Endometrial metastasis of a primitive neuroendocrine ovarian carcinoma: management and treatment of a case

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Summary

Background: Neuroendocrine tumours are a heterogeneous group of separate clinico-pathological entities which have a common characteristic, i.e., expression of potential endocrine differentiation. In the ovary, the term "neuroendocrine" relates mainly to widely known carcinoids, but it may also be applied to rare neuroendocrine carcinomas as non-small cell type and small cell carcinomas of pulmonary type. In the literature only 11 cases of primary ovarian non-small cell neurendocrine carcinomas have been described and ten of these were associated with a surface epithelial ovarian tumour. Small cell neuroendocrine carcinoma of the ovary is a rare malignant tumour of the ovary. Advanced small cell carcinoma of the ovary is a very aggressive tumour with an overall poor prognosis and unfavourable outcome. *Case report:* The case reported is unique in the literature because the authors describe a rare case of endometrial metastasis of a primary ovarian non-small cell neurendocrine carcinoma without any surface epithelial ovarian tumour association. The tumour invaded up to less than half of the myometrium. The first symptoms were related to endometrial metastasis as metrorrhagia and pelvic pain while the asymptomatic presence of primary ovarian carcinoma was not acknowledged with physical examination, routine biochemistry, tumour markers, blood count and traditional transvaginal greyscale ultrasound. *Conclusion:* Magnetic resonance and three-dimensional (3D) ultrasonography with power Doppler are a great help in the diagnosis of ovarian localisation but only immunohistochemistry on histological material can provide a correct diagnosis. Immunohistochemistry expression of Ki67 is a useful marker of malignancy. Due to the rarity of this neoplasm, a general consensus for optimal treatment has yet to emerge. The reported biological aggressiveness of these tumours prompts combined treatment with radical surgery and adjuvant polychemotherapy.

Key words: Neuroendocrine ovarian tumours; Endometrial metastasis.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of separate clinico-pathological entities which have a common characteristic, i.e., expression of potential endocrine differentiation. These tumours can be classificated as biologically active (BANETs) and inactive (BINETs) neuroendocrine tumors. The diagnosis is based on the use of cytoplasmatic markers (N-CAM, NSE, PGP 9.5, chromogranin A, synaptophysin, cytocheratin (l mw, Ki67). In the ovary, the term "neuroendocrine" relates mainly to widely known carcinoids, but it may also be applied to rare neuroendocrine carcinomas as non-small cell type and small cell carcinomas of pulmonary type [1]. Moreover neurendocrine differentiation may be expressed in a variety of ovarian tumours including epithelial tumours, Setoli Leydig cell tumours, teratomas, carcinoid tumour, small cell carcinoma of pulmonary type and non-small cell undifferentiated carcinoma of neurendocrine type [2]. The last has previously been described in association with surface epithelial tumours of the ovary [3, 7]. In the literature only 11 cases of primary ovarian non-small cell neurendocrine carcinomas have been described and ten of these were associated with a surface epithelial ovarian tumour. Small cell neuroendocrine carcinoma of the ovary is a rare malignant tumour [2, 8]. It is the most common undifferentiated ovarian carcinoma in young women. Approximately two-thirds of patients with ovarian small cell carcinoma have hypercalcemia [9, 10]. The few cases reported in the literature account for less than 1% of all cases of carcinoids in the body [11]. Advanced small cell carcinoma of the ovary is a very aggressive tumour with an overall poor prognosis and unfavourable outcome [12].

A rare case of endometrial metastasis of a primary ovarian non-small cell neurendocrine carcinoma without any surface epithelial ovarian tumour association is reported.

Case Report

A 56-year-old postmenopausal white female with no significant past medical history came under our care in March 2006 for abnormal uterine bleeding and pelvic pain. She complained of alterations in defecation and abnormal spotting of three months duration. She did not report any paraneoplastic or virilizing symptoms and her laboratory values, including calcium levels, were normal.

Vaginal examination showed the womb had increased volume and was deformed on the left by a mass of 80 x 80 mm. Rectal exploration confirmed the vaginal examination. The mass was fixed to the wall of the sigma rectum pouch deforming the caliber and profile.

Revised manuscript accepted for publication June 26, 2007

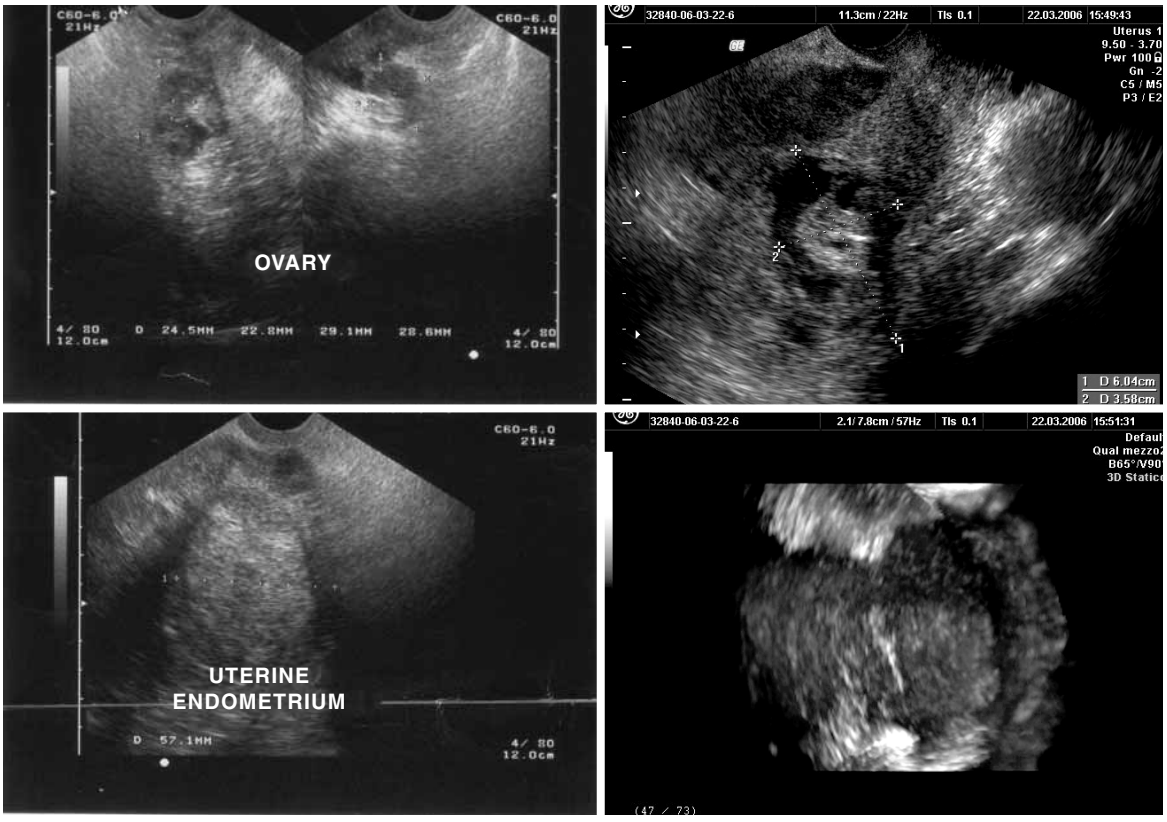

Fig. 1a B mode

Fig. 1b 3D probe

Figure 1. — Transvaginal ultrasonography.

Transvaginal ultrasonography (TVS) was performed (Figure 1a) and an urgent fractional curettage was carried out due to intense bleeding. TVS confirmed the suspicion of a mass on the left side fixed to the uterus, ovary and sigma rectum pouch with increased thickness of the endometrium.

Fractional curettage revealed a diagnosis of undifferentiated small cell carcinoma of the endometrium with neuroendocrine immuno-phenotype positive for CK35betaH11(low mw), NSE and with high mitotic activity (> 10/HPF), and clone Ki67 K-2 egualed 60%. The staging was performed in accordance with FIGO guidelines.

Clinical staging was performed: biochemistry and blood count, tumour markers, chest X-ray, magnetic resonance imaging (MRI), three-dimensional (3D) ultrasonography with power Doppler (Figure 1b), esophagogastroduodenoscopy (EGDS) and colonscopy.

MRI showed the tumour involved the left ovary with implants in the uterus, ascites and bilateral pleural effusion. There was hydrometra and presence of a subserous leyomioma (80 x 80 mm) on the left side. No metastasis nor lymph node (LN) involvement was found, confirmed by preoperative lymphoscintigraphy with technetium-99m (Tc-99m).

3D ultrasonography with power Doppler confirmed the diagnosis of ovarian cancer associated with endometrial involvement.

Explorative laparotomy (Figure 2) was performed revealing a left ovarian tumour fixed to the leyomioma and the wall of the sigma rectum pouch deforming the caliber and profile but without involving the wall of the rectum.

Laparohysterectomy and a bilateral salpingo-oophorectomy, infracolic omentectomy, appendectomy, paraaortic lymph node dissection and pelvic side wall biopsies were performed. Subsequent clinical work up did not disclose any evidence of an extrapelvic tumour. Pathologic examination revealed a diagnosis of undifferentiated small cell carcinoma with neuroendocrine immunophenotype positivity for CK35betaH11 (low mw), NSE and with high mitotic activity (> 10/HPF) and Ki67K2 = 60% (Figure 3). The primary origin was determined to be ovarian carcinoma involving the left endosalpinx and uterus. Tumour invaded up to less than half the myometrium.

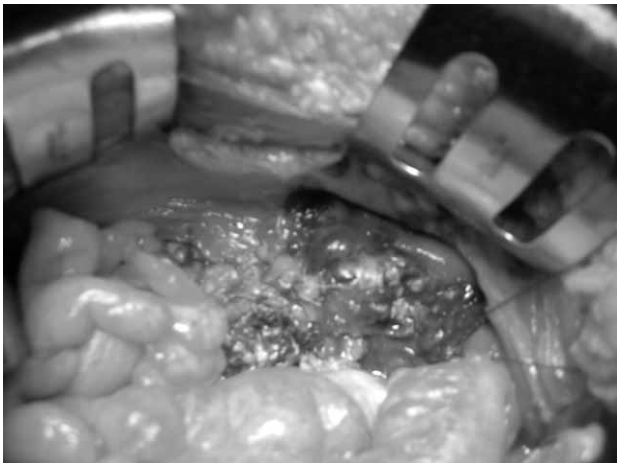

Figure 2. — Explorative laparotomy.

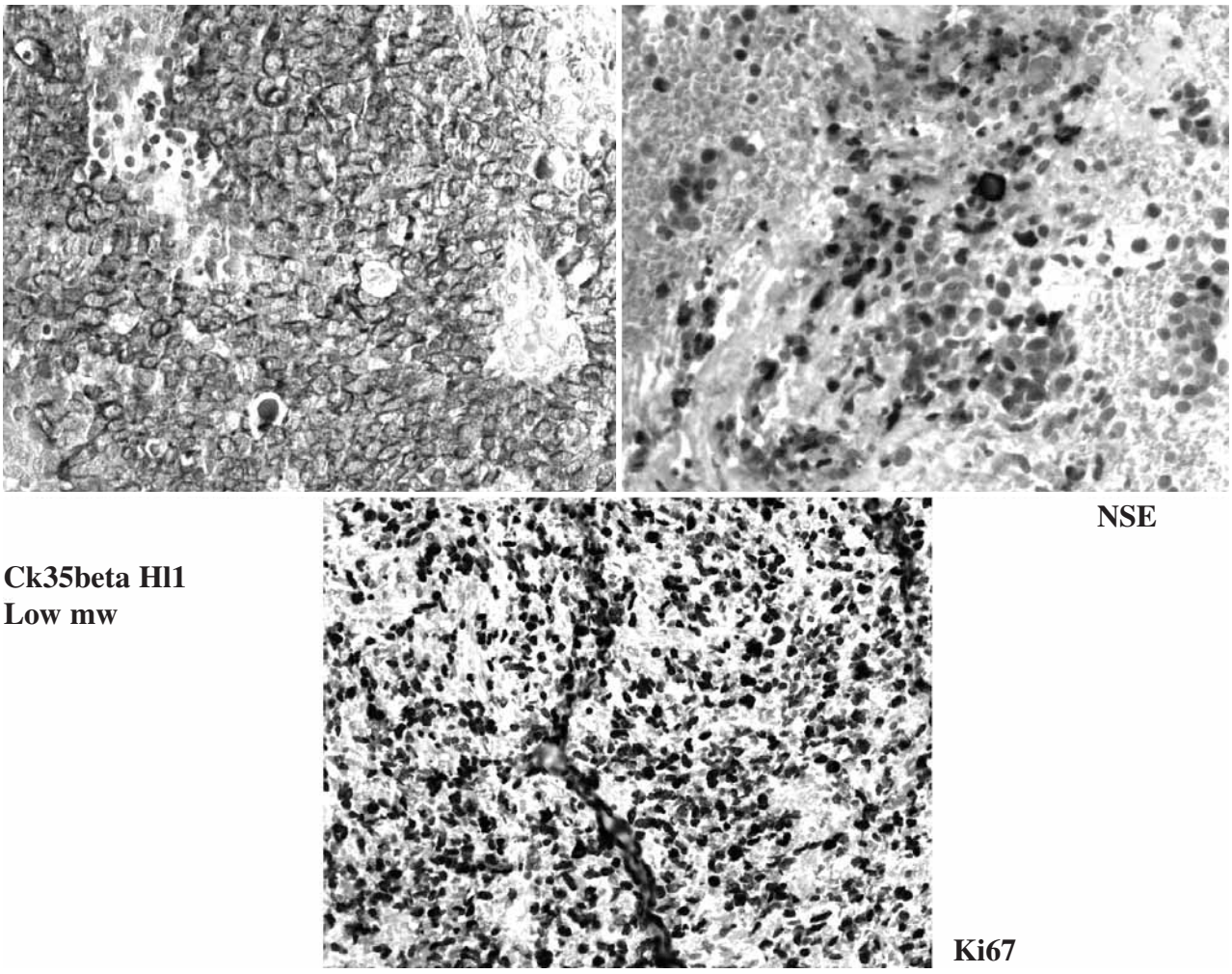

Figure 3. — Neuroendocrine immuno-phenotype positive.

There were no malignant cells in the ascites. FIGO Stage II A/T2aN0M0/G3 (WHO) was determined. Following surgery the patient received six cycles of taxol and carboplatinum.

Today, after a follow-up of ten months including total body CT and tumour markers, the patient shows no evidence of disease.

Discussion and Conclusions

NETs are a heterogeneous group of separate clinicopathological entities which have a common characteristic, i.e., expression of potential endocrine differentiation. In the ovary, the term "neuroendocrine" relates mainly to widely known carcinoids, but it may also be applied to rare neuroendocrine carcinomas of non-small-cell type and small cell carcinomas of pulmonary type. Ovarian carcinoids develop in pure form or in association with other tumours, mainly teratomas. They originate from endocrine cells, either of teratomatous origin or possibly also indigenous [1] Ovarian neuroendocrine carcinomas belong most probably to surface epithelial neoplasms, which express endocrine pathway differentiation [1]. NETs of the ovary are rare neoplasms with only 11 cases reported in the literature [2, 8] and they account for less than 1% of all cases of carcinoids in the body [11]. Advanced small cell carcinoma of the ovary is a very aggressive tumour with an overall poor prognosis and unfavourable outcome [12].

An extremely rare case of endometrial metastasis of a primary ovarian non-small cell neurendocrine carcinoma without a surface epithelial ovarian tumour association has been presented. The tumour invaded up to less than half the myometrium. The initial symptom was abnormal bleeding in a postmenopausal woman. The metrorrhagia and pelvic pain were suggestive of endometrial metastasis while the asymptomatic presence of primary ovarian carcinoma was not acknowledged at first physical examination with routine biochemistry, tumour markers, blood count and traditional TVS. Moreover, the 3D ultrasonography with power Doppler and the MRI were very useful in the diagnosis of ovarian localisation however, in these cases, only immunohistochemistry on histological material can provide an accurate diagnosis. Also immunohistochemistry expression of Ki67 is a useful marker of malignancy.

In comparison to transvaginal 2D grayscale or 3D

sonography, 3D power Doppler – and especially the combined use of 3D sonography and power Doppler imaging – significantly improve diagnostic accuracy in preoperative sonographic assessment of suspected ovarian lesions. Moreover they can enhance and facilitate the morphologic and functional evaluation of both benign and malignant ovarian lesions [13, 18].

The management and treatment of ovarian NETs are very difficult. In fact, due to the rarity of this neoplasm, a general consensus for optimal treatment has yet to emerge [8]. The reported biological aggressiveness of these tumours prompts a combined treatment with radical surgery and adjuvant polychemotherapy.

Numerous experiences using monochemotherapies show an unsatisfactory benefit in comparison to the use of polychemotherapies [Level C].

It is not always possible to perform radical surgery due to the often advanced stage of disease, nevertheless cytoreductive surgery together with a polychemotherapy often improves the quality of the life and offers a sure advantage in long-term survival. In fact, this case showed no progression of disease over ten months and the overall disease outcome has been excellent.

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