PANCREATIC NEUROENDOCRINE TUMOR PRESENTING WITH CARCINOID SYNDROME: CASE REPORT

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SUMMARY – Carcinoid is the most common neuroendocrine tumor. It is primarily localized in the ileum and the appendix, whereas other localizations are rare. Only a small number of the carcinoids present with carcinoid syndrome (flushing, diarrhea), usually after tumor has already metastasized. A case of carcinoid tumor of uncommon localization is reported. A 54-year-old male patient presented for evaluation because of weight loss, flushing and diarrhea. Laboratory value of 5-HIAA was 775.5 mmol/l (normal values up to 72.8) and the pancreatic tumor marker CA 19-9 was increased. Ultrasonographic and magnetic resonance findings localized the tumor in the prepapillary pancreatic region and visualized the spread to the liver. The diagnosis was confirmed by pathohistologic evaluation of a liver biopsy specimen. The patient was treated with Sandostatin (octreotide analog), which led to significant relief of the symptoms, although control 5-HIAA values were not reduced.

Key words: *Neuroendocrine tumors, diagnosis; Pancreatic neoplasms, diagnosis; Pancreatic neoplasms, drug therapy; Carcinoid tumor, diagnosis; Carcinoid tumor, drug therapy; Case report*

Introduction

Carcinoid is the most common neuroendocrine tumor[1-5]. It has traditionally been classified according to embryogenetic aspects into foregut, midgut and hindgut tumors, or to histologic characteristics as 'typical' or 'atypical' tumor. According to endocrinologic status, carcinoids are either functioning or nonfunctioning tumors[6]. Their metastatic potential correlates with the size and site of primary tumor, angioinvasiveness and number of mitoses[7]. If the tumor is greater than 2 cm in diameter, chances of spread are greater than 50%[8]. Approximately 20% (1/5) of the small intestine carcinoids will develop metastases and roughly 1/3 of those that have spread will develop symptoms of the carcinoid syndrome (hot red flushing of the face, diarrhea, and asthma-like wheezing attacks)[9]. The most common localization for carcinoids is the small intestine (39%), followed by the appendix (26%), rectum (15%), lungs (10%), colon (5%-7%), stomach (2%-4%), pancreas (2%-3%) and liver (>1%), whereas other localizations such as gallbladder and bile ducts, ovaries, testicles, urinary bladder, prostate gland, breast, kidneys and the thymus gland are extremely rare. As much as 25% of all gastrointestinal tract carcinoids are associated with another tumor of non-carcinoid type (especially colon cancer, lung cancer, breast cancer and prostate cancer)[4]. If distant metastases are present when a carcinoid from any site of origin is found, the 5-year survival rate drops to 27% if not treated[10]. The potent chemicals and hormones produced by carcinoid tumors, through their effects on the cardiovascular, gastrointestinal, pulmonary and other body systems, cause the carcinoid syndrome, which is in many cases worse than the symptoms from the growth of the tumor itself[11,12]. Once considered, the diagnosis usually can be confirmed by performing a urine 5-HIAA test or by measuring chromogranin A (CgA) and serotonin in the blood[13]. A universally approved way of detecting carcinoid as well as other neuroendocrine tumors now is Sandostatin receptor scintigraphy (octreoscan). It is positive in up to 85% of carcino-

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ids and it usually predicts a good response to treatment with octreotide (Sandostatin)[14].

Case Report

B.B., a 54-year-old male patient, presented with symptoms of weight loss, flushing and diarrhea. The symptoms first occurred in 1995, after he had been hospitalized for peptic ulcer, but correct diagnosis was not suspected until December 2001 when he was referred to our department. By that time, the patient lost 20 kg, had very frequent unprovoked flushing episodes followed by watery stool discharge and paresthesia around the mouth and hands. Despite weight loss he seemed to be in good health, eupnoic, cardiopulmonary compensated, with no palpable lymph nodes. Abdominal palpation revealed enlarged liver. After highly positive urine 5-HIAA and CA 19-9, radiologic and additional laboratory testing was performed in order to localize the primary site. Chest x-ray was negative, so further investigation was directed to the gastrointestinal tract and pancreas. Abdominal ultrasound showed enlarged liver with multifocal lesions in both hepatic lobes, irregular (rough) pancreatic parenchyma with dilated pancreatic duct, and enlarged lymph nodes around hepatic port. Histopathologic analysis of the two colonic polyps obtained from the colonoscopy performed at the referring hospital was negative for carcinoid and revealed hyperplastic tissue. Since the patient had only recently undergone esophagogastroduodenoscopy (EGD), which was negative for tumor, we performed barium radiographs of the small intestine but yet failed to find the primary site. The values of electrolytes and hormones (insulin, calcitonin, prolactin and gastrin) were within the normal range, confirming the sporadic tumor existence (Table 1). Cardiac ultrasonography and ECG findings were normal. Magnetic resonance of the pancreatic region showed tortuous tumorous narrowing of the ductus choledochus in the prepapillary region and dilatation of the pancreatic duct (Fig. 1), an exotic localization with a frequency of less than 1% for this type of tumor. Due to the extent of the disease, surgical treatment was not possible. We performed ultrasound guided liver biopsy of the lesion, which stained positive for chromogranin and synaptophisin. The histologic diagnosis was neuroendocrine tumor of the carcinoid type. Octreotide treatment at a dose of 100 μg was initiated, increasing the dose after a week to 300 μg divided into 3 daily doses. He experienced brief relief of the symptoms, reduction of flushing episodes and reduction in the number of stools, however, the values of urinary 5-HIAA did not decrease despite the treatment.

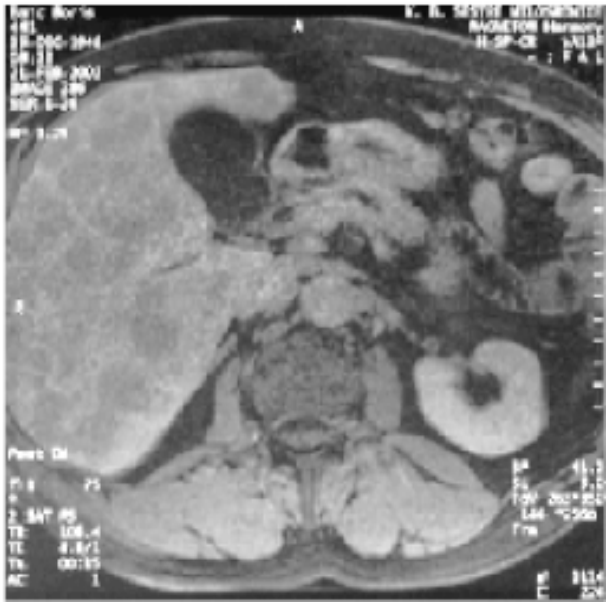

Fig. 1. MR findings

Discussion

Pancreas is not a common localization for the carcinoid, the incidence of the mentioned tumor being *2%-3%*. Some 50%-60% of pancreatic neuroendocrine tumors are functionally active due to the secretion of insulin, gastrin, glucagon, vasoactive intestinal polypeptide (VIP) or other less common hormones[15]. Pancreatic neuroendocrine tumors without hormonal symptoms, such as the one de-

Table 1. Laboratory findings

Test	CA 19-9(U/ml)	AFP (IU/ml)	CEA (ng/ml)	Gastrin (μU/ml)	5-HIAA (μmol/l)	PRL (μg/l)	PTH (pg/ml)	IGF I (IU/l)	ADR -urine	NORADR -urine	VMA -urine	INS (mIU/l)
Normal range	<37	<6	0-5	28-115	<72.8	5-25	11-62	600-2200	10.2-65.5	32.5-271.9	15.6-31.8	5-25
Finding	55	0.66	2.5	88	775.5	4.7	30.6	432	21.8	215.7	10.4	8

scribed, are infrequent and found incidentally or because of their local invasiveness when causing intestinal obstruction, changes in bowel habits or obscure bleeding. Only a small proportion of the pancreatic neuroendocrine tumors are responsible for symptoms of carcinoid syndrome[11,12]. The accompanying manifestations[16], such as peptic ulcer, sometimes described with carcinoid tumors, especially those localized in the 'gastrinoma triangle', were also found in our patient, although gastrin values were within the normal range. Muscle wasting or Peyronie's disease[17-19] were not observed. Carcinoid heart disease, occurring in as much as 50% of patients with developed carcinoid syndrome, and being a major mortality and morbidity cause among those patients, was not present either[20]. The importance of carcinoid tumors is that they are slow growing and often curable. The progression of the illness in patients with carcinoid syndrome is usually more rapid than in those without the functioning tumor. However, this has been changed remarkably with the advent of Sandostatin (octreotide)[21]. In the last 10 years, since the introduction of effective combinations of treatment with Sandostatin, various types of surgery, chemotherapy, hepatic artery injections and biologic response mediators, the average survival time from the start of treatment has increased to more than 5 years. Sandostatin therapy not only relieves flushing and diarrhea in 75% to 80% of patients, but has also been shown to successfully reduce tumor growth[22]. This antiproliferative effect was not observed in our patient.

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Sažetak

NEUROENDOKRINI TUMOR GUŠTERAČE S IZRAŽENIM KARCINOIDNIM SINDROMOM: PRIKAZ SLUČAJA

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Iako su karcinoidi rijetki, predstavljaju najčešći tip neuroendokrinih tumora, primarno smještenih u tankom crijevu i apendiksu. Mali broj ovih tumora, nakon što metastazira u jetru, prezentira se simptomima karcinoidnog sindroma (rumenjača, proljevi). Prikazan je karcinoid gušterače, neuobičajene lokalizacije za ovu vrst tumora. Bolesnik u dobi od 54 godine upućen je u kliniku zbog gubitka na težini, rumenjače i proljeva. Vrijednosti 5-HIAA i CA 19-9 bile su izrazito povišene. Ultrazvučno i magnetskom rezonancom prikazan je tumor predpapilarnog područja te uvećana jetra prožeta višestrukim sekundarizmima, a patohistološki nalaz govorio je u prilog neuroendokrinog tumora tipa karcinoida. S obzirom na proširenost procesa odustalo se od kirurškog liječenja te je započeta terapija Sandostatinom uza značajno kliničko poboljšanje, no bez učinka na 5-HIAA.

Ključne riječi: *Neuroendokrini tumori, dijagnostika; Neoplazme gušterače, dijagnostika; Neoplazme gušterače, lijekovi; Karcinoidni tumor, dijagnostika; Karcinoidni tumor, lijekovi; Prikaz slučaja*