Prolactin and colorectal cancer : is there a connection ?

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Abstract

The purpose of this study was to confirm the reported incidence of hyperprolactinemia in colorectal cancer and to find further evidence for an ectopic prolactin production by the tumor.

***Material and method.* Thirty two consecutive patients with an adenocarcinoma of the colon (n = 17) or the rectum (n = 15) were included. Preoperative serum prolactin concentrations were determined and correlated with CEA concentrations and tumor stages. To exclude an ectopic production by the colon cancer, prolactin concentrations were determined during the operation, in the peripheral blood and in the efferent venous drainage area of the tumor. After resection, immunohistochemical staining for prolactin was made in all resected tumors.**

***Results.* In all except two patients with a rectal cancer, preoperative plasma prolactin concentrations were normal. Peroperative serum concentrations of prolactin were high in all patients. No significant gradient was found between the peripheral venous concentration and the local venous concentration in the drainage area of the tumor. Immunohistochemical staining for prolactin was positive in only one rectal cancer. Finally, no correlation was found between plasma prolactin concentrations and tumor stages or CEA concentrations.**

***Conclusion.* Our results do not support the hypothesis of an ectopic prolactin production by colon adenocarcinoma. Only in a subgroup of rectal cancers, an ectopic prolactin production remains probable.**

At present, prolactin cannot be recommended as a tumor marker in colorectal cancer. (Acta gastroenterol. belg., **1998**, 61, **407-409**).

Key words : colorectal cancer, serum prolactin concentration, tumor marker.

Introduction

Prolactin is a pituitary hormone under a tonic inhibition of the hypothalamus. A hyperprolactinemia can be caused by a variety of medications, prolactinoma, liver cirrhosis, renal insufficiency or idiopathically. An elevated plasma prolactin concentration has also been observed as paraneoplastic phenomenon in several malignant tumors, such as breast, cervical, tongue and colorectal cancer (1,2,3,4,5,6).

In Dukes B and C colorectal cancer, prolactin has been reported to be a better overall tumor marker than carcinoembryonic antigen (CEA) (1). The purpose of this study was to determine prolactin concentrations in colorectal carcinoma, to confirm this statement and to find a possible evidence for an ectopic prolactin production by the tumor.

Patients and methods

Thirty two consecutive patients (14 ♀ and 18 ♂ ; median age : 67 years ; range : 55-87 years) with an adenocarcinoma of the colorectum were included. Fifteen tumors were located in the rectum, 12 in the sigmoid, 2 at the hepatic flexure and 3 in the transverse colon. All patients underwent surgery. Seven patients were classified as Dukes D, 10 patients as Dukes C, 14 patients as Dukes B and 1 patient as Dukes A adenocarcinoma. None of the patients received medication that could induce hyperprolactinemia.

At least 2 days before the operation, a venous catheter with a heparin lock was placed in the forearm of the overnight fasting patients at 8.30 a.m. Fifteen minutes later, blood samples were taken for prolactin and CEA dosage. In the 17 patients with a colon carcinoma, simultaneous blood samples for prolactin dosage were taken peroperatively from a peripheral vein and from a vein in the drainage area of the malignant tumor. Serum levels of prolactin were determined by immunoradiometric assay, using a commercial kit (RIA-gnost® ; Behringwerke AG, Marburg, Germany), calibrated against prolactin WHO IRIP 84/500 ; inter-assay coefficient of variation is 12% ; normal range is 4-33 ng/ml and 4-18 ng/ml for women and men, respectively. CEA concentrations were determined using a particle-enhanced immunonephelometric assay using a commercially available kit (N-Latex CEA ; Behringwerke, Marburg, Germany) on a Behring BN II nephelometer. Detection limit was 1 µg/l. Inter-assay variation coefficients varied between 6.0% and 11.3% for concentrations between 52.4 µl/l and 1.9 µg/l. Normal ranges in healthy adults are below 5 µg/ml.

Postoperatively, an immunohistochemical staining for prolactin was performed. From each tumor, 5 micron thick sections were cut and mounted on polylysin coated slides. After deparaffinising, the sections were washed twice in parasolve, incubated for 10 minutes in 290 ml ethanol and 10 ml 30% H_2O_2 for 5 minutes each. Then, the slides were rinced with ethanol and H_2O for 5 minutes, after which the tissue was put into Protein Blocking Reagent for 30 minutes.

After incubation with polyclonal anti-prolactin (Dako, Glostrup, Denmark) diluted at 1:250 for 30 minutes at room temperature, the immunostaining was revealed with the streptavidin-biotin-complex method, AEC being used as chromogen.

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Counterstaining was done with haematoxylin, and the sections were dehydrated and mounted. Positive and negative controls were included.

Results

Coloncarcinoma

The individual results for coloncarcinoma are given in table I. The preoperative prolactinemia was below 20 ng/ml in all studied patients. No significant correlation was found between these levels and the Dukes classification. CEA concentrations, taken preoperatively were raised in 9 of the 17 cases with levels according to the Dukes classification. High prolactin levels were found during the operation, but without a significant gradient between the peripheral venous circulation and the local venous drainage area of the tumor. For technical reasons, the surgeon was unable to take simultaneous blood samples peroperatively in 2 patients.

Table I. — **Biochemical and immunohistochemical results in 17 patients with colon cancer**

Dukes	Prol pre-op	Prol peri	Prol tum	CEA pre-op	Immuno
A	5.1	39.5	39.2	4.7	neg
B	7.3	120	100	1.1	neg
B	11.4	118	112	0.82	neg
B	3.6	150	124	7.8	neg
B	5.4	150	144	18.3	neg
B	6.6	50.2	52.3	3.4	neg
B	7.2	102	111	2.59	neg
B	4.7	133	107	0.4	neg
C	5.0	28.4	26	18.7	neg
C	4.6	54.2	52.1	4.7	neg
C	8.9	102	91.5	5	neg
C	3.3	55.1	50.5	14.1	neg
D	6.1	42.5	46.4	12	neg
D	11.6	46.4	47.9	119	neg
D	6.3	35.4	35.8	2200	neg
D	9.7	NA	NA	10.9	neg
D	6.0	NA	NA	24.6	neg

Prol: plasma prolactin concentration in ng/ml (normal values: 4-18 in ♂, 4-33 in ♀); pre-op: at least 2 days before the operation; peri/tum: respectively in peripheral and tumor drainage circulation. *CEA*: carcinoembryonic antigen in ng/ml (normal values: 0-5). *Immuno*: immunohistochemical staining for prolactin in the tumor. *NA*: not available.

Statistical analysis (Spearman rank correlation coefficient) showed no correlation between the preoperative prolactin concentrations and CEA levels (Dukes A/B: coefficient = −0.4 with $p = 0.28$; for Dukes C/D: coefficient = 0.2 with $p = 0.57$), nor between the peroperative prolactin concentration and CEA (for Dukes A/B: coefficient = 0.18 with $p = 0.63$; for Dukes C/D: coefficient = −0.6 with $p = 0.13$).

The immunohistochemical staining for prolactin was negative in all resected adenocarcinomas.

Rectal cancer

The individual results for rectal cancer are given in table II.

Table II. — **Biochemical and immunohistochemical results in 15 patients with rectal cancer**

Dukes	CEA	Prolactin	Immuno
B	1.3	42.7	neg
B	0.5	6.4	neg
B	3.6	12.8	neg
B	2.1	39.1	neg
B	1.8	8.8	neg
B	12.3	6.3	neg
B	7.3	11.1	neg
C	5.7	10.9	neg
C	5.1	13.2	neg
C	5.8	7.2	neg
C	NA	7.1	neg
C	12.5	8.7	neg
C	1.9	6.1	neg
D	7.6	13	neg
D	352	4.8	pos

CEA: pre-operative carcinoembryonic antigen in ng/ml (normal values: 0-5). *Prolactin*: preoperative prolactin concentration in ng/ml (normal values: 4-18 in ♂, 4-33 in ♀). *Immuno*: immunohistochemical staining for prolactin in the tumor. *NA*: not available.

High prolactin concentrations of respectively 42.7 and 39.1 ng/ml were found in 2 patients with Dukes B rectal cancer. In a third patient, the immunohistochemical staining for prolactin was positive in the resected tumor.

CEA was raised in 8 patients. No correlation was found between preoperative CEA and prolactin level.

Discussion

In several studies, Bhalavdekar and colleagues showed a correlation between colorectal cancer and hyperprolactinemia (1,2,3). In a large study of 107 patients with Dukes B and C colorectal cancer, they concluded that prolactin is a better overall tumor marker than CEA. Hyperprolactinemia was present in 45% of the cases. The authors recommended the use of plasma prolactin to identify more agressive cancers (1). More recently, this incidence of hyperprolactinemia in colorectal cancer was confirmed in one additional study. Furthermore prolactin was identified on immunohistochemistry in the tumor tissue of 3 out of 15 colorectal cancers (4).

In our study, hyperprolactinemia was only observed in 2 patients with rectal cancer (incidence: 6%). A positive staining for prolactin was found in one additional tumor. We found no correlation between plasma prolactin concentrations on the one hand and CEA concentrations or tumor stages on the other hand. Our findings are in agreement with the study of Molitch *et al.*, reporting normal plasma prolactin concentrations in 215 patients with various malignancies, including 23 colorectal cancers (7). The latter study was published in 1981, and used a double antibody radio-immunoassay test. It remains possible that aberrant tumor processing of prolactin resulted in an altered structure, not detectable by the standard RIA test at that time.

As prolactin might be produced by the tumor, we determined the peroperative gradient between prolactin

concentration in peripheral blood and in the venous drainage area of the colonic tumors. No significant difference was observed, excluding an ectopic production by the tumor. The absence of staining on immunohistochemistry confirms this statement.

The clinical value of a tumor marker as monitor of the therapy, as predictor of a relapse or prognosis, depends primarily on its sensitivity, specificity and the prevalence of the pathology in the studied population (8). The results of our study temper the initial enthusiasm for prolactin to be used as a tumor marker in colon cancer and rectal cancer. Considering the variety of interfering factors such as acute stress and medication, a high specificity of the test is also not to be expected. In view of the cost and the low sensitivity of the test, the use of plasma prolactin in all patients with colorectal cancer cannot be recommended in the routine preoperative management. Therefore we disagree with the recommendations of Patel *et al.* (1), and believe that further studies are necessary before their recommendations can be applied in clinical practice. On the other hand our results do suggest an ectopic prolactin production in a subgroup of rectal adenocarcinomas. It would be interesting to review the data of the aforementioned studies (1,4) with respect to the location of the tumor. The high incidence of hyperprolactinemia in the study of Patel *et al.* might be due to the preponderance of rectal (n = 73) versus colon (n = 41) cancer in their studied material.

Further work on ectopic prolactin production should include separate data for colon and rectal cancer, respectively. In this manner, a subgroup of colorectal cancer might be characterised in which prolactin may prove to be a better tumor marker than CEA.

Conclusion

Our data do not confirm the reported high incidence of hyperprolactinemia in colorectal cancer.

Therefore, the use of prolactin as a tumor marker for colorectal cancer cannot be advocated at this time.

However, the occurrence of ectopic prolactin production is possible in a subgroup of rectal adenocarcinomas. Further studies should focus on the clinical and pathogenetic importance of prolactin production in such tumors.

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