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Case Report

Rare birds in gynecologic oncology: ultrasound, hysteroscopic and pathologic features of an endometrial neuroendocrine carcinoma with extremely poor prognosis

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Abstract

Endometrial neuroendocrine carcinoma of the endometrium (NECa) arises predominantly in the sixth and seventh decades. There have only been small case series in literature to date while the largest one took 15 years to collect few patients. Consequently neuroendocrine carcinoma of the endometrium is a "rare bird" and solid rules coming from reference centers are hard to find. Here we report the case of a 68 year old woman who underwent surgical and medical treatment for a grade 3 NECa with specific reference to ultrasound, hysteroscopic and pathologic features predicting poor prognosis.

Introduction

Neuroendocrine tumors of the female reproductive tract account for about 2% of all gynecologic cancers and the features of each subtype are similar to those of their counterparts arising from other body sites. NECa (Neuroendocrine carcinoma) represents 0.8% of endometrial cancers and behaves aggressively with a propensity for systematic spreading and poor prognosis [1].

The age at the onset of small-cell neuroendocrine carcinoma of the endometrium (SCNCE) is approximately 10 years greater than that of the onset of normal endometrial cancer. It was also reported that most women with disease had already given birth. The average age at onset after giving birth two or more times is approximately 60 years [2]. We report the case of a 68 year old woman who underwent treatment for grade 3 NECa arising from the endometrium.

Case Presentation

A 68 years old Caucasian woman came to our institution in January 2017 as a second opinion for AUB with an unfulfilling histological sample. The patient is gravida 3, para 3; BMI 22 kg/m2. Absence of risk factors for inherited malignancies.After a general clinical assessment with normal findings, we performed an ultrasound scan describing an intramural-subserosal fibroid of the fundus (maximum diameter 35 mm) and a hypoechoic tumefaction occupying the cavity, color score 4 (maximum diameter 20 mm), with decreased endometrial thickness. Thus, we performed an office hysteroscopy with simultaneous biopsies using Bettocchi 4 mm Karl Storz hysteroscope; the operator described a bulky mass obliterating the uterine cavity from the fundus with rich and diffuse blood vessels: maximum diameter 3 cm. The sample was made up of cells with nuclear molding and fibrohyaline stroma, negative for cytokeratins-pool and chromogranin, otherwise focally positive CD10 and synaptophysin. Despite the exiguous sample, the pathologist leaned toward a poorly differentiated neuroendocrine carcinoma. CT scans showed an enlarged uterus with a lobulated contour secondary to a myometrial mass within the left part of the fundus uteri, whose maximum diameter was 37 mm, worthy of further clinical evaluation (**Figure 1**).

A type A Querleu-Morrow abdominal hysterectomy with salpingo-ooforectomy, omentectomy, multiple peritoneal biopsies and lymph-nodes sampling was performed. The patient was discharged four days after surgery without complications. Uterus was enlarged by a leiomyoma on the left side (4 cm diameter) and a whitish bulge (2.5 x 3 x 2 cm) within the myometrium of the fundus (**Figures 2-3**).

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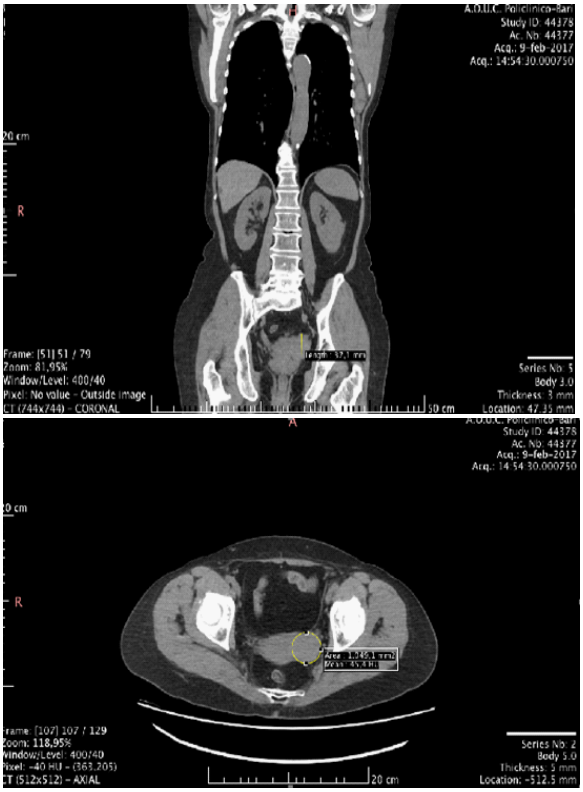
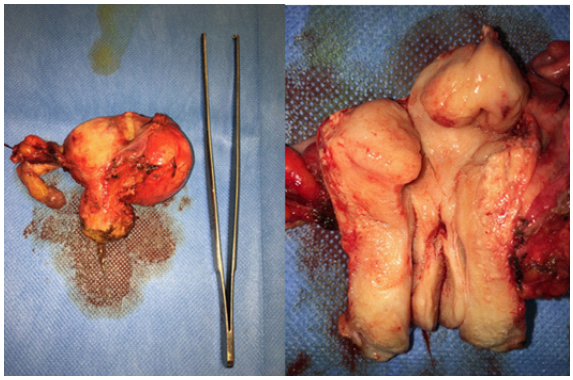


Figure 1: CT scan.

CA125, CA15.3, CA19.9, CEA, AFP, LDH prior to surgery were within normal limits.



Figures 2-3: intraoperative specimens.

The histopathological study demonstrated: "Macroscopic examination.

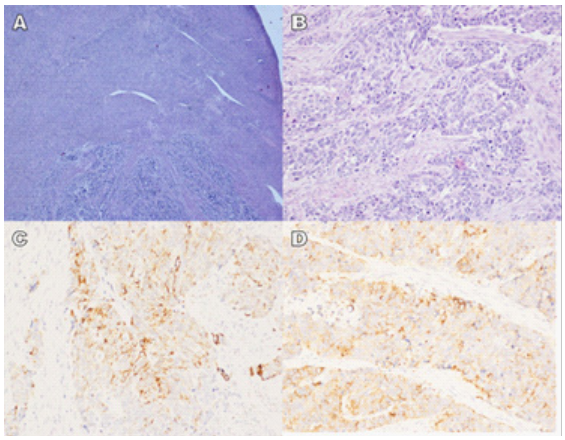


Figure 4: Histopathological samples and immunohistochemistry.

The uterus showed a subserosal leiomyoma (4 cm of maximum diameter) and an omogeneous whitish nodule of the fundus, extending from endometrium to external myometrium (3 cm of maximum diameter). Histological and immunohistochemical analysis. The histological analysis of the whitish nodule revealed a malignant, poorly differentiated, epithelial neoplasm of the endometrium, infiltrating the whole myometrium and focally the visceral peritonel layer. The neoplasm was composed of atypical cells with high nuclear/cytoplasmic ratio, coarse chromatin and incospicuous nucleoli, organized in clusters with trabecular and solid pattern. Multiple foci of necrosis, lymphovascular invasion and high mitotic count (>20/10HPF) were identified. The proliferative index, assessed with Ki67 immunohistrochemistry, was 70%. Immunoistochemical reactions showed positivity for synaptophysine, chromogranin A, CD56 and focally for CK19 and CD10, and negativity for actin and vimentin. The final diagnosis was of endometrial neuroendocrine carcinoma (NEC-G3), FIGO stage IB."

The patient was then administered 4 courses of cisplatin (80 mg/m2 day one) plus etoposide (100 mg/m2, day one, two and three). In order to prevent febrile neutropenia we prescribed pegfilgrastim prophylaxis. We did not grade 4 toxicities (CTCAE) except for alopecia. The patient died in February 2019, after two years from the diagnosis.

Discussion

Neuroendocrine carcinoma of the endometrium is a "rare bird" and solid rules coming from reference centers are hard to find in literature. However, there have only been 3 series and 90 cases of NECa in literature to date: the three largest series that fulfil the current WHO diagnostic criteria for endometrial NECa had 10, 16 and 25 cases. The largest case series comes from MD Anderson Cancer Center and it took 15 years to collect 24 patients [3]. Endometrial NECa arises predominantly in the sixth and seventh decades, like other cancers arising from uterine epithelium, usually with AUB-M (FIGO, PALM-COEIN) and even paraneoplastic syndromes have been described (retinopathy, Cushing, …) [4].

Data in literature are scarce to encourage generalizations; consequently no reliable guidelines for diagnosis and treatment are established. Imaging does not allow histological distinction since all endometrial cancers tend to present similarly: CT can show an hyperintense enhancing with or without central zones of low attenuation suggesting necrosis, while MRI may note heterogenic lesions with deep myometrial infiltration, low to moderate signal on T2 and hypo-intensity relative to the hyperintense enhancing myometrium on dynamic contrast-enhanced sequences [5]. Therefore, it is uncommon to come across this tumour in our clinical practice and it is also quite easy to miss the diagnosis when it comes to the pathologist. J. Kurman et al. divide neuroendocrine tumors of the corpus uteri into two categories: low-grade neuroendocrine tumors (carcinoid tumors; Grade 1) and high-grade neuroendocrine tumors (Grade 3) which includes small cell NECa (SCNECa) and large cell NECa (LCNECa) [6].

Macroscopically they usually produce bulky masses with variable myometrial invasion, although SCNECa and LCNECa differ for their

histopathology. Indeed, SCNECa resembles small cell carcinoma of the lung and is made up of ovoid, oat-cells with condensed nuclei and scant cytoplasm with frequent nuclear molding. It may arise with different growth patterns (diffuse, trabecular, nested or rosette-like). At the same time, the main feature of LCNECa are large polygonal cells with hyperchromatic nuclei arranged in well demarcated nests or trabeculae. There is high mitotic index per HPF and geographic necrosis with a single case in literature without necrosis. Vascular invasion with or without nodes involvement is typically present. SCNECa may react for chromogranin A, synaptophysin, CD-56, vimentin and cytokeratins. It should be acknowledged, however, that Tafe and Bartosch proposed that this diagnosis should require the expression of two NE markers and/or more than 20% of positivity. MMR protein abnormalities may be seen in almost 50% of tumors. A patchy or diffused positivity for p16 (FISH for HRHPV), PAX-8, CD117 and TTF-1 (rare) is also reported, although those are not required for diagnosis. Also remember that PNETs are commonly synaptophysin positive but chromogranin negative [3]. Expression of neuroendocrine markers is reported in 62.5% of FIGO grade 3 non-NECa endometrioid carcinoma, which behave more aggressively with deep myometrial invasion, metastasis and decreased survival [7]. However, a small percentage of SCNECa cases show distinctive histologic features of small cell carcinoma without any typical immunohistochemical evidence of neuroendocrine differentiation [8].

In this regard, we report the case of a woman who came to our institution in September 2020, hospitalized for the clinical suspect of locally invasive cervical tumor and liver metastasis (IVB FIGO). The patient was 63 years old, gravida 1, para 1, menopause 15 years before. We performed cervical biopsy and needle biopsy of the liver nodules. The histopathological study demonstrated: "Histological and immunohistochemical analysis: The histological analysis showed multiple endocervical fragments, almost completely infiltrated by solid and trabecular clusters of malignant cells, with high mitotic count (>20/10HPF) and extensive necrosis.

The microscopical examination of liver nodule biopsy revealed similar histological features. Proliferative index (Ki67-positive neoplastic cells) was about 80%. Immunoistochemically, the neoplastic cells showed positivity only for CK-CAM5.2 and negativity for synaptophysine, chromogranin A, CD56, CK7, TTF-1, CDX2, ER, PgR, p63, p40 and HepPar-1.

Although the neoplasm was chromogranin A and synaptophysine negative, the morphological aspect and the clinical features of the disease (paraneoplastic hypercalcemia) were likely to suggest the diagnosis of small cell neuroendocrine carcinoma." The patient did not receive chemotherapy and died two months after the diagnosis. Therefore, recognizing this neoplasia remains difficult due to its incidence (less than 1% of endometrial cancers) and its tendency to be intermingled with other histotypes. Fifty to 80% of SCNECa are mixed with serous or endometrioid histotypes, so it can be misinterpreted as dedifferentiated carcinoma [1]. When compared to mixed type of endometrial SCNEC, prognosis of a pure type was reported to be worse [9].

We cannot assess whether there is a dedifferentiation of epithelial component or there are two distinct populations ab initio. The diagnosis usually comes from consultation to a referral center for uncommon/unknown histological features; in literature, frequent misdiagnosis has been reported with: grade 3 endometrioid or serous carcinoma, PNETs, atypical carcinoid, carcinosarcoma, metastasis of breast carcinoma. Most cases arose in advanced stages with an advanced to early stage ratio of 1.3:1 or 1.8:1. It is an aggressive disease with mean survival (FIGO stage I to IV) of about 12 months, however there is a subset of cases with endometrial NECa surviving more than 5 years [3]. SCNECa and the presence of a predominant NECa component seem to be good prognostic items. Although there is no evidence that radical surgery has an impact in the course of the disease, primary surgical cytoreduction with total hysterectomy, salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy is usually performed as the first step in the management of these tumors. Complete surgery provided better outcomes compared to incomplete surgery [10].

If we consider the experience coming from MDACC to choose the best adjuvant regiment ever, we can find there is no evidence-based, univocal indication: patients responded to platinum (plus etoposide, cyclophosphamide, 5-fluorouracil, streptozocin or paclitaxel) with or without radiation therapy, although others underwent radiation therapy alone. Partial responses to octreotide have been reported. For FIGO stage I-II disease radical hysterectomy with pelvic lymph node dissection followed by adjuvant chemoradiation with concurrent cisplatin and etoposide is usually performed. Chemoradiation followed by additional chemotherapy with a goal of six total cycles is an option for locally advanced disease. Hoskins et al. reported that chemoradiation with etoposide/cisplatin (EP) along with pelvic radiation resulted in successful treatment of stage IA-IVB disease [11].

Consequently, the optimal management still remains unclear. Oncologists may consider prescribing neoadjuvant chemotherapy when a preoperative diagnosis of uterine NEC is possible, given the poor prognosis even after radical surgery. These malignancies are extremely rare, thus management is often extrapolated from small and large cell carcinomas of the lung (cisplatin, carboplatin, etoposide or cyclophosphamide) [12, 13].

Conclusions

Abnormal uterine bleeding with pelvic pain and lumbago in postmenopausal women are the earmarks of endometrial cancer. After our diagnostic checklist we were surprised to learn that we had to face such a rare disease.

Our case report fulfils the WHO criteria for diagnosis: positive to chromogranin, CD-56, synaptophysin, negative to vimentin and actin with spotty positivity to cytokeratin. It is a typical SCNEC with small clusters of neoplastic cells, high mitotic index and without any adenocarcinoma component. The pathologist also stressed the presence of CD10 which, according to Uehara et al. gives the chance for long survival [14]. In fact, this is reported as a favorable prognostic factor for some leukemias, NSC lung cancer or uterine cervical cancer while we have to be less enthusiastic meeting CD10 in gastro-intesti-

nal cancer or in skin cancers as it represents a poor prognostic marker. In fact CD10 is involved in the cleavage of FGF2 (fibroblast growth factor) or directly binds PTEN and inhibits cell migration and proliferation promoted through those pathways. This may contribute to suppress the aggressive behavior but it is not ascertained. Endometrial NEC is frequently associated with MMR (MisMatch Repair) proteins deficiency. Maybe the loss of MMR protein expression in the tumor cells may elicit more immune response due to incompetent repair of damaged DNA in the tumor cells. Such enhanced immune responses may contribute to a better prognosis compared to those NECs without MMR protein loss [15]. Kotaro et al. recommend universal screening for MMR/MSI status [16].

The main treatment of the disease remains surgery but without any agreement on adjuvant therapy. Neuroendocrine carcinoma patients which present in advanced stage are resistant to therapy and have an early demise [17]. The rate of metastasis and reoccurrence are high, and prognosis remains poor, even among patients with early-stage disease [2].

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