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Case report

Case report of a patient with initially inoperable well-differentiated midgut neuroendocrine tumor (WDNT) — PRRT and long-acting somatostatin analogs as the neoadjuvant therapy

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Abstract

A 43-year-old man was admitted to Surgery Department because of abdominal pain, vomiting, weight loss and flushes. Computed tomography (CT) examination revealed upper and middle abdomen tumor of about 110 × 110 mm. Histopathological analysis of the tissues obtained during the exploratory laparotomy confirmed WDNT (well-differentiated neuroendocrine tumor according to the WHO classification 2000). The patient received 5 doses of chemotherapy without any response. A positive result of ^{99m}Tc-[EDDA/Hynic] Octreotate scintigraphy (SRS) gave the possibility of PRRT (peptide receptor radionuclide therapy). The patient was treated with the total dose of 400 mCi of ^{90}Y-DOTA-TATE. CT performed after the PRRT revealed regression of the tumor size to 72 × 94 mm. A decrease of CgA level and release of symptoms were also observed. Aiming at the removal of the considerable diminished tumor the patient was qualified for the second laparotomy. "Cytoreduction" surgery with partial excision of the tumor was performed. Additionally tumor-affected appendix was removed. The second focus of WDNT (according to the WHO classification 2000) with Ki67 < 1% was found in the appendix. Pathologists confirmed the above-mentioned lesions as independent (an extremely rare clinical situation). The following treatment with long-acting somatostatin analogs and 300 mCi of ^{90}Y-DOTA-TATE resulted in further regression of the tumor size to 25 × 35 mm. Consecutive laparotomy is considered. If complete tumor removal might be achieved is an open question. The above case report shows the efficacy of combined therapy with the use of "hot" and "cold" somatostatin analogs not only in controlling the symptoms of the disease but also in obtaining tumor size regression making surgical intervention possible. Such a neoadjuvant therapy seems to be a promising tool in the management of patients with initially inoperable neuroendocrine tumors.

KEY words: PRRT, neoadjuvant therapy, well-differentiated neuroendocrine tumor

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Introduction

Midgut tumors are the most common neuroendocrine tumors (NET). Using morphological, immunohistochemical and bio-

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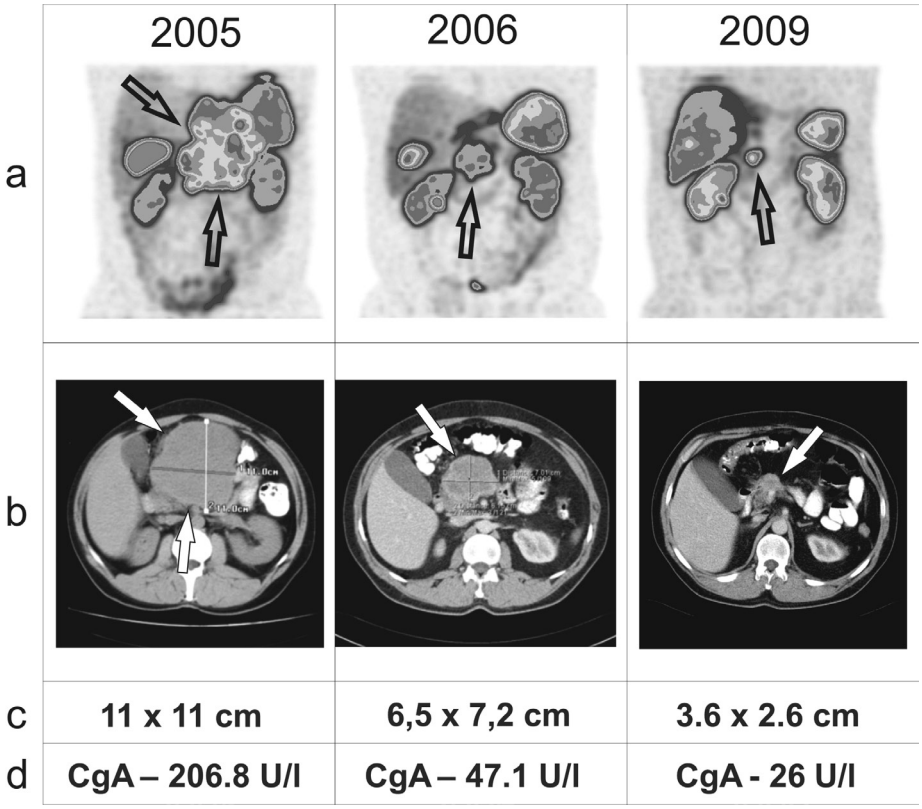

Figure 1. The picture presents the results of SRS (A) before the treatment (2005) after PRRT (2006) and after surgery (2009) with corresponding CT scans (B). Bellow the pictures the CgA levels are showed during the course of the treatment

logical criteria, the classification distinguishes between well differentiated neuroendocrine tumors (WDNT) with benign or uncertain behavior, well differentiated (low grade malignant) carcinomas and poorly differentiated (high grade malignant) carcinomas [1]. In 15% of cases the coexistence with other neoplasms is observed. Surgery remains the gold standard in the management of NETs. Majority of the tumors are well differentiated, but even when small (less than 1 cm) have the potency to metastasize. The problem are the invasive unresectable tumors and those which are already metastasized at the time of diagnosis. WDNT usually express somatostatin receptors and they can be targeted with peptide receptor radionuclide therapy (PRRT). In patients with advanced neuroendocrine tumors PRRT might be not only the palliative but also neoadjuvant therapy [1, 2].

Case report

43-years old man was admitted to Surgery Department because of abdominal pain, vomiting, weight loss and flushes. The computed tomography (CT) revealed the tumor of the upper and middle abdomen of about 110 × 110 mm. The initial cytological diagnosis was: *tumor epigastrii probabiliter GIST* (gastrointestinal stromal tumor). Immunohistochemical analysis changed the diagnosis to: *carcinoma neuroendocrinale bene differentiatium; atypical carcinoid; emboliae neoplasmaticae vasorum lymphaticorum*. On 13th July 2005 patient underwent the exploratory laparotomy. The 150 over 200 mm tumor of the mesentery radix mobile towards aorta was found. The tumor was passing through the transverse mesocolon to the omental sac and through the lesser omentum was reaching liver. The tumor was separated from the small and large intestine, but the vessels of intestines and the celiac trunk bifurcation were involved and this made the lesion unresectable. There were no liver metastases found. The histopathological analysis of the tissues obtained during the surgery confirmed the diagnosis of well differentiated neuroendocrine tumor (WDNT according to the WHO classification 2000). From 29.08.2005 to 06.01.2006 patient received 5 doses of chemotherapy streptozocin and 5-fluorouracil (5-FU) without any response. Patient was than referred to the Department of Endocrinology. Somatostatin receptor scintigraphy (SRS) with the use of ^{99m} [EDDA/Hynic] Octreotate revealed pathological uptake in the upper and middle abdomen. This gave the possibility of peptide receptor radionuclide therapy (PRRT). Patient was treated with the total dose of 400 mCi of ^{90}Y-DOTA-TATE — 100 mCi per one cycle every 6–9 weeks (from May to September 2006). To prevent nephrotoxicity an amino acid infusion lasting 8 to 10 hours was used during each cycle. The levels of 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A (CgA) prior to therapy were 21 μmol/24 h (normal range 10–40 μmol/24h) and 206.8 IU/l (normal range till 18 IU/ml), respectively. The blood profile and routine laboratory parameters (electrolytes, liver function tests, creatinine, and urea) were checked prior to therapy, then after 7 and 14 days after the PRRT and then every month. The computed tomography performed after the radioisotope therapy (10.2006) showed regression of the tumor size — from 110 × 110 mm at the time of diagnosis to 72 × 94 mm. The density of the tumor was 26 Hounsfield Units (HU). There was also the decrease in chromogranin A level to 47.1 IU/l and release of symptoms observed. After PRRT

patient was treated for four months with long-acting somatostatin analogs. The following CT (03.2007) revealed further regression of the tumor size to 49 × 77 mm, with the tumor density 20–33 HU. Aiming at the removal of the considerable diminished tumor the patient was qualified for the second laparotomy. "Cytoreduction" surgery with partial excision of the tumor was performed. On histopathological examination the diagnosis of well-differentiated neuroendocrine cancer with Ki67 3% was confirmed. Additionally the changed appendix was also excised. The second focus of WDNT (according to the WHO classification 2000) with Ki67 < 1% was found in the appendix. The pathologist confirmed above-mentioned lesions as independent. The tumor size on CT performed three months after surgery was 45 × 52 mm. Due to the very good response to the previous radionuclide therapy two additional doses of ^{90}Y-DOTA-TATE (2 × 100 mCi) were applied in 2008, and the treatment with long acting somatostatin analog was continued. The CT performed one month after the PRRT revealed 26 × 36 mm remaining part of the tumor in the pancreatic body.

Patient was referred again to the Surgery Department but the localization of the tumor (close to the vessels with a high risk of venous confluence and mesenteric vein injury) made the tumor inoperable and continuation of the radioisotope therapy was advocated. Eleven months after the last dose of radioisotope therapy patient received 100 mCi of ^{90}Y-DOTA-TATE. After this therapy the tumor size was 25 × 35 mm. There was no hematotoxicity or nephrotoxicity observed during and after the first and then repeated cycles of radioisotope therapy. The consecutive laparotomy is considered. If the complete tumor removal might be achieved is an open question.

Discussion

Above case report shows the efficacy of combined therapy with use of "hot" and "cold" somatostatin analogs not only in controlling the symptoms of the disease but also in regression of the tumor size what enabled the surgical intervention. PRRT is usually used as a palliative treatment. Presented case report and other reported in literature show the efficacy of PRRT also as neoadjuvant therapy in the treatment of inoperable neuroendocrine tumors with positive somatostatin analogs receptor scintigraphy (SRS) [1]. SRS has proven its role in the diagnosis, staging of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NET) and follow-up of patients with known disease. It might be also used for the selection of patients with inoperable or metastatic tumors for PRRT [2]. Because reported patient was treated with both — radionuclide therapy and long-acting somatostatin analogs — it is impossible to distinguish which therapy resulted in regression of tumor size. PRRT as guided therapy is probably mainly responsible for the regression of the tumor size. But as the results of a placebo-controlled, double-blind, phase IIIB study in patients with well-differentiated metastatic midgut NETs (PROMID) show the long-acting somatostatin analogs are effective not only in symptoms control, but also might significantly lengthen time to tumor progression in patients with functionally active and inactive metastatic midgut NETs [2, 3]. The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor [3]. Moreover PROMID study have confirmed the antiproliferative effect of octreotide LAR in patients with well-differentiated metastatic GEP-NETs [3, 4].

Neoadjuvant therapy with both radiolabeled somatostatin analogs and "cold" somatostatin analogs seems to be a promising tool in the management of patients with initially inoperable neuroendocrine tumors [1–6].

Above case-report is also an example of the coexistence of two independent neuroendocrine tumors — well-differentiated neuroendocrine cancer of the mesentery radix with Ki67 3% and well-differentiated neuroendocrine tumor of the appendix with Ki67 < 1%. According to the literature up to 29% of patients with carcinoid tumor of the small intestine have multiple synchronous carcinoid tumors [7]. The co-incidence of GEP-NET in different organs is an extremely rare clinical situation. Only a few such tumors have been described so far [8–10]. The coexistence of GEP-NET and secondary primary malignancy (SPM) was observed in 2.3% of surgical cases and 8.1% of autopsy examinations [7]. In 59–87% GEP-NET and SPM were synchronous [11]. Metachronous neoplasms were revealed 1–7 years after diagnosis of GEP-NET [11].

Conclusions

The presented case report shows the efficacy of combined therapy with the use of "hot" and "cold" somatostatin analogs not only in controlling the symptoms of the disease but also in obtaining tumor size regression making surgical intervention possible.

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