Endokrynologia Polska/Polish Journal of Endocrinology
Tom/Volume 60; Numer Number 3/2009
ISSN 0423–104X

A jejunal stromal tumour in a patient with metastatic neuroendocrine cancer of unknown origin; a rare coexistence, diagnostic and therapeutic challenge

Guz stromalny jelita cienkiego u pacjentki z przerzutowym rakiem neuroendokrynnym o nieznanym ognisku pierwotnym; rzadkie współistnienie, diagnostyczne i terapeutyczne wyzwanie

Ziad El Ali[1], Katarzyna Iwanik[2], Jerzy Sowiński[3], Ewelina Swora[1], Marian Grzymislawski[1]

[1]*Department of Internal Diseases, Metabolic Disorders and Dietetics, University of Medical Sciences, Poznan*
[2]*Department of Pathology, University of Medical Sciences, Poznan*
[3]*Department of Endocrinology and Metabolism, University of Medical Sciences, Poznan*

Abstract

A 59-year-old woman presented to the Department of Gastroenterology complaining of progressing weight loss, unexplained diarrhoea, and, as revealed by abdominal ultrasound, numerous hyperechogenic foci in the liver. The immunohistochemical evaluations of the specimens from biopsy revealed well-differentiated hepatic neuroendocrine metastases. The biochemical marker levels, including serum chromogranin A (CGA) and urine 5-hydroxyindolacetic acid (5-HIAA) 24-hour excretion, were significantly elevated. Whole body somatostatin receptor scintigraphy showed tracer accumulation in the liver lesions, with no extrahepatic tumour, possibly the primary origin. Long-term somatostatin analog therapy was initiated and a peptide-receptor targeted radionuclide therapy decision was made parallel to this treatment. Therefore, a followed-up CT scan of the abdomen showed, as well as the metastatic changes within the liver, a well-vascularised jejunal tumour suspected to be the primary focus of the disseminated neuroendocrine neoplasm. Unexpectedly, the pathological examination revealed a positive cell reaction for CD 117, confirming the diagnosis of a rare jejunal stromal tumour. Two months later peptide-receptor therapy with 90Y/77Lu-DOTA-TATE was commenced. **(Pol J Endocrinol 2009; 60 (3): 216–220)**

Key words: *metastatic neuroendocrine tumour of unknown origin, jejunal GIST, coexistence, radionuclide therapy*

Streszczenie

Pacjentkę 59-letnią przyjęto do Kliniki Gastroenterologii z powodu postępującego spadku masy ciała, biegunki o niewyjaśnionej etiologii, oraz wykrytych w badaniu ultrasonograficznym licznych ognisk hyperechogenicznych w wątrobie. Wykonano celowaną biopsją cienkoigłową i rozpoznano zmiany przerzutowe o utkaniu neuroendokrynnym o wysokim stopniu zróżnicowania (cytologia + immunohistochemia). Badania biochemiczne wykazały podwyższone stężenie chromogranin A (CGA) w surowicy krwi i zwiększone wydalanie kwasu 5-hydroksyindolooctowego (5-HIAA) w dobowej zbiórce moczu. Scyntygrafia receptorowa ujawniła dodatnią ekspresję receptorów somatostatynowych w obrębie zmian w wątrobie, natomiast nie znaleziono żadnego pozawątrobowego patologicznego ogniska gromadzenia znacznika mogącego odpowiadać pierwotnemu guzowi neuroendokrynnemu. Rozpoczęto leczenie objawowe długodziałającym analogiem somatostatyny i równolegle do tego podjęto decyzję o zakwalifikowaniu pacjentki do celowanej peptydowej receptorowej terapii radioizotopowej. W tym celu wykonano kontrolne badanie tomografii komputerowej jamy brzusznej, które oprócz zmian w wątrobie, wykazało nieopisanego wcześniej dobrze unaczynionego guza w jelicie cienkim (pierwotny guz neuroendokrynny?). Pacjentkę skierowano do leczenia operacyjnego. Ku zaskoczeniu autorów pracy badanie histopatologiczne wykazało dodatnią ekspresję CD117 potwierdzającą rozpoznanie rzadkiego guza stromalnego jelita cienkiego. Dwa miesiące później rozpoczęto peptydową receptorową terapię radioizotopową z użyciem 90Y/77Lu-DOTA-TATE. Pacjentka otrzymała dwie dawki tego leku, obecnie jest stabilna, zaplanowano dalsze leczenie.
(Endokrynol Pol 2009; 60 (3): 216–220)

Słowa kluczowe: *rozsiany guz neuroendokrynny o nieznanym ognisku pierwotnym, GIST jelita cienkiego, współistnienie*

Introduction

Neuroendocrine tumours (NET) represent a rare, heterogenous, slowly growing group of neoplasms. NETs are classified according to classical structural criteria combined with proliferation index Ki67 into well differentiated endocrine tumours (Ki67 < 2%), well differentiated endocrine carcinoma (Ki67 > 2% but < 15%),

Ziad El Ali M.D., Department of Internal Disease, Metabolic Disorders and Dietetics, University of Medical Sciences, Przybyszewskiego St. 49, 60–355 Poznan, Poland, tel.: +48 61 869 13 14, faks: +48 61 869 13 14, e-mail: zio73@poczta.fm

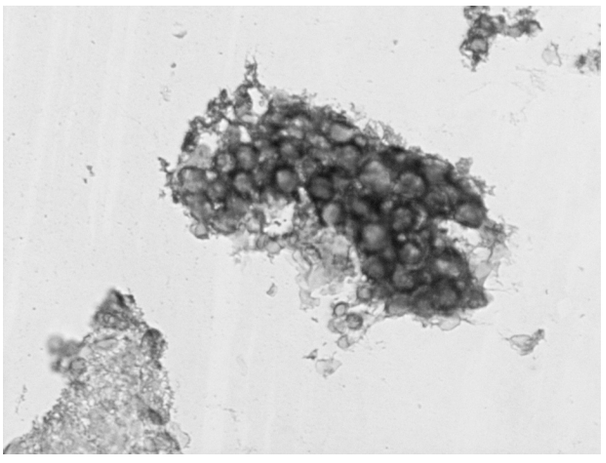

Figure 1. *Cytological evaluation showing positive expression of chromogranin A in neuroendocrine tumour cells, demonstrated with immunohistochemical technique (objective 300 ×)*

Rycina 1. *Badanie immunohistochemiczne materiału otrzymanego z biopsji wątroby pokazujące dodatnią ekspresję chromograniny A (300 ×)*

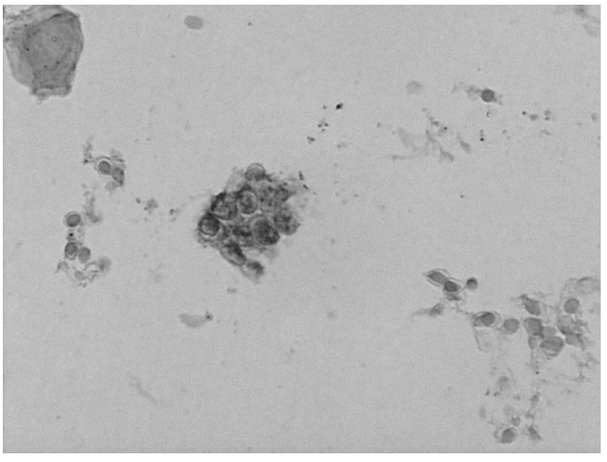

Figure 2. *Cytological evaluation showing positive expression of synaptophysin in neuroendocrine tumour cells, demonstrated with immunohistochemical technique (objective 300 ×)*

Rycina 2. *Badanie immunohistochemiczne materiału otrzymanego z biopsji wątroby pokazujące dodatnią ekspresję synaptofizyny (300 ×)*

poorly differentiated endocrine carcinoma (> 15%), and mixed exocrine-endocrine tumours [1, 2]. Previous studies showed that approximately 20% of patients with NETs develop other cancers, one third of which arise in the gastrointestinal tract [3].

Stromal tumours of the gastrointestinal tract (GIST) are rare neoplasms that account for < 1% of all gastrointestinal malignancies. Most GISTs (95%) are immunohistochemically positive for c-kit protein (CD 117) and CD 34 [4–6]. The percentage of patients with GIST, in whom other neoplasms may be diagnosed, ranges between 2.95% and 33.3%. The most common secondary tumours are colorectal cancer, prostate cancer, pancreatic cancer, and neoplasms derived from lymphoid tissue [7].

The coexistence of a second different neoplasm in a patient with metastatic disseminated neuroendocrine tumour creates a unique challenge and has particular importance in the prognosis and therapeutic approach to the management of both neoplasms.

Case report

A 59-year-old female was referred to the Gastroenterological Outpatient Clinic in September 2005 due to loss of weight and diarrhoea. An interview revealed that the disturbances started about 4 months earlier with a gradual weight loss despite good appetite. Two months later diarrhoea developed (up to 6 times a day), the stool was loose with no blood. There were no typical symptoms for carcinoid tumour, namely: abdominal pain, flushes, blood pressure drop, or signs of right heart failure. Ultrasonography of the abdomen showed numerous hyperechogenic strongly suspected to be metastatic foci in the liver. Consequently, the patient was referred to the Gastroenterology Department of Poznan Medical University. On admission, the woman weighed 40 kg/163 cm (BMI 17). Laboratory examinations showed only slightly elevated liver enzyme levels. A computed tomography (CT) of the abdomen revealed an enlarged liver with numerous compact and cystic lesions, metastatic in nature, as well as a slightly enlarged spleen and enlarged periaortal lymphatic nodules. The remaining abdominal organs in CT presented no change. Chest X-rays were negative for metastatic disease. In order to interpret the lesions in the liver an ultrasonography-guided fine-needle aspiration biopsy was performed. Cytological and immunohistochemical staining revealed: positive chromogranin (Fig. 1), positive synaptophysin (Fig. 2), and proliferation index ki 67 positive only in a few cell nuclei < 2% (Fig. 3). The following diagnosis was made: metastases of a neuroendocrine cancer belonging to the group I B according to the 2000 WHO histopathological classification of NET.

Endoscopic examinations, including gastroscopy and colonoscopy, were performed to find the primary neoplastic focus. No abnormalities justifying the pathological changes in the liver were found. The patient underwent also a gynaecological examination with no pathological changes found. The echocardiography did not reveal any typical changes for a carcinoid syndrome. The biochemical marker evaluation revealed: elevated chromogranin A serum concentration 604 ng/ml (N: 20–98 ng/ml, Cis bio International kit), high serotonin serum level 1.16 ng/ml (N: 0.069–0.199 ng/ml), and increased 5 HIAA urine excretion > 100 mg/24 h (N: 2–

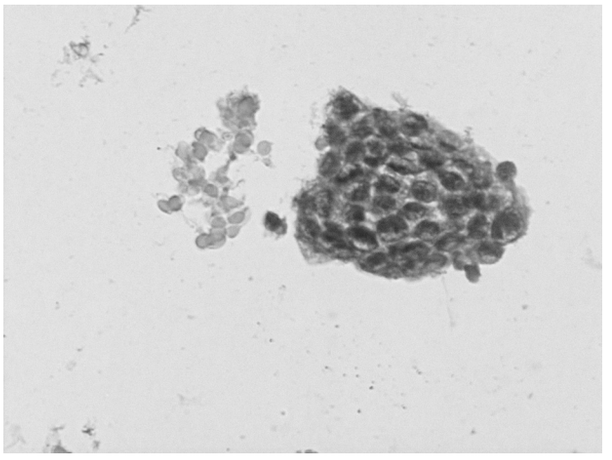

Figure 3. *Cytological evaluation showing Expression of proliferation marker Ki-67 in cell nucleus of neuroendocrine cancer, demonstrated with immunohistochemical technique (Objective 300 ×)*

Rycina 3. *Badanie immunohistochemiczne materiału otrzymanego z biopsji wątroby pokazujące ekspresję Ki-67 w pojedynczych jądrach komórkowych (300 ×)*

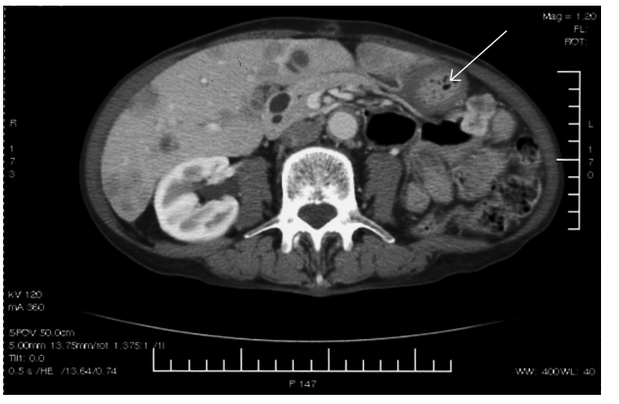

Figure 5. *Abdominal CT scan image showing multiple metastatic neuroendocrine lesions in the liver and a well-vascularized tumour bound up with the jejunum — GIST (single arrow)*

Rycina 5. *Tomografia komputerowa jamy brzusznej pokazująca liczne neuroendokrynne ogniska przerzutowe w wątrobie oraz unaczyniony guz wyrastający z jelita cienkiego (strzałka)*

6 mg/24 h). Clinically, the symptoms listed above persisted: diarrhoea (5–6 times per day), abdominal pain, and general weakness. As a consequence of the diagnosis of a neuroendocrine tumour of unknown origin, a somatostatin receptor scintigraphy with the application of labelled somatostatin analog 99mTc- HYNIC — TOC was performed. The scanning showed numerous pathological foci of marker accumulation in the liver projection, which corresponded to the changes revealed by CT (Fig. 4).

In order to control the clinical symptoms presented by the patient, a somatostatin analog therapy was initiated (Sandostatin LAR 30 mg s.c./ 28 days). A decrease in the chromogranin A level to 334 ng/ml was noted after two shots of Sandostatin LAR, and the 5- HIAA excretion in 24-hour urine showed 52.3 mg/24 h. Parallel to this treatment, numerous tests qualifying the patient for targeted radionuclide therapy were carried out. Therefore, a followed-up CT of the abdomen showed, besides the metastatic changes within the liver, a well-vascularised tumour of size 14 × 23 × 16 mm, bound up with the jejunum, growing into and out of its lumen (Fig. 5).

Considering the fact that the tumour could be the primary focus of the neuroendocrine neoplasm, the patient was referred to the Surgery Clinic of Poznan University. Unexpectedly, the histopathological and immunohistochemical examination revealed a positive cell reaction for CD 117, confirming the diagnosis of a rare jejunal stromal tumour. The size of the tumour (< 2 cm) and the mitotic activity (< 5 per 50 HPF [high powered field]) suggested a low risk of aggressive behaviour of the stromal tumour (Fig. 6, 7).

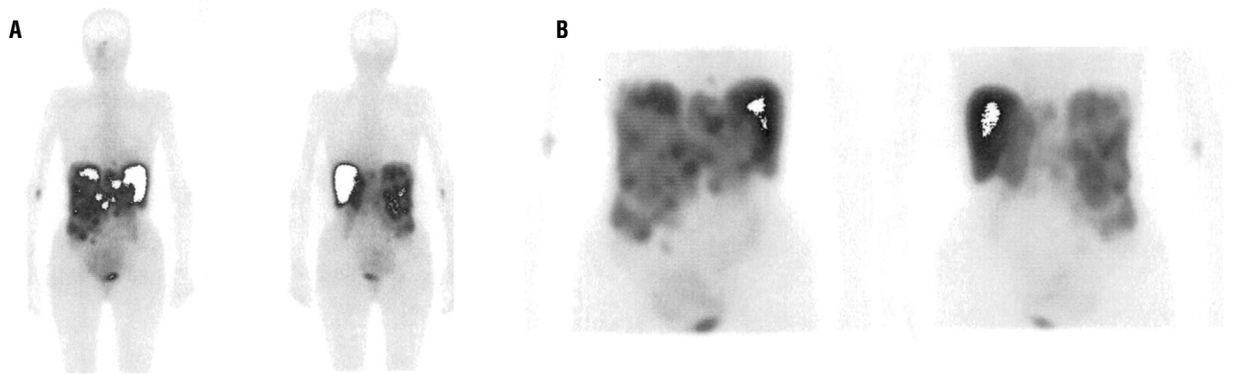

Figure 4. *Technetium 99m octreoscan demonstrating pathological tracer accumulation in numerous metastatic foci in the liver on the anterior (A) and posterior projection (B)*

Rycina 4. *Scyntygrafia receptorowa całego ciała: widoczne liczne ogniska patologicznego gromadzenia znacznika w rzucie wątroby. Zmiany widoczne w projekcji przedniej (A) i tylnej (B)*

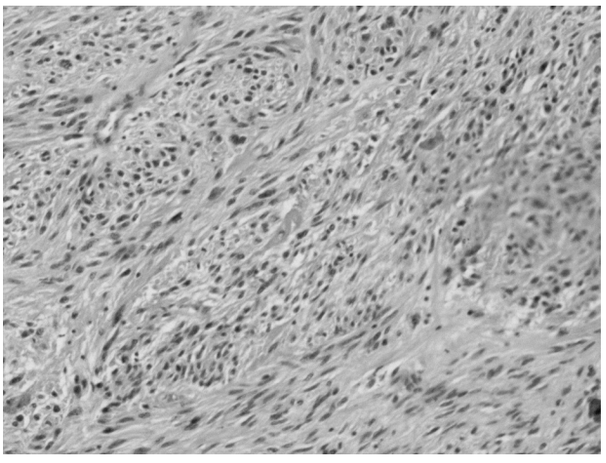

Figure 6. *Histopathological evaluation showing the GIST tumour bound up with the jejunum (H + E, 10 × magnification)*

Rycina 6. *Badanie histopatologiczne tkanki guza stromalnego jelita cienkiego (H + E)*

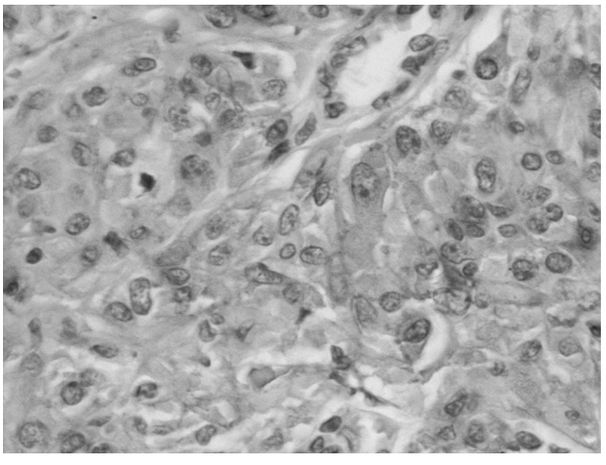

Figure 7. *Positive expression of CD11 in GIST cells demonstrated with immunohistochemical technique (40 × magnification)*

Rycina 7. *Badanie immunohistochemiczne pokazujące dodatnią ekspresję CD117 potwierdzające rozpoznanie guza typu GIST w obrębie jelita cienkiego*

Two months later, peptide-receptor therapy was initiated. Our patient received two doses of 90Y/ 77Lu — DOTA-TATE (100 millicuries per dose), with a two-month interval. The last noted chromogranin A level was 540 ng/ml, suggesting stabilization of the disease. Further therapy is expected.

Discussion

Developments in recent years have shed some light on the role of growth factors like IGF-1, TGF, VEGF, and PDGF on the regulation of differentiation, growth, and secretion of tumour cells. Basic fibroblast growth factor, a potent stimulant of endothelial cell growth, is expressed in both carcinoid tumour tissue and carcinoid cell line [8].Vascular endothelial growth factor (VEGF) expression has been demonstrated in both gastrointestinal and pulmonary carcinoids [9]. Expression of TGF-alpha, TGF-β, and epidermal growth factor receptor (EGFR) has been found on carcinoid tumours [8]. On the other hand, to understand the mechanism of tumour genesis, progression, and differentiation of GISTs, Nakayama et al. investigated the immunohistochemical expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR-1 and 2 in 33 specimens of GISTs. The authors found positive expression of VEGF in the cytoplasm of the GIST (79%), and expression of VEGFR-1 (70%) and VEGFR-2 (91%) in the membrane and cytoplasm of GIST [10].

Both neuroendocrine tumours with GISTs may be seen in neurofibromatosis type I [11, 12]. Our patient had no familial history or clinical manifestation, neither of neurofibromatosis nor of multiple endocrine neoplasia. The neuroendocrine neoplasm was disseminated and was of unknown primary origin; however, symptoms presented by the patient (abdominal pain, diarrhoea), elevated biochemical marker (CGA, 5 HIAA), and negative result of chest X-ray, gastroscopy, and colonoscopy suggest a small bowel localization of the primary focus. At this advanced disease stage, a jejunal, highly vascularised tumour appeared. For us, this tumour was strongly suspected to be the primary origin of the neuroendocrine metastases, and for that reason, before starting the peptide-receptors therapy, the patient was sent to the operating room. Unexpectedly, the histopathological report revealed GIST, a completely different cancer, which required another diagnostic and therapeutic approach.

We conclude that in patients with metastatic disseminated neuroendocrine neoplasms of unknown origin, tumours suspected to be the primary focus should be removed because they could turn out to be a second completely different cancer, which is of particular importance in the prognosis and therapeutic approach to the management of both neoplasms. Additionally, our case shows that in disseminated, well-differentiated tumours with positive SRS neuroendocrine, targeted peptide-receptors therapy should be considered.

References

1. Schnirer II, Yao JC, Ajjani JA. Carcnioid. Acta Oncol 2003; 42: 672–692.
2. Kaltsas GA, Besser GM, Grossman AB. The Diagnosis and Medical Management of Advanced Neuroendocrine Tumors. Endocr Rev 2004; 25: 458––511.
3. Ramage JK, Davies AH, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005; 54: 1–16.
4. Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 2002; 38: 39–51.

5. Pidhorecky I, Cheney RT, Kraybill WG et al. Gastrointestinal Stromal Tumors: Current Diagnosis, Biologic Behavior, and Management. Ann of Surg Oncol 2000; 7: 705–712.
6. Loong HHF. Gastro-intestinal stromal tumours: a review of current management options. Hong Kong Med J 2007; 13: 61–65.
7. Liszka Ł, Zielińska-Pająk E, Gołka D et al. Coexistence of gastrointestinal stromal tumors with other neoplasms. J Gastroenterol 2007; 42: –641–649.
8. Chaudhry A, Funa K, Oberg K. Expression of growth factor peptides and their receptors in neuroendocrine tumors of the digestive system. Acta Oncol 1993; 32: 107–114.
9. Terris B, Scoazec J Y, Rubbia L et al. Expression of vascular endothelial growth factor in digestive neuroendocrine tumours. Histopathology 1998; 32: 133–138.
10. Nakayama T, Cheul Cho Y, Mine Y et al. Expression of vascular endothelial growth factor and its receptor VEGFR-1 and 2 in gastrointestinal stromal tumors, leiomyomas and schwannomas. World J Gastroenterol 2006; 12: 6182–6187.
11. Leung VL, Lee SW, Yuen NW et al. Epigastric pain in a patient with neurofibromatosis type I. Hong Kong Med J 2005; 11: 213–215.
12. Yantiss RK, Rosenberg AE, Sarran L et al. Multiple gastrointestinal stromal tumors in type I neurofibromatosis: a pathologic and molecular study. Mod Pathol 2005; 18: 475–484.