

CASE REPORT

Uterus neuroendocrine tumor – a severe prognostic factor in a female patient with alcoholic cirrhosis undergoing chronic hemodialysis

RUXANDRA DIANA SINESCU¹⁾, ANDREI NICULAE²⁾, ILEANA PERIDE²⁾, FLORINA VASILESCU³⁾,
 OVIDIU GABRIEL BRATU⁴⁾, DAN LIVIU DOREL MISCHIANU⁴⁾, MARIANA JINGA⁵⁾,
 IONEL ALEXANDRU CHECHERIȚĂ²⁾

¹⁾Department of Plastic Surgery and Reconstructive Microsurgery, "Elias" Emergency University Hospital, Bucharest, Romania;
 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²⁾Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital, Bucharest, Romania;
 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

³⁾"Victor Babeș" National Institute for Research and Development in Pathology and Biomedical Sciences, Bucharest, Romania

⁴⁾Department of Urology, "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania;
 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

⁵⁾Department of Gastroenterology, "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania;
 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

There is increased evidence that end-stage renal disease patients, especially the hemodialyzed population, may present various unexpected forms of complications, contributing to a poor prognosis. Furthermore, neuroendocrine tumors, rarely encountered in daily practice, present in dialyzed individuals can significantly exacerbate the inflammatory condition with negative impact on patients' quality of life. We present an unusual case of uterus neuroendocrine tumor with multiple metastases in a 49-year-old female hemodialyzed patient with a history of alcoholic liver cirrhosis and uterus fibromatous. Multiple endoscopic techniques (e.g., upper endoscopy, colonoscopy, upper and lower echoendoscopy), histological evaluation of biopsy samples from involved areas (the operatory piece) were performed in order to complete and refine the diagnosis.

Keywords: neuroendocrine tumor, uterus, hemodialysis, alcoholic cirrhosis.

Introduction

Neuroendocrine tumors (NETs) are rare tumors that have the capacity to secrete peptides and amines; their secretion causes appearance of specific clinical syndromes [1]. Bioactive amines secreted by neuroendocrine tumors are serotonin and histamine [1]. The secretion of these bioactive amines causes carcinoid syndrome that is present in advanced stages [1].

An important fact to emphasize is that neuroendocrine tumors can be identified in several organs such as the gastrointestinal tract (the highest prevalence – 67.5% [2]) and lungs [3, 4], and because the tumors characteristics are specific of the involved organ, a rigorous and unifying classification is sometimes difficult to perform [5].

The positive diagnosis of neuroendocrine tumors should include [1]:

- clinical aspects: asymptomatic, carcinoid syndrome or other manifestations (e.g., abdominal pain, intestinal obstruction, etc.);
- biohumoral features: general (e.g., serotonin) and/or specific markers (e.g., level modifications of insulin, calcitonin, glucagon, metanephrine, etc.);
- histopathology confirmation;
- imagistic evaluations.

Usually, the treatment protocol suggests several options

depending on tumor mass localization, the presence of metastasis, clinical status: surgery intervention associating or not adjuvant therapy, chemotherapy, radio-frequency ablation, targeted radionuclide therapy, etc. [6].

Neuroendocrine genital tumors are rare [7] and their diagnosis is challenging for every doctor because current guidelines for medical diagnosis and treatment requires adjustments and improvements [3, 4]. Furthermore, uterus endometrium does not often involve neuroendocrine tumors [8] and according to Eichorn & Young, uterine corpus can present endometrial adenocarcinoma with neuroendocrine cells, and small cell undifferentiated carcinoma [9]. Therefore, this represents a controversial topic in medical practice [3, 4] and still further experimental and clinical trials are required for better understanding the involved pathophysiological mechanisms.

Aim

Considering the previously mentioned features related to neuroendocrine tumors' development, incidence, diagnosis, and therapy, our case presenting a hemodialyzed patient associating alcoholic cirrhosis with positive confirmed NET diagnosis is unusual and the aim of our study is to emphasize if there is a clear correlation between NET development and concomitant renal and hepatic failure presence.

Case report

We report the case of neuroendocrine tumor in a 49-year-old female patient with history of uterus fibromatosis and alcoholic hepatic cirrhosis, undergoing chronic hemodialysis for over 1.5 years (primary chronic glomerulonephritis is the etiology of chronic kidney disease; not previous use of cytotoxic drugs for glomerulonephritis treatment). She was admitted to our Department after a screening ultrasonography (ambulatory performed) for pelvic-abdominal pain, abnormal uterine bleeding and palpatory mass in the hypogastric region.

At physical exam, she was hemodynamically balanced, and the following features were noticed: pallor of skin and extremities, heart rate of 98 beats/minute and respiratory rate of 17 breaths/minute. Digital rectal examination revealed normal stool on the glove exam. Laboratory tests showed hypochromic, microcytic anemia (Hb – hemoglobin 7.7 g/dL, MCV – mean corpuscular volume 72.9 fL, MCH – mean corpuscular hemoglobin 22.8 pg; patient being under treatment with Epoetinum Beta 5000 UI/week),

decreased serum iron concentration (35 µg/dL), elevated values of BUN (blood urea nitrogen) 85 mg/dL and serum creatinine level (6.47 mg/dL); CRP (C-reactive protein), serum potassium, blood sodium levels, glycemia, CA125 (carcinoma antigen 125) were in normal range. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum level were elevated (AST 69 UI/L, ALT 98 UI/L). Chest X-ray describes a parahilar opacity (almost 21 mm diameter) in the left lung.

We performed an abdominal ultrasound, which showed a few hypoechogenic and transonic images behind the uterus.

An upper endoscopy was made and revealed an outer compression on stomach wall (Figure 1). An endoscopic ultrasonography exam was also performed, highlighting a tumor mass of 23/21 mm independent of the other organs (Figure 2).

Colonoscopy (Figure 3) and lower endoscopic ultrasonography emphasized another tumor of 24.6/20.7 mm situated 16 cm from the anus, with similar aspect like the one from the stomach wall, and located between rectum and uterus (infiltrating the uterus) (Figure 4).



Figure 1 – Upper digestive endoscopy revealed a sub-epithelial tumor covered by normal mucosa, localized in the stomach (indicated by arrow).



Figure 2 – Endosonographic (EUS) evaluation of the subepithelial lesion localized in the stomach showed a tumor originated in the muscular layer of the digestive wall, with irregular outline, about 20/19 mm diameter, with mixed structure, with predominantly solid content and with a transonic central area.

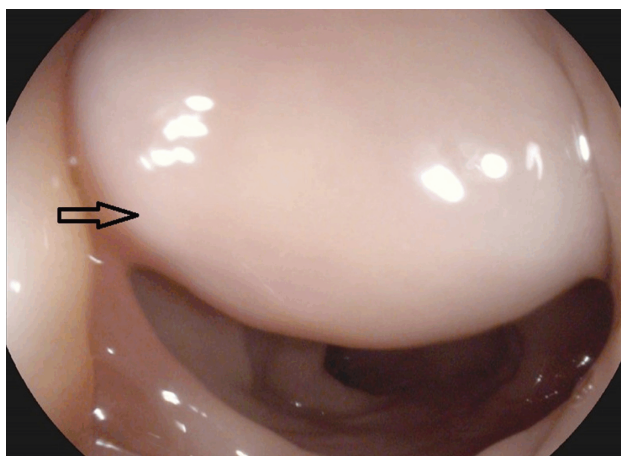


Figure 3 – Colonoscopy revealed a subepithelial tumor covered by normal mucosa at the level of the recto-sigmoidian junction (indicated by arrow).

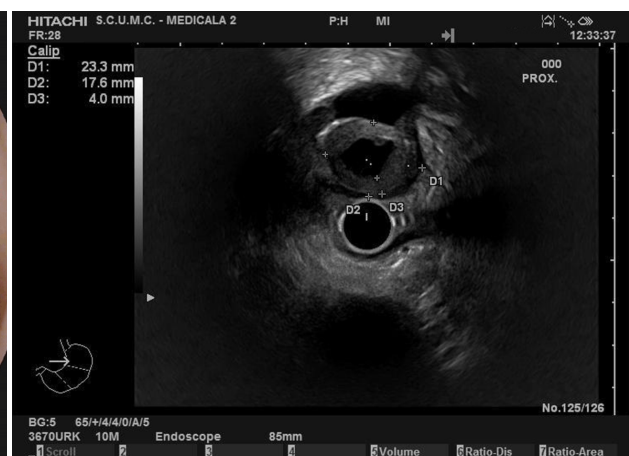


Figure 4 – Endoscopic ultrasound of the lower intestine showed a tumor localized at the level of the recto-sigmoidian junction, approximately 23.3/17.6 mm in diameter, with a mixed structure, similar to the one located in the stomach: solid with a central transonic area inside.

Additionally, colposcopy was performed describing a firm lump in the right wall of uterus.

Hysterectomy was performed followed by the histological exams that revealed a small cell neuroendocrine tumor, which was expanded on all the layers of the uterus wall and invasion of annexes. Immunohistochemistry emphasized proliferation index Ki67 positivity in 60–65%, neuron specific enolase (NSE) regional positive,

SYN (synaptophysin – marker for neuroendocrine tumors) regional positive, CA125 positive in endometrial glands, positive carcinoembryonic antigen (CEA) in rare tumor cells. Chromogranin A (Chromo) was also positive (Figures 5 and 6). Ki67 positive (Figure 7) suggested neuroendocrine carcinoma with high aggressive biological potential.

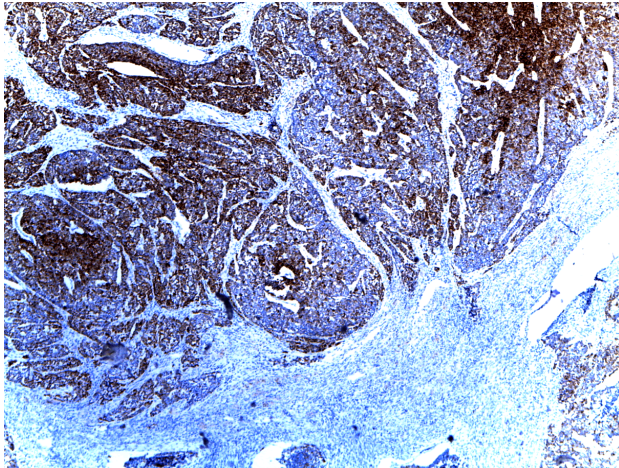


Figure 5 – Myometrium: poorly differentiated neuroendocrine tumor (Chromo positive, ×40).

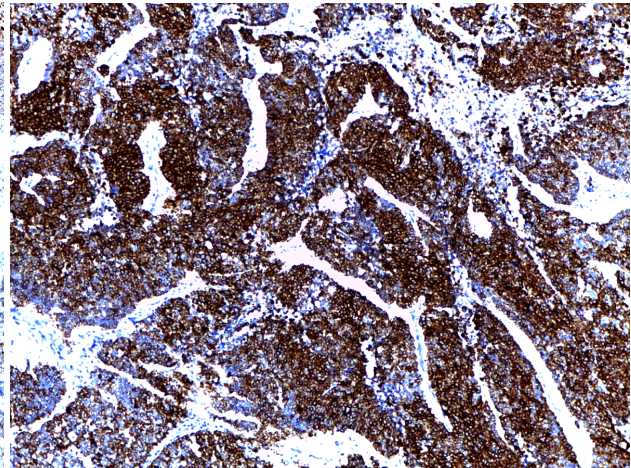


Figure 6 – Myometrium: poorly differentiated neuroendocrine tumor (Chromo positive, ×100).

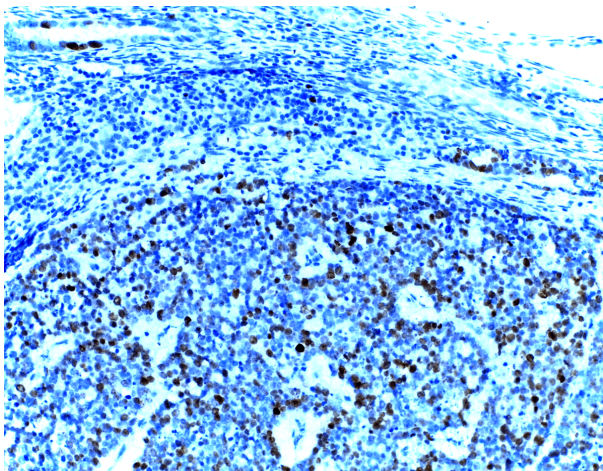


Figure 7 – Myometrium: poorly differentiated neuroendocrine tumor (Ki67 positive 50%, ×200).

The computed tomography of the abdomen and thorax showed numerous metastases both lungs, hepatic, rib and peritoneal carcinomatosa, and consequently, the long-term prognosis was extremely poor. Unfortunately, the patient presented low compliance to the indicated therapy and therefore she only followed one dose of standard chemotherapy concomitant with hemodialysis. Therefore, palliative treatment was indicated, but again our patient strongly refused, and one month later, she died.

Discussion

In 1907, Siegfried Oberndorfer proposed the term carcinoid tumors [10–13], and a few years later, Friedrich Feyrter described the endocrine origin of these tumors [13–15]. Later genital tract neuroendocrine tumors were also identified, especially in the ovarian region, and rarely

in uterus [9, 16, 17]. World Health Organization (WHO) suggested to replace the term carcinoid with neuroendocrine carcinoma [10, 18]. Neuroendocrine carcinomas are classified according to the degree of differentiation – well, moderately or poor differentiated neuroendocrine carcinomas [10]. In daily practice, NET can be identified in association with non-NET components (e.g., adenocarcinoma and squamous carcinoma) [10].

Neuroendocrine tumors of the genital tract are rare, mainly found in female population [9, 16, 17, 19]. NET are aggressive and genital tract shows poor prognosis of the patient in the long term [9, 16, 17, 19]. Classification consists of well-differentiated tumors and there are included atypical carcinoid tumors and poorly differentiated – small cell NETs and large cell NETs; the two categories differ clinically and morphologically but are similar in terms of expression markers: enolase, synaptophysin and chromogranin (immunohistochemical neuron specific markers) [9, 16, 17, 20]. The two classes of neuroendocrine tumors of the genital tract can be found associated with invasive squamous cell carcinoma or adenocarcinoma. Neuroendocrine tumors affect genital cervix, ovary, uterus, vagina or vulva [9, 16, 17, 20]. Carcinoid, well-differentiated neuroendocrine tumors component, is classified into insular, trabecular, mucinous, mixed [9, 16, 17, 20]. Carcinoid is met at ovarian area and the most common is the island type; small cell NECs is described in the ovary, uterus, cervix, vagina and vulva [9, 16, 17, 20]. Uterus small cell NETs frequently may be associated with other endometrial neoplasia, patients with this type being diagnosed at an advanced stage of the disease [9, 16, 17, 20]. There are being described many similarities with small cell lung cancer [9, 16, 17, 20]. Neuroendocrine uterine tumors with endometrial origin are extremely rare and similar to other neuroendocrine tumors of other sites [9, 16, 17, 20].

Therefore, our case, describing a tumor mass invading the myometrium, is interesting and notable for this particular medical area. Histopathologically, tumor cells of small cell carcinoma are grouped in cords, nests, or as unique cell presenting sparse cytoplasm and hyperchromic nuclei with high mitotic rate [21, 22].

According to the literature data [9, 16, 17, 20], the immunohistochemistry showed positive values of neuron specific markers, such as enolase [23], synaptophysin [24] and chromogranin in association with immunohistochemical markers for genital tract tumors Ki67 [25], CA125 and CEA.

Clinic neuroendocrine tumors of the female genital tract implies the presence of tumor masses, confirmed by abnormal Babeş–Papanicolau tests, and often also reporting symptoms of ectopic hormone production [10, 16, 17, 20]. If other organs (liver, bone, lung, etc.) are affected, characteristic manifestations appear [16, 17, 20, 26].

Best treatment approach for the patient with neuroendocrine tumor is multimodal: combination of chemotherapy with radiotherapy and surgery is required in most cases [6, 17, 27, 28]. Patient prognosis is poor, on one hand due to tumor aggressiveness, and on the other hand, due to patients coming in the advanced stages of the disease, when surgery cannot be done considering the tumor extension [9, 10], chemotherapy remains the only option [6, 20, 27, 28].

According to recent oncological recommendation, tyrosine kinase inhibitors and somatostatin analogues (used in radiopeptide treatment with great success [29]) represent specific target-therapy in case of NETs [30, 31], but in our case, because of patient's lack of compliance and additionally, the severity of the disease (associating life-threatening comorbidities and the presence of numerous metastasis), the treatment options were limited and therefore standard chemotherapy and later palliative treatment were indicated. Two months postoperatory, the patient died.

Our patient showed a small cell neuroendocrine tumor in the entire uterine wall, with annexes invasion. Interesting to note is that metastases were found in the wall of the digestive tract (stomach and colon) in the lung, liver, rib and in the peritoneum. Literature does not describe the presence of metastases in the wall of the digestive tract [20, 32–34], which is why we believe this case report adds knowledge in neuroendocrine tumors of the female genital tract. Once again, we emphasize the fact that immunohistochemistry of neuroendocrine specific markers was positivity according to the international literature data. Additionally, chromogranin A was positive, a marker shown in previous studies to be variable: in some cases positive, but most often negative [9, 16, 17, 20].

As mentioned above, our case was a female hemodialyzed patient, known also with alcoholic liver cirrhosis. Chronic hemodialysis and alcoholic liver cirrhosis can be associated with the development of neoplasms, and literature mentions that most frequent cancer in dialyzed patients is renal cell carcinoma. There were also cited cases of liver, prostate and uterus carcinomas, along uterine neuroendocrine tumors. Alcoholic cirrhosis is mostly associated with hepatocellular carcinoma not with neuroendocrine tumors as primary carcinoid tumor [35, 36]; accor-

ding to the literature, usually NETs induce hepatic metastasis [37–40].

The association of chronic kidney disease and alcoholic liver cirrhosis in this case is purely coincidental and there is no cause-effect relationship, but in correlation with the whole clinical and biohumoral milieu, we can estimate that the overall prognosis of our patient is extremely poor, considering that in advanced forms recurrence is noticed within almost 24 months of specific therapy [20].

Conclusions

We concluded that our hemodialyzed and cirrhotic patient presents a rare type of neuroendocrine tumor, quite unique in the literature data. Furthermore, chronic dialysis patients with alcoholic cirrhosis have increased risk of developing various cancers, but up to this moment the development of NETs has not been yet studied, and therefore, future experimental and clinical trials are required to emphasize the underlining pathophysiological mechanisms.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Author contribution

All authors had equal contribution.

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Corresponding author

Mariana Jinga, Associate Professor, MD, PhD, Department of Gastroenterology, “Carol Davila” University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Sector 1, 020022 Bucharest, Romania; Phone +40722–232 530, e-mail: mariana_jinga@yahoo.com

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