ONCOLOGY

Clinical and Biochemical Aspects of the Carcinoid Syndrome in Neuroendocrine Tumors of the Abdominal and Retroperitoneal Organs and Its Impact for the Disease Prognosis

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Overall and relapse-free survival of 238 patients with neuroendocrine tumors of the abdominal and retroperitoneal organs was evaluated with consideration for the presence of the carcinoid syndrome. The incidence of the carcinoid syndrome was 15.6%. The presence of the carcinoid syndrome was inessential for survival and relapse prognosis in patients with neuroendocrine tumors of the abdominal and retroperitoneal organs. A trend to the development of earlier relapses was noted in patients with this syndrome. Diarrhea was found to be a prognostically unfavorable factor. The time of the carcinoid syndrome development was prognostically significant in patients with malignant neuroendocrine tumors. The mean secretion of epinephrine, norepinephrine, and dopamine with daily urine was significantly higher in patients with the carcinoid syndrome. A significant positive correlation between urinary excretion of catecholamines was detected (r=0.53; p<0.05).

Key Words: *neuroendocrine tumor; carcinoid syndrome; serotonin; 5-hydroxyindolacetic acid; histamine; catecholamines*

Carcinoid syndrome (CS) develops in less than 10% patients with neuroendocrine tumors (NET). It usually manifests clinically only in metastases in the liver and often emerges in malignant tumors, which manifests in diarrhea (83%), hot flushes (49%), dyspnea (20%), excessive sweating (6%), and tricuspid valve disorders [6,14].

CS is determined by the release of peptides and amines (mainly histamine, other 5-hydroxytryptophane metabolites, kinins, and prostaglandins) produced and accumulated by NET cells into the circulation. Some compounds produced by NET were isolated and used as diagnostic and prognostic markers. Modern laboratory diagnosis of NET is based on evaluation of serum levels of chromatogranin A, serotonin, gastrin, glucagone, pancreatic peptide, vasoactive intestinal peptide, calcitonin, and neuropeptides, as well as of 5-hydroxyindolacetic acid (5-HIAA; serotonin metabolite).

Clinical manifestations of CS are caused by excessive production of tryptophane and hence, its de-

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rivatives (mainly serotonin) and poor discharge of their metabolites. This is particularly demonstrative for excessive production of serotonin in the presence of metastases in the liver. High incidence of CS in patients with metastases in the liver and low incidence in limited or local forms confirms this association. Differences in the main symptoms of CS are worthy of note. Vascular tone shifts (hot flushes), abdominal symptoms, and asthmatic attacks are obviously paroxysmal. It seems that they develop during a sharp increase of blood serotonin level as a result of its release from the tumor. In addition, many patients develop more stubbornly (permanently) manifesting symptoms (cyanosis, telangiectasias, pellagra-like dermatosis, oliguria, heart involvement), which determine the status of the patients between the attacks. These pathological changes result from persistent high content of serotonin and changes in tissue metabolism caused by it [8,10].

The incidence of CS varies depending on tumor location. It occurs in 11% patients with gastric tumors [5], in 5-20.3% patients with tumors of the small intestine [3,6], in 5% colonic tumor cases, in 34% pancreatic tumor cases [7], and in 13.8-29% ovarian cancer patients [4,12]. CS is extremely rare (less than 1% observations) in rectal tumors [11] and tumors of the vermiform process [2,13]. It was shown that 94% pheochromocytomas and 25-86% intra-abdominal paragangliomas were associated with arterial hypertension (crises) [1,9].

Clinical manifestations of CS are well studied; however, there is no consensus about its impact for the course and prognosis of cancer; CS and its manifestations in relation to the malignant potential of the tumor also deserve more profound study.

We studied the relationship between CS and disease prognosis in patients with abdominal and retroperitoneal NET.

MATERIALS AND METHODS

The study was carried out in 238 patients with abdominal and retroperitoneal NET, treated at N. N. Blokhin Cancer Research Center in 1955-2003. The mean age of the patients was 46.9±6.6 years (21.2-78.5 years). The disease was diagnosed for the first time in all patients and the diagnosis was confirmed by the results of histological study of the tumor.

The tumor location in these patients was as follows: gastric tumors in 50 (21%) patients, small-intestinal in 36 (15%), tumors of the vermiform process in 18 (7.6%), colonic tumors in 24 (10.1%), rectal tumors in 23 (9.7%), pancreatic tumors in 43 (18.1%), adrenal tumors in 26 (10.9%), and extraorgan retroperitoneal tumors in 18 (7.6%) patients.

Serum concentrations of histamine and serotonin and urinary concentrations of epinephrine, norepinephrine, dopamine, and 5-HIAA were measured spectrofluorometrically.

Serum concentrations of histamine and serotonin and urinary concentration of 5-HIAA were measured in 65 (27.3%) patients with morphologically verified NET. Urinary excretion of epinephrine, norepinephrine, and dopamine was measured in 32 (72.7%) patients with catecholamine-releasing tumors.

The data were statistically processed using Excel, SAS (version 11.0) software on the base of the Paradox database. The survival curves were analyzed by Kaplan–Meier method and compared by the log-rank method.

The linear relationships were evaluated using Pearson correlation test and Spearman rank correlation coefficient. The differences were considered significant at a probability of at least 95% ($p<0.05$).

RESULTS

CS was observed in 37 (15.6%) patients. Its main clinical manifestations were diarrhea (18 patients, 48.6%), blood pressure rise (periodical crises; 13 patients, 35.1%), hot flushes (10 patients; 27%). Combinations of these symptoms were observed in 5 (13.5%) patients, while in the rest 32 (86.5%) CS manifested by only one of these symptoms. CS most often developed in the presence of endocrine cell tumors of the adrenals (25%) and gastrointestinal tract (10.4-12.5%), but not in tumors of the appendix.

CS was most incident in patients with malignant tumors (23 patients; 62.2%) than in benign tumors (14 patients; 37.8%), but this difference was statistically negligible ($p>0.05$). The prognosis for life and disease relapse did not depend on the presence or absence of CS. Five-year overall survival of patients with and without CS was 74.6±8.3 and 75.3±4.1%, respectively ($p=0.9$); 5-year relapse-free survival was 28.6±7.6 and 42.6±3.8%, respectively ($p=0.4$). However, a trend to an earlier relapse was observed in patients with CS: the median of relapse-free survival in CS was 21.5 months *vs.* 27.3 months without this syndrome.

No statistically significant differences were detected in overall ($p=0.7$) and relapse-free ($p=0.7$) survival of patients with malignant endocrine cell tumors with and without CS or in the group of patients with benign tumors ($p=0.6$ and $p=0.9$ for overall and relapse-free survival, respectively).

The development of CS at the debut of the disease was observed in 25 (10.5%) and during disease progress in 12 (5%) patients. The life and relapse prognosis also did not depend on the time of CS development (at the debut or during progress of the disease). Overall 5-year survival in these two groups was 72.2±10.1 and 79.1±13.8%, respectively ($p=0.9$); 5-year relapse-free

survival was 38.8±10.1 and 11.0±8.3%, respectively (p=0.2).

Statistically significant differences in 3- and 5-year overall survival were obtained for patients with malignant NET, depending on the time of the CS development (at the beginning of the disease, 12 patients, and during its progress, 11 patients): 62.3±13.4 and 90.9±8.7%; 46.8±16.8 and 77.9±14.1%, respectively (p=0.05).

All patients with malignant NET with CS manifesting at the beginning of the disease developed relapses by year 5 of observation, while patients in whom the CS developed during the disease progress had relapses only by year 10 of observation.

Significantly worse 3-, 5-, and 10-year overall survival values were observed in patients with diarrhea (18 cases; median 4.5 years): 68.1±11.9, 40.8±16.6, and 0%, respectively, in comparison with patients in whom the CS manifested by hot flushes to the face (10 cases): 100, 100, 75.0±21.7%, respectively (p=0.009), or blood pressure rise (13 cases): 91.7±7.9% for all survival periods (p=0.01).

Significantly higher relapse-free survival (3, 5, and 10 years) was observed in the group of patients with blood pressure elevation: 68.2±13.9% for all periods of observation *vs.* patients in whom the CS manifested by hot flushes (median 10.8 months): 13.8±10.1, 9.2±8.7, and 0%, respectively (p=0.0006) or diarrhea (median 2.0 months): 23.8±10.8, 13.6±8.9, and 0%, respectively (p=0.001). Differences in relapse-free survival of patients with hot flushes and diarrhea were statistically negligible (p=0.9). Differences in the overall and relapse-free survival were most likely caused by the malignant potential of the tumor. A total of 78% patients with diarrhea had malignant tumors, while blood pressure rises in 75% patients were associated with a benign course of the disease; hot flushes were observed in 57% patients with malignant tumors.

On the other hand, analysis of the impact of clinical manifestations of CS for life and relapse prognosis in the patients with malignant NET showed that these parameters were worse for all periods of observations in patients with diarrhea *vs.* patients with hot flushes. The 3-, 5-, and 10-year overall survival in these groups were 60.1±14.2, 36.1±15.7, and 0% and 100, 100, and 75.0±21.7%, respectively (p=0.005).

The disease relapse prognosis in malignant tumors did not depend on the CS symptoms (p=0.6).

Overall survival of patients with sympathoadrenal tumors did not depend on the presence/absence of CS. The 5-year survival in these groups was 100 and 75.0±21.7%, respectively (p=0.2).

The relapse-free survival prognosis for the periods of 5 and 10 years was significantly worse for patients with sympathoadrenal tumors without CS (p=0.03), because in the absence of clinical symptoms these tumors were diagnosed at a more disseminated stage.

The mean serum concentration of histamine was 0.09±0.03 μg/ml (0.01-0.82 μg/ml), mean concentration of serotonin 0.16±0.06 μg/ml (0.01-1.6 μg/ml). The mean daily urinary excretion of 5-HIAA was 6.1± 3.8 mg (0.32-69.1 mg/day). Hence, the mean values of these biochemical markers were within the normal range. Presumably, this was due to the fact that the majority of gastrointestinal and pancreatic NET in our study were nonfunctioning.

It is known that the most informative laboratory test for the diagnosis of adrenal and extraorgan retroperitoneal NET is measurement of daily urinary excretion of catecholamines (epinephrine, norepinephrine, and dopamine). The mean epinephrine excretion was 47.8±30.7 μg/day (1.5-544.3 μg/day), of norepinephrine 62.2±20.6 μg/day (3.7-393.7 μg/day), and of dopamine 208.2±100.1 μg/day (14.4-1280 μg/day). Hence, the mean catecholamine values in NET have been significantly higher than normally, which is characteristic of these tumors.

No statistically significant differences in the mean concentrations of biochemical markers (serotonin, histamine, epinephrine, norepinephrine, and 5-HIAA) in men *vs.* women, in patients with malignant *vs.* benign tumors, and in different age groups (up to 40, 40-60, and over 60 years of age) were detected. The exclusions were mean daily urinary excretion of norepinephrine in patients aged under 40 and over 60 years: 69.7±20.2 and 22.9±13.4 μg (p=0.05), respectively. The mean daily urinary excretion of 5-HIAA in these age groups was 2.6±0.5 and 4.6±0.8 mg, respectively (p=0.05). The mean concentrations of serotonin, histamine, and 5-HIAA in patients with and without CS did not differ.

The mean daily urinary excretion of epinephrine, norepinephrine, and dopamine was significantly higher in patients with CS than in those without it: epinephrine 109.5±40.7 and 12.6±3.6 μg/day, respectively (p=0.047), norepinephrine 128.7±35.8 and 27.2±3.8 μg/day, respectively (p=0.048), and dopamine 389.8±129.5 and 113.1±15.9 μg/day, respectively (p=0.05). A significant positive correlation was detected between the daily urinary excretion of epinephrine, norepinephrine, and dopamine in patients with catecholamine-secreting adrenal tumors (32 cases; r=0.53; p<0.05).

Hence, the presence/absence of CS is inessential for life and disease relapse prognosis in patients with abdominal and retroperitoneal NET. On the other hand, a trend to earlier relapsing was traced in patients with CS. The worst life and disease relapse prognosis was noted in patients with diarrhea. In addition, the time of CS development is prognostically important for patients with malignant NET.

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