Case report

Small cell neuroendocrine carcinoma of the endometrium with pulmonary metastasis: A clinicopathologic study of a case and a brief review of the literature

Antonio D'Antonio, Maria Addesso, Alessia Caleo, Maurizio Guida, Pio Zeppa

Department of Pathologic Anatomy and Oncology, A.U.O. "San Giovanni di Dio e Ruggi d'Aragona", via S. Leonardo, Salerno, Italy

Unit for Pathologic Anatomy, ASL Salerno, Hospital Tortora, Pagani, SA, Italy

University of Medicine and Surgery, Unit Obstetrics and Gynecology, Salerno, Italy

University of Medicine and Surgery, Unit Pathologic Anatomy, Salerno, Italy

Highlights

- Neuroendocrine carcinomas (NEC) of endometrium are aggressive and rare tumors.
- As pulmonary counterpart may express Thyroid transcription factor-1 (TTF-1).
- To date, no effective treatment protocol has been established for this rare type of tumor.
- A multidisciplinary therapy represents until this time the only therapeutic option.

Abstract

Neuroendocrine carcinomas (NEC) of the female genital tract are aggressive and rare tumors that usually involve the cervix and ovary, and are seen rarely in the endometrium in perimenopausal or postmenopausal women. We presented a case of a 71 year-old postmenopausal woman with vaginal bleeding and abdominal pain. A subsequent computerized tomography (CT) scan of pelvis showed an enlarged uterus (20.0 × 12.0 cm) with para-aortic and pelvic lymph node metastases. She underwent surgical debulking and staging of an endometrial tumor with omental metastasis and positive lymph nodes. The pathological diagnosis was primary small cell carcinoma (SCC) combined with endometrioid carcinoma of uterine corpus. Her final FIGO stage was IVB. Three months after surgery CT-total body showed a metastasis to left lung of SCC. Because the small-cell component of endometrial tumor showed a strong positivity for TTF1 as pulmonary counterpart a differential diagnosis with a primary small cell carcinoma of the lung should be made. Identifying an appropriate therapeutic management for SCC of endometrium is challenging since these are extremely rare tumors. An optimal initial therapeutic approach to this rare disease, especially at an advanced stage, has not yet been clearly defined. However, in these a multidisciplinary therapy, including surgery, chemotherapy, and radiotherapy represent until this time the only therapeutic option.

© 2015 Published by Elsevier Ltd on behalf of IJS Publishing Group Limited. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Neuroendocrine carcinomas (NEC) of the endometrium, small-cell and large-cell type, are rare tumors that can be pure, combined with endometrioid adenocarcinoma, or a component of malignant mixed müllerian tumor [1–10]. The main clinicopathological features of NEC of the endometrium are the evidence of neuroendocrine differentiation and has a high propensity for systemic spread and poor prognosis [1–10]. Thyroid transcription factor-1 (TTF-1) is commonly considered as sensitive and relatively specific for tumors of pulmonary/thyroid origin. Moreover, it is known that thyroid transcription factor-1 (TTF-1) is expressed in extrapulmonary SCC and in a small percentage of primary gynecological adenocarcinomas with problems of differential diagnosis with lung tumors.

Here we discuss the clinical course of a 71 year-old woman with
2. Case report

A 73 year-old woman, with postmenopausal vaginal bleeding, abdominal pain and significant anemia (hemoglobin was 9 g/dl). She underwent an endometrial biopsy which revealed a poorly differentiated tumor with extensive necrosis. A CT of pelvis showed an enlarged uterus measuring 20.0 cm × 12.0 cm with omental metastasis and positive lymph nodes. Bilateral adenexae were normal. She underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy.

Macroscopic examination of surgical specimen showed a bulky tumor of corpus uteri and a virtual uterine cavity (Fig. 1). Cut surface of mass was gray white tumor with necrotic areas. Microscopically the mass showed a malignant tumor composed of two component: a small round to oval cells with hyperchromatic nuclei, moderate pleomorphism and brisk mitotic activity (Fig. 2a and b) and neoplastic gland of Grade 2 endometrioid adenocarcinoma (Fig. 2c). Areas of geographic necrosis were present in the tumor. The tumor infiltrated the myometrium deeply and was associated with neoplastic angioinvasion (Fig. 2d). Sections from isthmus, cervix, both ovaries and fallopian tubes were unremarkable. Omental metastasis with 8/25 positive lymph nodes were also present but were represented only by the small cell component of tumors. Immunohistochemistry revealed diffuse positivity for synaptophysin, chromogranin, CD56 (Fig. 3a) and TTF1 (Fig. 3b) but immunonegativity for cytokeratin-pan, CD10, vimentin. Neoplastic gland were positive for CK8-18, and focally for ER. A diagnosis of high grade neuroendocrine carcinoma, small cell type combined with an endometrioid adenocarcinoma stage IVB was made. Thereafter, the patient was offered adjuvant chemotherapy (etoposide and cisplatin) which she tolerated well. CT-total body done after 3 months revealed a left lung mass (Fig. 4). A fine-needle aspiration (FNA) of this lesion showed a SCC (Fig. 4; inset). Although a differential diagnosis with a primary SCC of lung could be made, this tumor was considered metastatic. The patient died six months after chemotherapy from respiratory failure.

Fig. 1. The tumor appear as a large, bulky mass of uterine corpus.
is essentially extrapolated from that for small cell lung cancer. The local and distant aggressiveness of this disease renders it difficult to perform a optimal therapeutic approach. Surgery and systemic, multi-modal therapy is warranted for the treatment of this neoplasm. The most common initial management of uterine NEC is cytoreductive surgery, based on prior published reports [2–6,13]. In literature has been reported a case of SCC of endometrium in early stage treated with laparoscopic surgery and radiotherapy with most favorable outcome [20]. Adjuvant chemotherapy with a variable number of active agents as cisplatin, carboplatin, etoposide, 5-fluorouracil, etc. has been used in the management of NEC of the lung and cervix rate[21] [21]. In our case, after the surgery
the patient was proposed for the chemo-radiotherapy, with protocols including etoposide and cisplatin. Unfortunately the follow-up in our case is short because the woman died after three months after diagnosis to make the possibility for this therapy to improve the survival of patient. Some authors reported encouraging results using concurrent chemoradiation or neoadjuvant chemotherapy in patients with SCC of cervix and advanced disease [22]. In conclusion this followed by radical surgery and adjuvant chemotherapy in patients using concurrent chemoradiation or neoadjuvant chemotherapy the survival of patient. Some authors reported encouraging results after diagnosis to make the possibility for this therapy to improve up in our case is short because the woman died after three months.

Fig. 4. CT scan showed a mass in the upper lobe of the left lung. Inset: FNA was diagnostic for SCC (Papanicolaou x40).

Ethical approval
None.

Sources of funding
None.

Author contribution
Antonio D’Antonio, Maria Addesso, Alessia Caleo, Pio Zeppa and Maurizio Guida critically reviewed the manuscript for important intellectual content and approved the final version of the manuscript to be submitted.

Conflicts of interest
None.

Trial registry number
None.

Guarantor
Antonio D’Antonio M.D.

References
[1] J. Albores-Saavedra, B. Martinez-Benitez, E. Luevano, Small cell carcinomas and large cell neuroendocrine carcinomas of the endometrium and cervix: polypoid tumors and those arising in polyps may have a favorable prognosis, Int. J. Gynecol. Pathol. 27 (2008) 333–339.
[2] D.G. Huntsman, P.B. Clement, C.B. Gilks, Small-cell carcinoma of the endometrium. A clinicopathological study of sixteen cases, Am. J. Surg. Pathol. 18 (1994) 364–375.
[3] H. Tsujioka, F. Eguchi, M. Emoto, T. Hachisuga, T. Kawarabayashi, K. Shirakawa, Small-cell carcinoma of the endometrium: an immunohistochemical and ultrastructural analysis, J. Obstet. Gynaecol. Res. 23 (1997) 9–16.
[4] M. Varras, Ch Akrivis, A. Demou, G. Hadjopoulos, S. Stefanaki, N. Antoniou, Primary small-cell carcinoma of the endometrium: clinicopathological study of a case and review of the literature, Eur. J. Gynaecol. Oncol. 23 (2002) 577–581.
[5] A. Katahira, J. Akahira, H. Niikura, K. Ito, T. Moriya, S. Matsuura, S. Makinoda, T. Oda, K. Fujiiwara, N. Yaegashi, Small cell carcinoma of the endometrium: report of three cases and literature review, Int. J. Gynecol. Cancer 14 (2004) 1018–1023.
[6] E. Petru, C. Pasterk, O. Reich, A. Obermair, R. Winter, G. Breitenecker, Small-cell carcinoma of the uterus and the vagina: experience with ten patients, Arch. Gynecol. Obstet. 271 (2005) 316–319.
[7] H. Tsuchioka, F. Eguchi, M. Emoto, T. Hachisuga, T. Kawarabayashi, K. Shirakawa, Small-cell carcinoma of the endometrium: an immunohistochemical and ultrastructural analysis, J. Obstet. Gynaecol. Res. 23 (1997) 9–16.
[8] S. Meirmanov, M. Nakashima, T. Rogourovitch, E. Fukuda, T. Nakayama, F. Sato, I. Sekine, Small cell carcinoma of the endometrium: report of a case with analysis of Wnt/beta-catenin pathway, Pathol. Res. Pract. 199 (2003) 551–558.
[9] T. Terada, KIT-positive primary small cell carcinoma of the endometrium: a case report with immunohistochemical and molecular genetic analysis of KIT and PDGFRa genes, Arch. Gynecol. Obstet. 282 (2010) 413–416.
[10] H. Sato, G. Kanai, H. Kajiwara, J. Itoh, R.Y. Osamura, Small-cell carcinoma of the endometrium presenting as Cushing’s syndrome, Endocr. J. 57 (2010) 31–38.
[11] Z. Bing, L. Levine, J.A. Lucci, S.S. Hatch, M.A. Eltorky, Primary small cell neuroendocrine carcinoma of the vagina: a clinicopathologic study, Arch. Pathol. Lab. Med. 128 (2004) 857–862.
[12] S. Tsumoda, T. Jobo, M. Arai, M. Imai, T. Kanai, T. Tamura, J. Watanebe, A. Obokata, H. Kuramoto, Small-cell carcinoma of the uterine cervix: a clinicopathologic study of 11 cases, Int. J. Gynecol. Cancer 15 (2005) 295–300.
[13] J.G. Cohen, D.S. Kapp, J.Y.J. Shin, R. Urban, A.E. Sherman, L.M. Chen, K. Osann, J.K. Chan, Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients, Am. J. Obstet. Gynecol. 203 (2010) e1–e6.
[14] T.D. Jones, K.M. Kernek, A. Lopez-Beltran, G.T. MacLennan, J.N. Eble, et al. TTF-1 expression in primary ovarian carcinomas with analysis of 188 patients, Am. J. Obstet. Gynecol. 203 (2010) e1–e6.
[15] D. Penman, I. Downie, F. Roberts, Positive immunostaining for thyroid transcription factor-1 in primary and metastatic colonic adenocarcinoma: a note of caution, J. Clin. Pathol. 59 (2006) 663–664.
[16] A.D. Graham, A.R. Williams, D.M. Salter, TTF-1 expression in primary ovarian epithelial neoplasia, Histopathology 48 (2006) 764–765.
[17] K. Siami, W.G. McCluggage, N.G. Ordonez, D.E. Euscher, A. Albores-Saavedra, B. Martinez-Benitez, E. Luevano, Small cell carcinomas of the endometrium and large cell neuroendocrine carcinomas of the endometrium and cervix: an immunohistochemical and molecular genetic analysis of KIT and PDGFRα genes, Arch. Gynecol. Obstet. 282 (2010) 413–416.
[18] S.M. Brennan, D.L. Gregory, A. Stillie, A. Herschtal, M. Mac Manus, D.L. Ball, Thyroid transcription factor-1 expression in endometrial and endocervical adenocarcinomas, Am. J. Surg. Pathol. 31 (2007) 1759–1763.
[19] A. Ervine, S. Leung, C.B. Gilks, W.G. McCluggage, Thyroid transcription factor-1 (TTF-1) immunoreactivity is an adverse prognostic factor in endometrioid adenocarcinoma of the uterine corpus, Histopathology 64 (2014) 840–846.
[20] S.M. Brennan, D.L. Gregory, A. Stillie, A. Herschtal, M. Mac Manus, D.L. Ball, Should extra-pulmonary small cell lung cancer be managed like small cell lung cancer? Cancer 15 (116) (2010) 888–895.
[21] K. Siami, W.G. McCluggage, N.G. Ordonez, D.E. Euscher, A. Albores-Saavedra, B. Martinez-Benitez, E. Luevano, Small cell carcinomas of the endometrium and large cell neuroendocrine carcinomas of the endometrium and cervix: an immunohistochemical and molecular genetic analysis of KIT and PDGFRα genes, Arch. Gynecol. Obstet. 282 (2010) 413–416.
[22] K. Nasu, T. Hirakawa, M. Okamoto, M. Nishida, K. Nakamura, T. Kanai, T. Tamura, J. Watanebe, A. Obokata, H. Kuramoto, Small-cell carcinoma of the uterine cervix: a clinicopathologic study of a case and review of the literature, Eur. J. Gynaecol. Oncol. 23 (2002) 577–581.