ARTICLE – CLINICAL STUDY

Malignant carcinoid in two brothers

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Abstract

Familial occurrence of malignant carcinoid is rare (about 3 %). Authors describe occurrence of the malignant carcinoid in two brothers. In the older one the diagnosis was estimated in 1991. He had multiple intestinal carcinoid tumor with multiple liver metastases histological type III by Soga classification. Patient is intermitently treated with somatostatin analogue — lanreotid and with interferon alfa. By this therapy the disease is stabil. In the younger of brothers the diagnosis was estimated in 1999. The disease had rapid progression and in ten months patient died despite of the therapy. Definitive diagnosis was a malignant neuroendocrine tumor of pancreas-mixed low differentiated carcinoid with calcitonin overproduction. *(Fig. 4, Ref. 15.)*

Key words: malignant neuroendocrine tumor, carcinoid, calcitonin, octreoscan, familial occurrence of carcinoid.

Carcinoid tumors are thought to arise from cells of the diffuse neuroendocrine system. Carcinoid tumors are localized in the gastrointestinal tract (85 %), in the bronchial tract and lungs (about 10 %). Remaining 5 % we can find in ovary, testes, in kidneys, in the thymus or in another rare localisation. 40 % of gastrointestinal tumors are in the appendix, 20 % in the small intestinum, 15 % in the rectum, and remaining part belong to oesophagus, stomach, duodenum or colon (Memon, 1997). The incidence of the disease is 2—7 new cases per 100 000 inhabitants per year. The prevalence is highest in the 5th and 6th decade of a life (Dalay, 1983). Carcinoids are characterised by positive reaction to silver stain and chrom. Cytosolic neuroendocrine markers are neuron specific enolase, protein S and polymorphal epitelial peptid, from markers of neurosecretory granuls to chromogranin A,B,C, synaptophysin and neurokinin A,B. Specific marker is positive reaction to serotonin, calcitonin, gastrin and also to another peptides and amines.(Memon, 1997). The best clasiffication for neuroendocrine tumors is proposed by Capella. It is based on the primary localisation of the tumor, tumor size, extension to surrounding tissue, angioinvasion, biologic behaviour, histologic differentiation and functional status of the tumor. The "functionality" of the tumor in this context signify the presence of clinical signs of carcinoid syndrome together with elevated plasma concentration of specific hormones (Capella et al., 1994). From the point of embryologic origin carcinoid tumors are divided into 3 groups. 1. Foregut group: tumors are localised in the respiratory tract, in the oesophagus, in the stomach and in the duodenum. 2. Midgut group: the place of occurence is the small bowel, the appendix and the right side of the colon. 3. Hindgut group: tumors are localised in the distal part of large bowel and in the rectum (Soga, 1998; Sweeney and Rosemurgy, 1999).

Very important diagnostic modality is Somatostatine receptor scintigraphy — octreoscan. The Indium 111 labeled analog pentetreotid binds on the somatostatine receptors on the surface of tumor cells. The degree of accumulation in the scintigram corresponds with the receptor density in the tissue. Appart from the advantages of the localisation of the primary tumor and its metastases this method provides the selection of patients suitable for the treatment with somatostatine analogues (Lamberts, 1993). Another diagnostic tool — ^{131}I-metaiodbenzylguanidin (MIBG) scintigraphy is positive in 50—60 % of patients (Taal et al., 2000).

Case 1

Since 1991 we follow a patient 1 borned in 1948 with diagnosis of malignant carcinoid in our department. By ultrasound examination the liver metastases were found and patient was reffered for futher evaluation. History of the watery diarrhoea after ingestion of fluid and intermittent subileous states dominated. Tachycardia and flush of the face, neck and the upper part of thorax was presented intermitently. The urinary excretion of 5-hydroxyindolacetic acid

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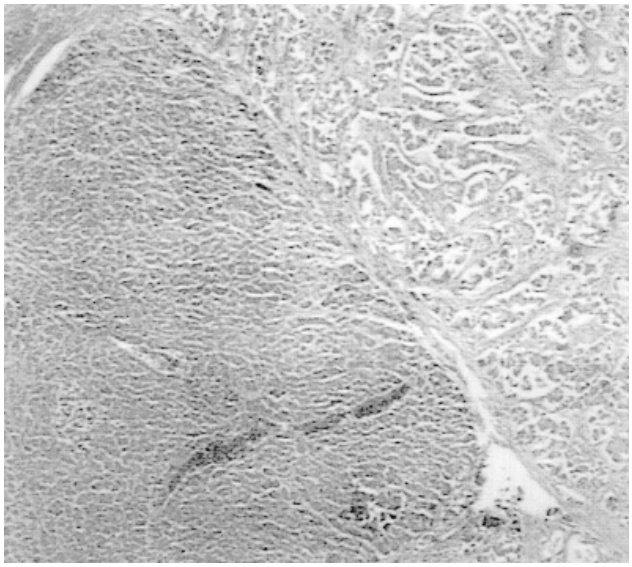

Fig. 1. Histological finding: low differentiated mixed carcinoid of pancreas. x27.
Obr. 1. Histologický nález: málo diferencovaný zmiešaný karcinoid pankreasu. Zväčš. 27-krát.

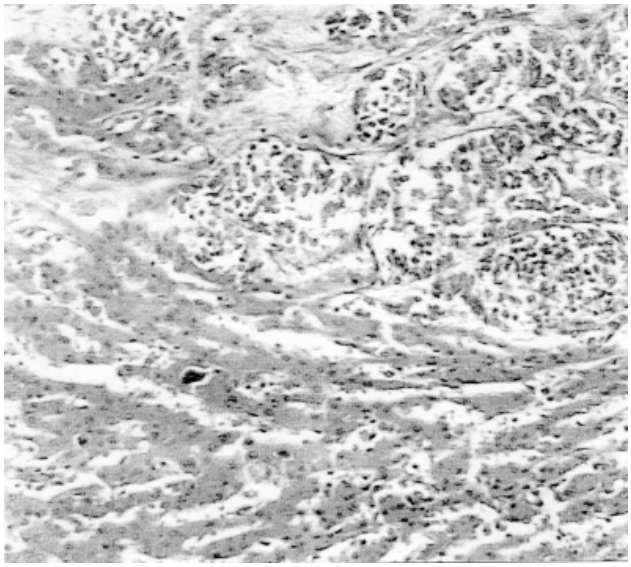

Fig. 2. Histological finding: metastasis of the pancreatic carcinoid in the liver. x27.
Obr. 2. Histologický nález: metastáza karcinoidu pankreasu do pečene. Zväčš. 27-krát.

(5-HIAA) was elevated 100 μmol/24 h (normal range is less than 35 μmol/24 h). On the X-ray enteroclysis suspection of the small bowel tumor was supposed and patient was send to probator laparotomy. By the laparotomy 3 tumors diamater of 10, 13 and 9 mm in the jejunum and distal ileum were found. Histomorphological examination revealed the low differentiated carcinoid type III by Soga. Intraoperatively a catether in the arteria hepatica propria was guided. During the postoperative course the locoregional therapy with native somatostatin in continual infusion and streptozotocin was done. Diarrhoea and flush disappeared. Urinary excretion of 5-HIAA decreased to the levels of 50—60 μmol/day. After 3 years we recorded the aggravation of clinical symptoms and the elevation of urinary excretion of 5-HIAA. Somatostatine receptor scintigraphy has shown the metabolic activity in the liver metastases. We started the treatment with long acting analogue of somatostatine, octreotide, in dosis 150 ug subcutaneously twice daily. Later octreotid was replaced with lanreotid in dosis of 30 mg i.m. once in 14 days. During the treatment the clinical status improved and the urinary excretion of 5-HIAA decreased. From 1998 on the basis of another elevation of 5-HIAA urinary excretion (180—220 μmol/24 h) interferon alfa in dosis of 5 MU s.c. 3 times a week was added to the treatment regimen. By the combination of lanreotid and interferon alfa therapy the disease is stable, the metabolic activity of the disease decreased. The number and the diameter of metastases in liver are also stabil without any progression. We do repeat the treatment regimen on the basis of the disease activity. Patient is now without carcinoid syndrome. He survives 10 years after the diagnosis was fixed.

Case 2

Younger brother of the above mentioned patient was admitted to the Ist Department of Internal Medicine, Comenius University.

He was 46 yrs old with history of 20 kg weight loss in the last 6 mts. At this time (february 1999) was started insulin therapy for diabetes mellitus. After a short period of improvement, profuse diarhea (20—30 stools per day) began and at this time multiple metastatic lesions in the liver and lungs were revealed. Biopsy from the liver mts has shown low-differentiated carcinoma probably originating in pancreas. Thyroid gland scintigraphy has shown "cold node". Despite of 3 cycles of 5-FU and leucovorin therapy the progress of the disease was evident. Increasing level of calcitonin led to suspicion of medullary carcinoma of thyroid gland and with this diagnosis was patient sent to our department.

Physical examination showed dyspnoic patient with cachexia, hepatomegaly and leg edema. Laboratory findings : hypoproteinemia, hypoalbuminemia, basal calcitonin 3080 pg/ml (norm 60 pg/ml) after i.v. calcium: 4127 pg/ml, high positivity of NSE, slightly increased CEA.

Normal values of 5-HIAA, adrenalin, nor-adrenalin and dopamin in urine were found.

Sonography revealed multiple metastases in the liver, 2 lesions in the pancreas (corpus and head). Biopsy of thyroid node has not confirmed supposed carcinoma. Whole body scintigraphy MIBG (metaiodinebenzylguanindin) revealed above mentioned metastatic lesions plus mts in skull, columna, minor pelvis and retroperitoneal lymphonodes.

With regard to these findings diagnostic conclusion of the neuroendocrine neoplasia — carcinoid has been done. Somatostatin (octreotid) therapy 300—500 mig/day started. Patient died 1 month later in the malignant cachexia and metabolic disintegration. Anatomical diagnosis: Low-differentiated mixed carcinoid of the pancreas (Fig. 1) with metastatic spread to the liver (Fig. 2) lungs (Figs 3, 4) and retroperitoneal lymphonodes and bone marrow.

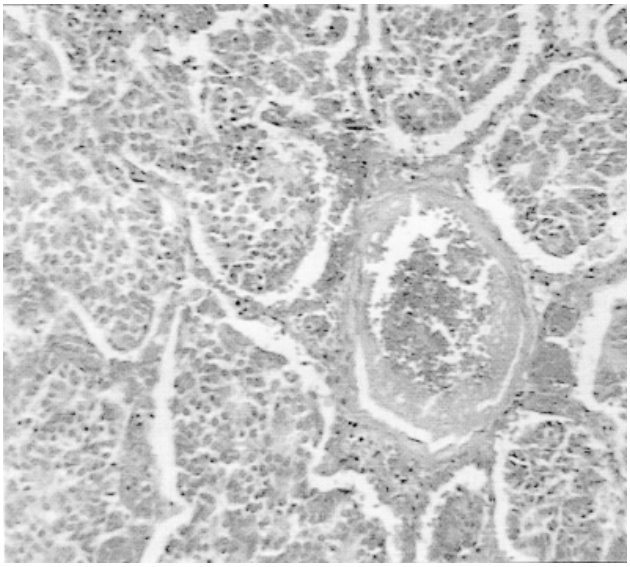

Fig. 3. Histological finding: metastasis of the pancreatic carcinoid to the lungs. x90.
Obr. 3. Histologický nález: metastáza karcinoidu pankreasu do pľúc. Zväčš. 90-krát.

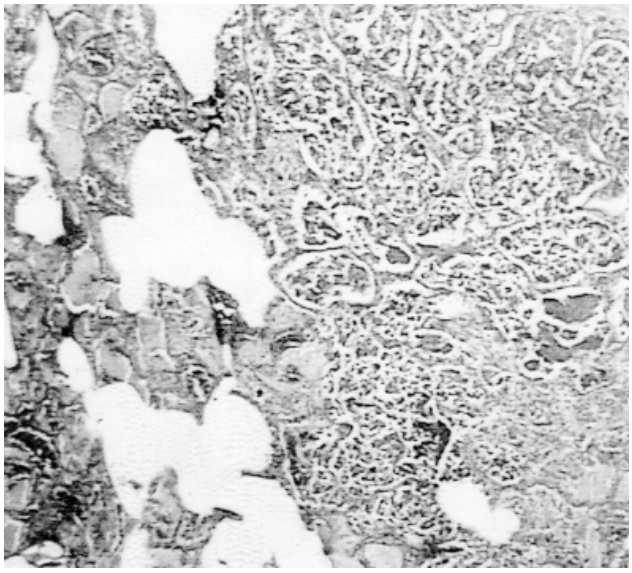

Fig. 4. Histological finding: metastasis of the pancreatic carcinoid to the lungs. x27.
Obr. 4. Histologický nález: metastázy karcinoidu pankreasu do pľúc. Zväčš. 27-krát.

Discussion

Carcinoids don't belong to common tumors. Familiar incidence is rare. Until now we have not met brothers association of this disease. The genetic predisposition of the occurence of neuroendocrine tumors in the syndroma of multiple endocrine neoplasia (MEN) is well known. While the cold nodus in the thyroid gland and high level of calcitonin in plasma were found, the suspicion on medular thyroid carcinoma raised. A complet diagnostic work-up including the genetic examination for MEN syndroma was realised, the MEN syndroma was not confirmed. The definitive diagnosis of low differentiated carcinoid of pancreas with calcitonin overproduction on the basis of histomorphological and immunohistochemical features after patient death was stated. The low differentiation of the tumor was responsible for quick generalisation of the disease. The older from brothers had carcinoid tumor localised in the small bowel. In the time of diagnosis the liver metastases were present. 5-years survival in such cases in non-treated patients is about 35 % (Kulke et al., 1999). We suppose that the reason of the long survival of our patient is partially due to intermittent treatment with long acting somatostatin analog and interferon alfa. One sister of our patients is followed up for the diagnosis of eufunctional nodular struma. A complete diagnostic work-up failed to find a malignant tumor.

The group of workers from Mayo Clinic, which analysed the group of 245 patients with carcinoid found that 3.7 % patients with carcinoid tumor had at least one first-degree relative with the same malignancy. The cummulative probability for developing a carcinoid tumor was calculated to be 1.5 % at age 80 (Babovic-Vuksanovic et al., 1999).

Carcinoids of the small intestine cause nonspecific gastrointestinal symptoms which arise not only on the basis of mechanical effect of the tumor or metastases, but also as a result of desmoplastic mesenterial reaction with a malrotation and a shortage of the mesenterium. Ischaemia or bowel infarction, rarely the enterorhagia can be presented. A carcinoid syndrome occurs in 10—20 % patients with carcinoid tumor. Classic carcinoid syndrome typically includes vasomotor, cardiac and gastrointestinal manifestation. To the skin manifestation belongs erythematous flush affecting face, neck, upper chest, pellagra, telenagiectasias and hyperkeratosis. The gastrointestinal symptoms present with water diarrhea (20 times /day) and abdominal cramps. In our patient case 1 the carcinoid syndrome was presented with flush, diarrhea and tachycardia before the surgery and before the interferon alfa and somatostatine analog administration. After few asymptomatic years the reccurence of diarrhea occured. By the using of INF alfa and lanreotide treatment diarrhea dissapeared. In the patient case 2 profuse diarrhoea caused by overproduction of calcitonin dominated. Number of stools was reduced after the treatment with somatostatine analog octreotide. Somatostatine analogues suppress the release of serotonin, bradykinins, tachykinins and also another hormonal substances and peptides from the tumor cells and inhibit their action in target tissue.Samatostatine analogues have antiproliferative and antimitotic action, tumor mass regression occurs during the treatment in 10 % of patients (Jacobsen et al., 1996; Ruszniewski et al., 1996; Kulke et al., 1999; Dermot et al., 2000). Octreotide is usually used in the dosis 50—200 μg subcutaneously 2 or 3 times daily, lanreotid in dosis of 30 mg i.m. per 10—14 days or Sandostatin LAR 10—30 mg i.m. once in 28 days.

A treatment of malignant carcinoid starts with the surgery resection of primary tumor and metastases. Extent of the resection is based on the primary origin and diameter of the tumor. In patient n.1 the partial resection of jejunum and ileum with remove of 3 tumors was done. In patient 2 the surgery was not indicated beca-

use the advanced stage of disease. The chemotherapy was also without effect. On the basis of serious adverse events and the low response rate chemotherapy is today indicated only in low differentiated carcinoid tumors. Adriamycin, combination therapy with streptozotocin and 5-fluorouracyl (5-FU), or cis-platine and 5-FU can be used (Moertel et al., 1991; Oberg et al., 1994). Today the combination treatment with long acting somatostatine analogues and interferon alfa seems to be the most effective. Reduction in urinary excretion of 5-HIAA occurs in 50 % of patients treated with interferon alfa and in 10 % of patients also tumor mass reduction occures. The dosis is 3—6 M.U. s.c three times a week (Oberg, 1993; Kulke et al., 1999). In symptomatic treatment of carcinoid syndrome serotonin antagonists — cyproheptadine, lisurid, metylsergit and also serotonin receptor antagonist — alosetron, ondasetron are used. Treatment with cyproheptadine had minimal effect on the number of stool reduction in our second patient. In these cases the treatment with somatostaine analogues is indicated.

In our 36 patients group of carcinoid disease the familial occurence of carcinoid tumor we found only in 2 patients. For clinical practice is very important to know about this possibility and to follow-up also the first-degree relatives.

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Abstrakt

Kiňová S., Ďuriš I., Kováčová E., Štvrtina S., Galbavý Š., Makaiová I.:
Familiárny výskyt malígneho karcinoidu
Bratisl. lek. Listy, 102, 2001, č. 5, s. 231–234

Familiárny výskyt karcinoidu sa udáva približne 3 %. Autori opisujú výskyt malígneho karcinoidu u dvoch bratov. U staršieho diagnózu určili roku 1991. Išlo o viacpočetný karcinoid ilea III. typu podľa Sogu s mnohopočetnými metastázami do pečene. Pacient je intermitentne liečený analógmi somatostatínu a interferónu alfa, pri uvedenej liečbe je stav stabilizovaný. U mladšieho brata diagnózu určili roku 1999. Ochorenie malo rýchly priebeh, počas 10 mesiacov sa napriek liečbe skončilo smrťou pacienta. Histologicky išlo o malígny neuroendokrinný nádor — málo diferencovaný zmiešaný karcinoid pankreasu produkujúci kalcitonín. *(Obr. 4, lit. 15.)*
Kľúčové slová: malígny neuroendokrinný nádor, karcinoid, kalcitonín, oktreoscan, familiárny výskyt karcinoidu.

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