, 8–12].

The marker is used in diagnosing pancreatic, colorectals, gastric and esophagus carcinomas, especially in association with CEA (carcinoembrionar antigene). The tendency in dozing CA 19-9 is a pancreatic cancer indicator.

II. Associations between CA 19-9 presence and different types of cancer

The question imposed to the medical practitioners and researchers is: can marker CA 19-9 be associated with a certain type of cancer, or with a certain moment of its evolution? Without having reached an absolute conclusion, we know that this marker can be associated with various types of cancer, namely:

Pancreatic cancer

Immunological and radioimmunological research has confirmed the existence of substances secreted by pancreatic tumor cells. The mostly used marker is CA 19-9, its recurrence value reaching in some studies, the ultrasonograma ones. Measuring tumor marker CA 19-9 can be useful for:

- removal interventions efficiency control with radical intentions: CA 19-9 marker, present before surgically excision, disappears after surgical period if there is no residual tumor tissue;
- in order to detect precociously recurrence or metastasis: the marker that had disappeared after the surgery, reappears before the clinical signs of recurrence or metastasis [2, 3, 6, 7, 9, 15–19, 21].

Other measurable markers with lower specificity and sensitivity are: alfa-fetoprotein, galactoziltranspherase 2 [1, 3, 9, 21].

Colorectal cancer

Measuring the carcinoembrionar antigene and CA 19-9 is important for post-surgery follow up of patients who showed high pre-surgery serum values and who were subjects of surgery with the intention of total removal of the tumor. At these patients, the serum concentration of anti-genes comes back to normal in approximately four weeks, and post-surgery persistence of high concentrations in antigenes (CEA and CA 19-9) show the recurrence. It precedes by several months the appearance of clinical and endoscopical signs of recurrence [12, 21].

Gastric cancer

Tumor markers have higher specificity through measuring monoclonal anti-bodies:

- carcinoembrio anti-gene is a good marker for post-

surgery follow up, without offering details of an early cancer;

- CA 19-9 carbohydrate anti-gene has numerous fractions: high values mat in gastrointestinal cancers (40-50%) and pancreatic cancers (70%); comparative to CEA, CA19-9 has higher sensitivity (68.8%, respectively 38.2%) [1, 3, 21].

Esophagus cancer

The prognostic can be appreciated by determining tumor markers from the surface the cell that can have different expression in tumor cells. It can be appreciated through determining high expressions of receivers for Epidermal Growth Factor (EGF-R), Transforming Growth Factor Alfa (TGF-alfa), CEA, CA 19-9 and CA 50. The same significance can be given by determining the DNA pattern with aneuploidy or the 19 cytokeratin fragments through CYFRA 21-1 [1, 3, 21].

III. Cancer of the exocrine pancreas

It still is a depressingly difficult problem even for modern medical world [1, 3, 4, 8, 10, 13, 14, 20, 22].

This high mortality rate cancer has a silent and difficult to observe evolution, so that at the time of the diagnosis the neoplasms are rarely curable, generally with a survival rate of 2–3 months after diagnosis, regardless of the therapy.

The rate of mortality from pancreatic cancer is 5% in the US (28.000 new pancreatic cancers are diagnosed and 26.000 cases die every year).

The age of neoplasm occurrence: after 60 years, in 6th, 7th and 8th decade; only 10% of the patients are younger.

Favoring factors:

- smoking (the risk of pancreatic cancer is 1.5% higher in smokers than in non-smoking persons);
- a fat rich diet;
- gastrectomy (the risk of having pancreatic cancer is 2–4 times higher in those who had gastrectomy than in those who did not have this surgery), because of the high level of bacterial N-nitroso compounds.

Localization: 60% of pancreatic cancer is localized at the head of the pancreas; 15–20% of pancreatic cancer are localized in the body of the pancreas; 5% of pancreatic cancers are localized in the tail of the pancreas.

Clinical aspects

Cancer of the exocrine pancreas, including the one in the head of the pancreas, is an insidious affection, present months and even years before the appearance of the symptoms determined by tumor expansion [1, 3, 4, 10, 13]. The major symptoms are: loss of weight, chest pains, back pains, anorexia, nausea, vomiting, and weakness.

Icter appears most of all (90%) in patients with cancer of the head of the pancreas and in 10–40% at those with body or tail pancreas cancer.

10% of patients present migrating thrombophlebitis (Trousseau's syndrome), determined by the elaboration of platelets aggregation factors and by procoagulating by the tumor or its necrosis products.

The development of the exocrine pancreatic cancer

It is slow and progressive [1, 3, 4, 8, 14, 20, 22].

Although the cancer of the head of the pancreas has an early tendency to obstruct the biliary system, less than 15% of the tumors are resectable at the time of the diagnosis. 20% of these patients survive 1 year, and a 5 year survival is found in fewer than 3%.

The evolution of cancer in the head of pancreas takes place through: obstructing the biliary system, taking over the duodenum, retroperitoneal growth.

We rarely come across peripancreatic extension, infecting portohepatic nodes, hepatic metastasis.

The body or tail pancreatic cancer evolves through: infecting the adjacent spine, infecting the inferior and superior retroperitoneal space, sometimes invading the spleen or adrenal, infecting the transverse colon or stomach, infecting the nodes groups: peripancreatic, gastric, mesenteric, omental, protohepatic, infecting the liver that may take the shape of nodular tumor, determining massive hepatomegaly.

Hepatic metastases are frequent.

Only in tumors in advanced stages – body and tail pancreatic tumor – pulmonary, pleural and bone metastasis occur.

Only rarely cerebral metastases appear. After the surgical resection, local recurrence is frequent and is one of the factors that influence survival.

Histopathological aspects

Exocrine pancreatic cancer, histologically, can be classified in: epithelial malign tumor, non-epithelial malign tumor [4, 10, 13, 14, 20, 22].

1. Epithelial malign tumor can be:

▪ “solid tumors”, meaning:

(a) ductal adenocarcinoma

(b) its variants:

– mucous non-cystic adenocarcinoma;

– squamous carcinoma.

(c) rarely:

– acinous cells carcinoma;

– pancreatoblastom.

(d) 6%:

– serous and mucinous cystic tumors;

– pseudo-papillary solid tumor;

– intraductal papillary mucinous tumors.

2. Non-epithelial primal malign tumors of the exocrine pancreas:

- sarcomas;

- malign lymphomas.

The World Health Organization classification of the exocrine pancreatic cancer

This classification refers to [1, 3, 10, 13, 22]:

▪ staging and grading pancreatic adenocarcinoma – TNM staging that, in the new version, takes into consideration:

– the size of the primal tumor (pT1–pT4);

– the presence or absence of regional nodular metastasis (pN1a or pN1b if multiple nodular groups are involved);

– remote metastasis (pM).

▪ the classification of cystic mucinous tumors and of intraductal papillary cystic mucinous tumors, depending on their biological behavior:

– benign tumors;

– “borderline tumors” (with uncertain malign potential);

– malignant tumors.

IV. Objectives

We want to study the values of one of the tumor markers, naming the carbohydrate antigen CA 19-9 at patients with pancreatic cancer at the time of the diagnosis, four weeks after surgery and 12 weeks after surgery, as well as the correlation of this parameter with the histopathological aspect of these tumors.

Material and methods

To determine this marker we used serum from patients with pancreatic cancer (25 subjects) treated in the Surgery and Oncology Departments of the Emergency Clinical Hospital of Craiova.

In order to determine the quantity of CA 19-9 antigen we used the ELISA indirect technique.

The kit used is Can Ag CA 19-9 EIA which determines the quantity of CA 19-9 antigen in human serum.

The investigated patients came to the doctor's with digestive symptoms.

The suspicion of pancreatic cancer was based on:

– clinical examination (clinical symptoms and objective signs were different depending on the place of the tumor in head and body pancreatic tumor);

– ultrasound examination;

– computed tomography, that showed the dimensions and place of the tumor;

– endoscopic examination, that was associated with endoscopic ultrasound-guided fine-needle aspiration.

The confirmation of the diagnosis took place on the basis of the cytopathological diagnosis or/and histopatological examination done on the samples taken during surgery, whenever was possible. It also showed the histological type of each tumor.

Results and discussions

I. CA 19-9 values at the time of the diagnosis

The time of the diagnosis of pancreatic cancer is considered to be the moment when the endoscopic ultrasound-guided fine-needle aspiration was done.

From the sample taken were made between 6–13 slides that were stained not only with May Grunwald Giemsa (MGG) stain, but also with Papanicolaou stain.

Depending on the presence or the absence of the malign characters we have put the smears in one of the following categories:

– inconclusive smear;

– benign smear;

– suspicious smear, probably benign;

– suspicious smear, probably malign;

– malignant smear (positive).

From assessing the slides provided from all the patients, we obtained results as follows:

- 2 cases suspicious (Figures 1 and 2);
- 18 were considered malignant, especially with nuclear and nucleolar atypia (Figures 3–6);
- 5 cases were inconclusive.

At these patients we have determined the value of CA 19-9 in serum.

CA 19-9 values were higher in pancreatic cancer of the head and body of the pancreas.

CA 19-9 values were higher at the moment of diagnosis of the middle pancreas cancer, than at the moment of the head pancreatic cancer diagnosis. Explanation is given by the time of the diagnosis (Figure 7).

Therefore, pancreatic cancer of the head has as dominant symptoms icter and prurit, symptoms that trouble the patient and drown the attention of the entourage too, and make the patient go to the doctor's.

In pancreatic cancer of the body or tail of the pancreas the clinical panel is uncharacteristic, dominated by the serious decline of the general state, most noticeable being the loss in weight and the deep and intense epigastric pain with back irradiation, resistant at ordinary painless drugs.

As a consequence establishing the diagnosis is done late, later than the cephalic localization (the patient going later to the physician).

	Cancer of the middle pancreas	Cancer of the pancreatic head
Number of cases	10	15
Average value of CA 19-9	285.20	129.40
Standard deviation	92.62	51.09
p value	0.000317	

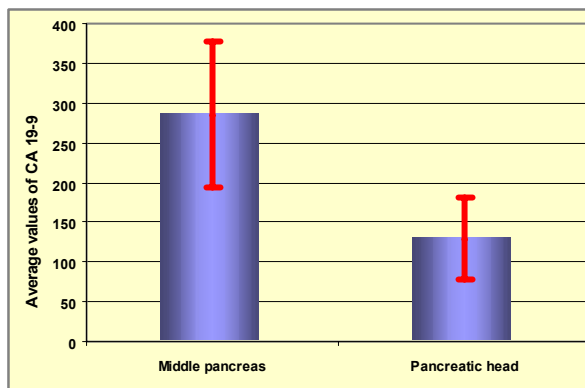


Figure 7 – Average values and standard deviation

II. CA 19-9 values 4 weeks after the surgery

All patients investigated were submitted to surgery, by having radical or partial surgery all cases being surgically overwhelmed.

After the surgery, CA 19-9 values decreased (Figure 8).

We have noticed that after four weeks the CA 19-9 post-surgery values decreased comparatively to those in pre-surgery in both pancreatic cancers, within the head and body of the pancreas (Table 1).

	Cancer of the pancreatic body	Cancer of the pancreatic head
Number of cases	10	15
Average value of CA 19-9	54.60	45.13
Standard deviation	26.47	28.34
p value	0.404569	

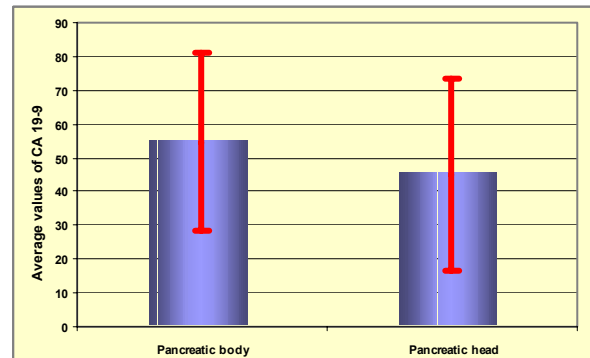


Figure 8 – Average CA 19-9 values at patients with head and body pancreatic cancer, at the second determination (4 weeks after surgery)

Table 1 – Pre- and postsurgery values of CA 19-9 (head and middle pancreatic cancer)

	Cancer of the pancreatic head		Cancer of the middle pancreas	
	Presurgery	Postsurgery	Presurgery	Postsurgery
Number of cases	15		10	
Average value of CA 19-9	129.4	45.13	285.2	54.6
Standard deviation	51.09	28.34	92.62	26.47

Histopathologically, the exocrine pancreatic carcinomas were:

- ductal adenocarcinomas:
 - well-differentiated (Figure 9);
 - moderately differentiated (Figure 10);
 - poorly differentiated (Figure 11).
- adenosquamous carcinoma (Figure 12).
- undifferentiated carcinoma (Figure 13).
- mucinous noncystic carcinoma (Figure 14).

The highest values of CA 19-9 were found at patients with cancer of the pancreatic body, adenosquamous carcinoma and undifferentiated carcinoma, those being ductal adenocarcinoma having values of this marker under 100 UI/ml. Lower values, but higher than normal, show residual tumor tissue after surgery. Mucinous noncystic carcinoma is associated with normal values of CA 19-9 after surgery.

III. CA 19-9 values 12 weeks after surgery

All patients were treated, after surgery, with chemotherapy. At part of the subjects (6) we faced the problem of metastasis (4 with middle pancreas cancer, 2 with cancer within the pancreatic head) or of local recurrence (2 with cancer within the pancreatic head, 3 with cancer of the middle pancreas); 2 patients died.

CA 19-9 values are much higher at patient with metastasis (liver, lung), than at patients with recurrences.

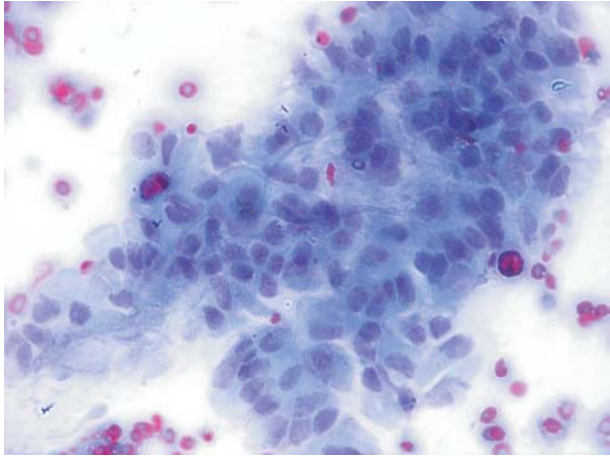


Figure 1 – Suspicious smear.
Sheet of canalicular cells with moderate anisonucleosis
(Papanicolaou stain, ob. ×20)

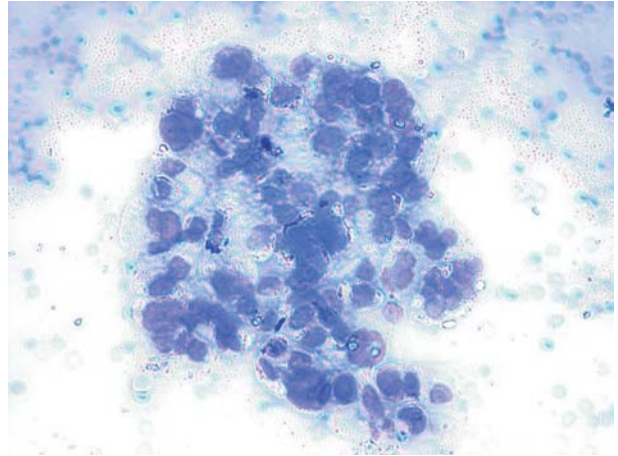


Figure 2 – Suspicious smear.
Another aspect
(MGG stain, ob. ×20)

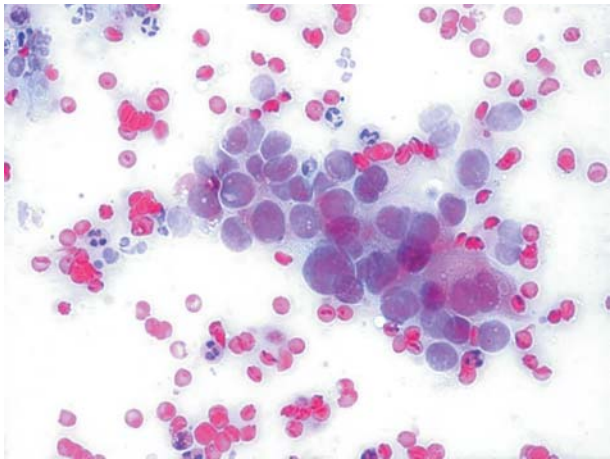


Figure 3 – Positive smear.
Sheet of epithelial cells, with moderate atypias
(anisonucleosis, binuclearity, anizocariocromy),
on hematic background and with rare PMN
(Papanicolaou stain, ob. ×20)

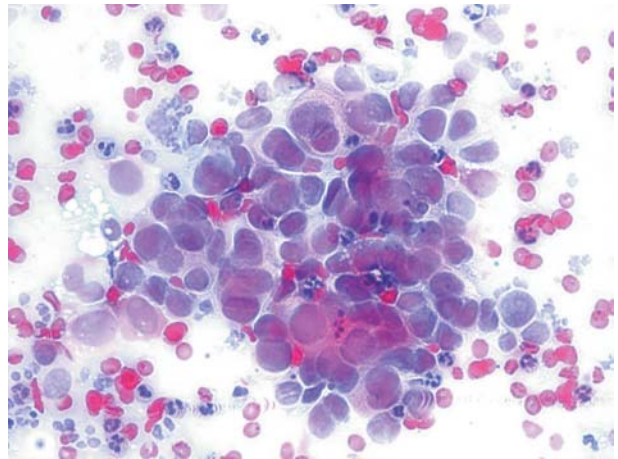


Figure 4 – Positive smear.
Sheet of atypical cells, on inflammatory background
(Papanicolaou stain, ob. ×20)

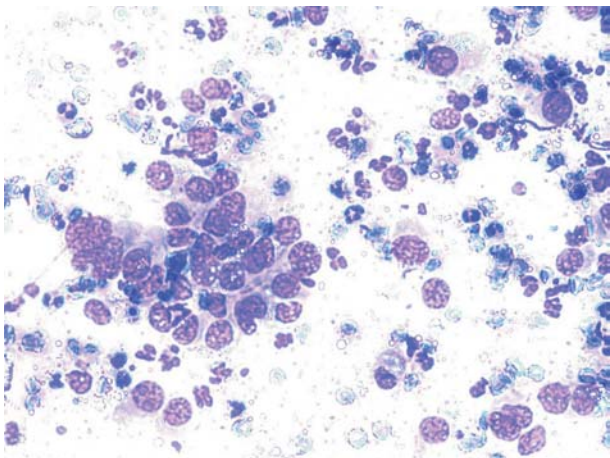


Figure 5 – Positive smear.
Atypical epithelial cells (nuclear and nucleolar severe atypias)
grouped in sheets, but also isolated
(MGG stain, ob. ×20)

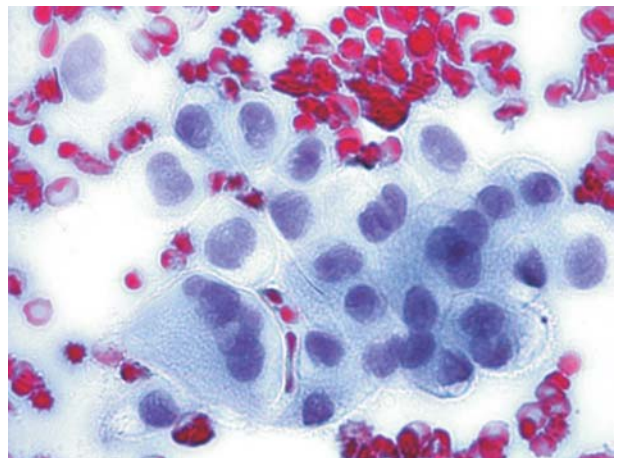


Figure 6 – Positive smear.
Severe nuclear atypias (multinuclear overlapping)
(Papanicolaou stain, ob. ×40)

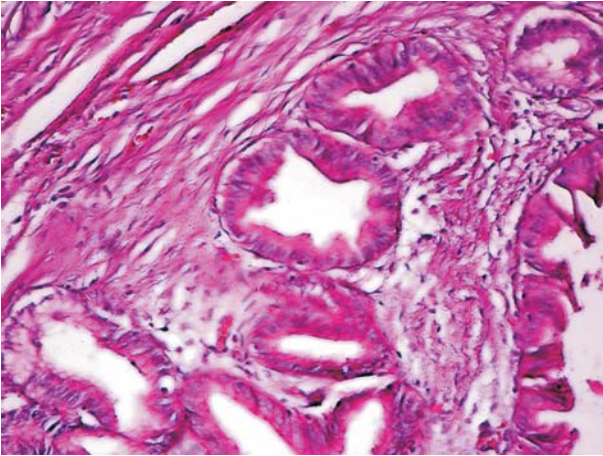


Figure 9 – Ductal adenocarcinoma.
Well-differentiated form (grade I).
Columnar cells line duct-like structures
(H-E stain, ob. $\times 10$)

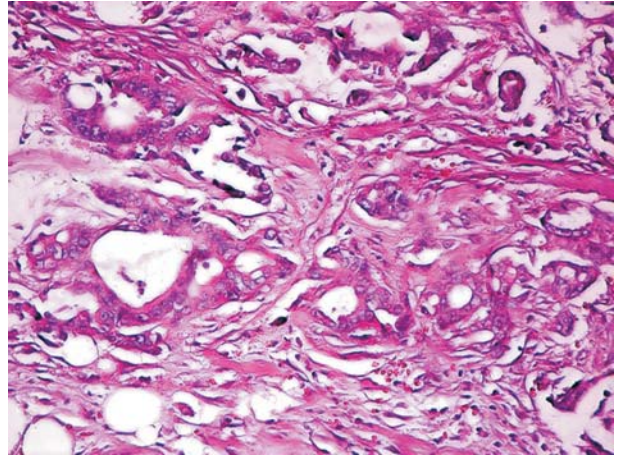


Figure 10 – Ductal adenocarcinoma.
Moderately differentiated form (grade II).
Duct-like spaces are lined by cuboidal cells
(H-E stain, ob. $\times 10$)

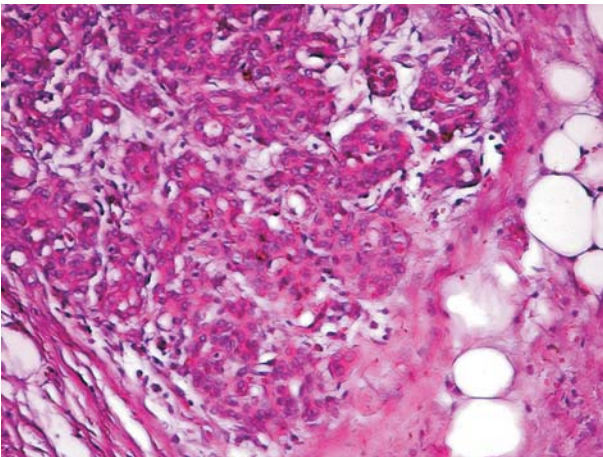


Figure 11 – Ductal adenocarcinoma.
Poorly differentiated form (grade III).
Several poorly formed ducts, a few signet-ring cells,
cellular pleomorphism
(H-E stain, ob. $\times 10$)

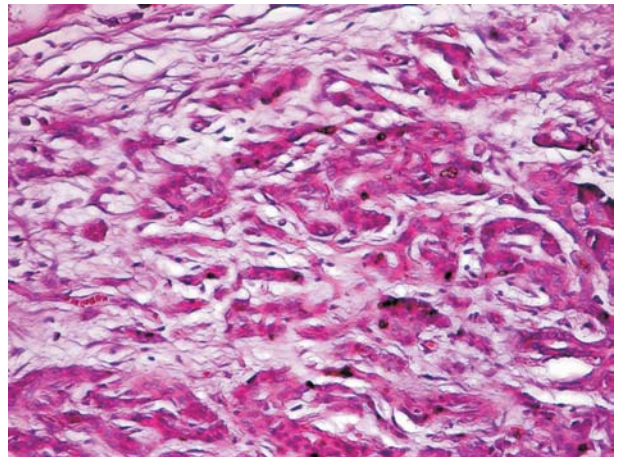


Figure 12 – Ductal adenocarcinoma.
Poorly differentiated form (grade III) – another aspect.
Moderate desmoplasia
(H-E stain, ob. $\times 10$)

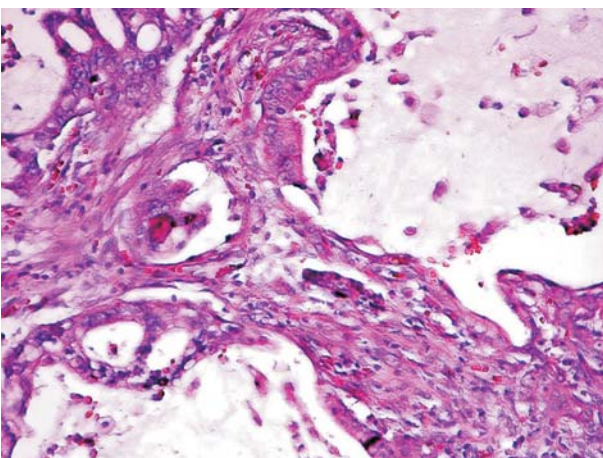


Figure 13 – Mucinous noncystic carcinoma. Mucin-filled spaces are partially lined by columnar, mucin-secreting epithelium and are partially bounded by connective tissue. This is a recurrent pattern (H-E stain, ob. $\times 10$)

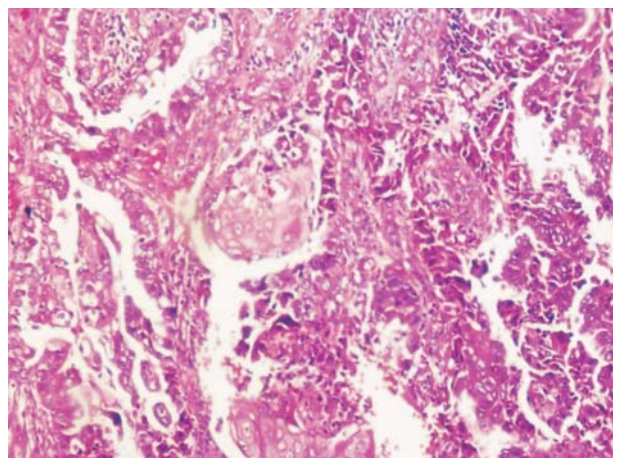


Figure 14 – Adenosquamous carcinoma. Most cells show squamous differentiation. The tumor was highly invasive (H-E stain, ob. $\times 10$)

	Metastasis	Recurrence
Number of cases	6	5
Average value of CA 19-9	652.50	268.80
Standard deviation	100.48	75.72
p value	0.000050	VHS

	Metastasis	Without metastasis or recurrence
Number of cases	6	19
Average value of CA 19-9	652.50	25.45
Standard deviation	100.48	5.70
p value	0.000022	VHS

	Recurrence	Without metastasis or recurrence
Number of cases	5	20
Average value of CA 19-9	268.80	25.45
Standard deviation	75.72	5.70
p value	0.001992	VHS

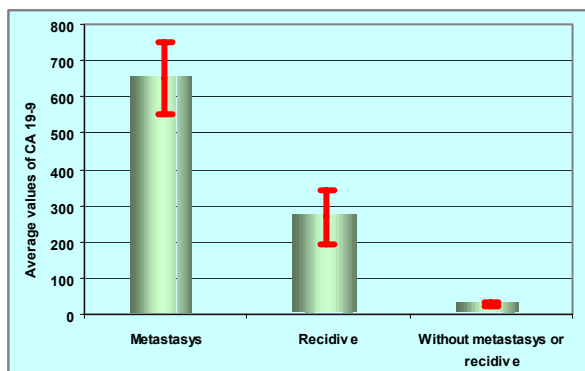


Figure 15 – CA 19-9 average values depending on the presence of a recurrence or metastasis

Adenosquamous carcinoma and undifferentiated carcinoma of the middle pancreas and also ductal adenocarcinomas have metastasized or had local recurrences; the latter are common for cephalic pancreatic cancer which is more frequently ductal adenocarcinomas.

Conclusions

CA 19-9 has presented high values regardless of the type of pancreatic cancer. As a result we can consider that CA 19-9 is more characteristic for pancreatic cancer.

The later the illness is discovered, the higher the CA 19-9 values are associating it with loco-regional recurrences or with metastasis. CA 19-9 cannot be used as an early indicator of the presence of this illness.

CA 19-9 can be used as criteria of appreciating treatment efficiency (surgical or chemotherapeutical).

When efficient, radical surgery is associated with low values of CA 19-9 comparative to marker values at the time of the diagnosis of the tumor or even with its normalization. Residual tumor tissue is associated with high persistency of CA 19-9 values. We can say that CA 19-9 can be used as a marker in evaluating surgical excision.

Applying radical surgery treatment, followed by chemotherapy, can be correlated with normal values of the CA 19-9 during the favorable evolution period

(more noticeable in colorectal cancer).

The lack of treatment response is associated with persistency of high values of CA 19-9 or the increase in these values much more than those at the time of the diagnosis or after surgery.

Adenocarcinoma is associated with the high values of CA 19-9.

The low rate of survival in patients with pancreatic cancer is an obstacle in methodic research of the CA 19-9 marker and towards obtaining real conclusions and useful to the therapy clinician. Moreover we can add to this aspect the high price of one determination.

For a complete diagnosis we recommend associating CA 19-9 determinations with other tumoral markers – e.g., for pancreatic cancer: CA 19-9 with CA 50 or with CEA or with CA 242; for gastric cancer, association with CA 72-4; for anal cancer, with SCC or Cyfra 21-1; for esophagus cancer: CEA, CA 50, Cyfra 21-1.

Diagnosis accuracy increases when associating tumor markers (CA 19-9) with ultrasonograma, computer tomography and endoscopic biopsy.

References

- ANGELESCU N., *Tratat de patologie chirurgicală*, Ed. Medicală, București, 2003, vol. I: Cancer esofagian (1469-1470), Cancer gastric (1592-1594); vol. II: Cancer pancreatic (2026-2032), Cancer de colon (1670-1674), Cancer de rect (1714-1717).
- BANFI G., BRAVI S., ARDEMAGNI A., ZERBI A., *CA 19-9, CA 242 and CEA in the diagnosis and follow-up of pancreatic cancer*, Int J Biol Markers, 1996, 11(2):77-81.
- BĂDULESCU FL., *Oncologie generală. Elemnte de curs*, Reprografia Universității din Craiova, 1997, 110-192.
- BRAT D.J., LILLEMÖE K.D., YEO C.J. et al., *Progression of pancreatic intraductal neoplasia to infiltrating adenocarcinomas of the pancreas*, Am J Surg Pathol, 1998, 2:1635-1639.
- CAMIZERES F., SOLA J., PEREZ M., *Preoperator values of CA 15-3 and CEA as prognostic factors in breast cancer: a multivariate analysis*, Tumor Biol, 2001, 22(5):273-281.
- FREBOUNG T., BERCOFF E., MANCHON N. et al., *The evaluation of CA 19-9 antigen level in the early detection of pancreatic cancer*, Cancer, 1988, 62(11):2287-2550.
- GOETZ M., STEEN P.D., *False elevation of CA 19-9 levels in a patient with a history of pancreatic cancer*, Am J Gastroenterol, 1997, 92(8):1390-1394.
- GRODIS L., GOLD E.B., *Epidemiology and etiology of pancreatic cancer*. In: GO V.L.W. et al. (eds), *The Pancreas. Biology, Pathobiology and Disease*, Raven Press, New York, 1993, 837-855.
- HAYAKAWA T., NARUSSE S., KITAGAWA M. 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*, Int J Pancreatol, 1999, 25(1):23-29.
- ***, *TNM Classification of malignant tumours*, 5th edition, International Union Against Cancer (IUAC), Wiley-Liss, New York-Chichester-Weinheim-Brisbane-Singapore-Toronto, 1997.
- IMAI A., HORIBE S., TAKAGI A., TAMAYA T., *Drastic elevation of serum CA 125, CA 72-4 and CA 19-9 levels during menses in a patient with probable endometriosis*, Eur J Obstet Gynecol Reprod Biol, 1998, 78(1):79-81.
- KOURI M., NORDLING S., KUUSELA P., PYRHONEN S., *Poor prognosis associated with serum CA 19-9 level in advanced colorectal carcinoma, independent of DNA ploidy or SPT*, Eur J Cancer, 1993, 29A(12):1691-1696.
- KLÖPPEL G., *Pathology and classification of tumours of the exocrine pancreas*. In: TREDE M., CARTER D.C., *Surgery of the pancreas*, 2nd edition, Churchill Livingstone, Edinburgh, 1997, 447-462.

- [14] KLÖPPEL G., SOLCIA E., LONGNECKER D.S. et al., *Histological typing of tumours of the exocrine pancreas*, 2nd edition, WHO International Histological Classification of Tumours, Springer Verlag, Berlin, 1996.
- [15] MC LAUGHLIN R., O'HANLON D., KERIN M. et al., *Are elevated levels of tumour marker CA 19-9 of any clinical significance-an evaluation?*, *Yr J Med Sci*, 1999, 168(2):124-126.
- [16] MONTGOMERY R.C., HOFFMAN Y.P., RILEY L.B. et al., *Predictions of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas*, *Ann Surg Oncol*, 1997, 4(7):551-556.
- [17] NAKAO A., OSHIMA K., NOMOTO S. et al., *Clinical usefulness of CA 19-9 in pancreatic carcinoma*, *Semin Surg Oncol*, 1998, 15(1):15-22.
- [18] NAZLI O., BAZDAG A.D., TANSUG T. et al., *The diagnostic importance of CEA and CA 19-9 for the early diagnosis of pancreatic carcinoma*, *Hepatogastroenterol*, 2000, 47(36):1750-1752.
- [19] NISHIDA K., KANEKO T., YONEDA M. et al., *Doubling time of serum CA 19-9 in the clinical course of patients with pancreatic cancer and its significant association with prognosis*, *J Surg Oncol*, 1999, 71(93):40-46.
- [20] NISHIHARA K. et al., *Papillary cystic tumors of the pancreas. Assessment of their malignant potential*, *Cancer*, 1993, 71-82.
- [21] OCHI Y., OKABE H., INUI T., YAMASHIRO K., *Tumor marker – present and future*, *Rinsho Byori*, 1997, 45():875-883.
- [22] WARSHAV A.L., FERNANDEZ-DEL CASTILLO C., *Medical progress: pancreatic carcinoma*, *New Eng J Med*, 1992, 326-455.
- [23] ZAMBONI G., SCARPA A., BOGINA G. et al., *Mucinous cystic tumours of the pancreas: clinicopathological features, prognosis and relationships to other mucinous cystic tumours*, *Am J Surg Pathol*, 1999, 23:410-422.

Mailing address

Adriana Turculeanu, Associate Professor, M. D., Ph. D., Department of Microbiology-Immunology, University of Medicine and Pharmacy of Craiova, Avenue Avenue 1 May no. 66, 200628 Craiova, Romania; Phone +40251-524 441(2)

Received: 25 April, 2005

Accepted: 5 September, 2005