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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

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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.

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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 a73 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.

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 clinico-pathological 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

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SCC of endometrium with aberrant expression of TTF1 and widely metastatic disease.

The pathology with immunohistochemical review, therapeutic management and prognosis of these cases are also reviewed.

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 adnexae 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.

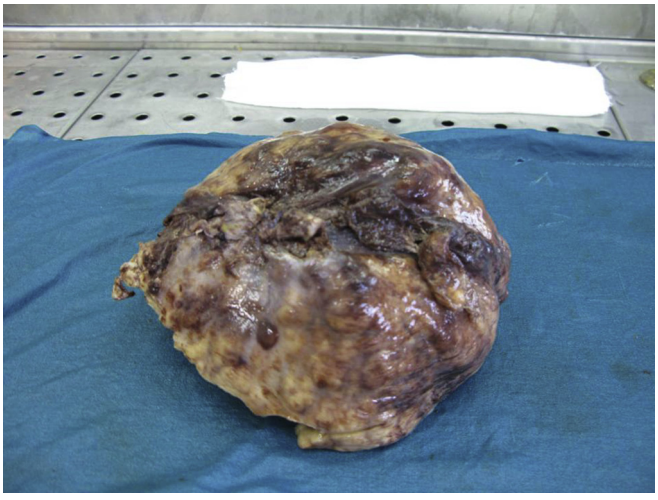

Fig. 1. The tumor appear as a large, bulky mass of uterine corpus.

3. Discussion

Small cell carcinoma (SCC) is an aggressive tumor with neuroendocrine differentiation that usually occurs in the lung. These tumors may also occur in the female genital tract [6–11], where it shows most commonly in the cervix [12,13]. Primary SCC of the endometrium that resemble a SCC of the lung is extremely rare [1–9]. This uncommon disease is extremely aggressive and has an unfavorable outcome. This is due to the early development of lymph node and distant organ metastases and vascular invasion tends toward rapid extra-pelvic distant metastasis to areas such as the lung, liver, brain, bone and lymph nodes, resulting in a shorter overall survival time than that seen in patients with other histopathological subtypes of endometrial carcinoma [1–10]. Clinical presentations include postmenopausal bleeding, lower abdominal mass, chronic abdominal pain and menorrhagia [1–10]. On gross examination, the tumors were usually characterized by bulkiness and predisposition to invasion of the myometrium with abundant necrosis. Some cases were described a polypoid mass [1,3]. Extrauterine spread was documented in the majority of cases including widespread intra-abdominal and ovarian or tubal involvement, vaginal involvement, para-aortic lymph node metastases. Histologically, these tumors showed sheets, cords, and nests composed of population of small or intermediate-sized cells with scanty cytoplasm, ill-defined cytoplasm, hyperchromatic nuclei, and high mitotic rate. Diffuse or single-cell necrosis and vascular invasion were typically present. Frequently a synchronous endometrial endometrioid adenocarcinoma was present in association with SCC [1,3]. Immunohistochemical evidence of neuroendocrine differentiation was demonstrated in most tumors (neuron specific enolase, chromogranin, synaptophysin, leu-7, CD56) [1–10]. In some cases was described a positive immunostains for cytokeratin and epithelial membrane antigen (EMA) [3]. Ultrastructural evaluation showed scattered intracytoplasmic electron-dense neurosecretory granules [3]. An intriguing feature is the nuclear expression of Thyroid transcription factor 1 (TTF-1) of small cell component of tumor.

Thyroid transcription factor-1 (TTF-1) is commonly considered as sensitive and relatively specific for tumors of pulmonary/thyroid origin.

Instead, it is known that thyroid transcription factor-1 (TTF-1) has been reported be positive also in a subset of extrapulmonary SCC as carcinoma of bladder [14], colonic adenocarcinoma [15], ovarian epithelial neoplasms [16], uterine tumors [17] and in a small percentage of primary gynecological adenocarcinomas with problems of differential diagnosis with lung tumors [18]. Because TTF-1 can be positive in different cases, it should be used with caution to differentiate a metastatic SCLC from primary extrapulmonary SCC. Moreover a diagnosis of metastatic SCLC should be always excluded in these cases by thoracic computed tomography or chest radiography. Other differential diagnosis are with malignant lymphoma, leukemia, stromal sarcoma, embryonal rhabdomyosarcoma, primitive neuroectodermal tumors and malignant mixed mullerian tumor. We wish to distinguish SCC of the endometrium from other small cell tumor because of the former's distinctive immunohistochemical, and ultrastructural characteristics demonstrating the neuroendocrine differentiation of the endometrium, A careful histological examination is more than enough to differentiate SCC from conventional epithelial and mullerian tumors although this tumor often show an admixture with ordinary adenocarcinoma. Like their counterparts in the lung, SCC of endometrium are aggressive tumors with a propensity for systemic spread and a poor prognosis. To date, no effective treatment protocol has been established for this rare type of tumor [19]. The treatment of extrapulmonary SCC arising in female genital tract

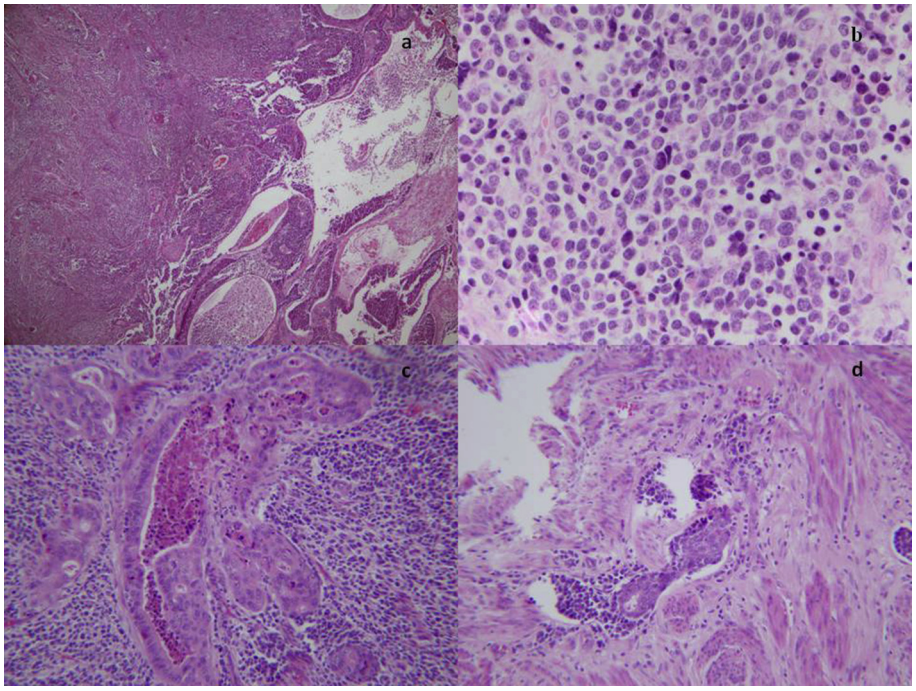

Fig. 2. a Histological examination showed a prevalent solid pattern with nests or large cords composed of small cells (Hematoxylin-eosin x10). b Tumor was composed of small or intermediate-sized cells with scanty cytoplasm, hyperchromatic nuclei, and high mitotic rate resembling SCC of the lung. (Hematoxylin-eosin x40). c. Vascular invasion was present; neoplastic emboli were composed of both SCC and adenocarcinoma. (Hematoxylin-eosin x20). d A synchronous endometrioid adenocarcinoma was present in association with SCC component (Hematoxylin-eosin x20).

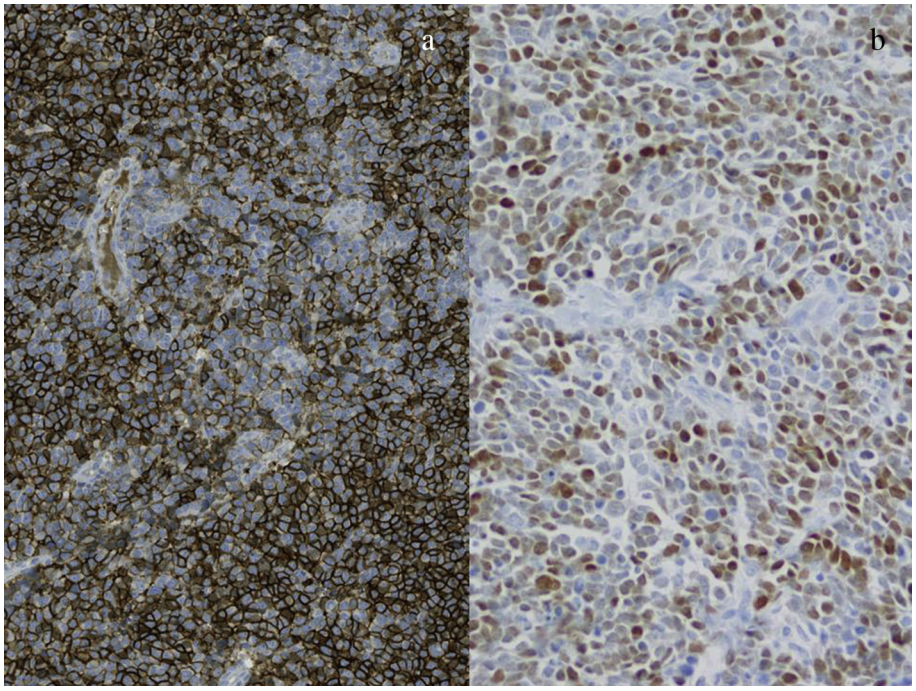

Fig. 3. a Immunohistochemistry, small cells stained positively for TTF-1 (immunoperoxidase x40). b and for CD56 (immunoperoxidase x40).

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

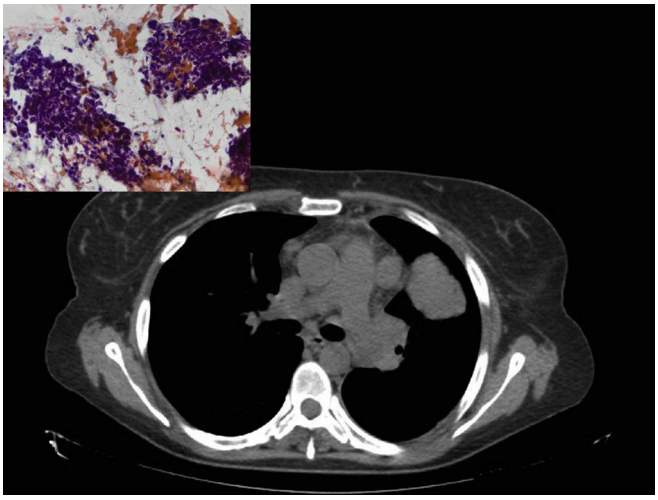

Fig. 4. CT scan showed a mass in the upper lobe of the left lung. Inset: FNA was diagnostic for SCC (Papanicolaou x40).

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 followed by radical surgery and adjuvant chemotherapy in patients with SCC of cervix and advanced disease [22]. In conclusion this study confirms that small-cell carcinomas of the endometrium are a histologically distinctive subtype of endometrial carcinoma, which, like their counterparts in the uterine cervix, are aggressive tumors with a propensity for systemic spread and a poor prognosis. Although the current therapies have usually resulted in poor outcomes, a multidisciplinary therapy, including surgery, chemotherapy, and radiotherapy represents until this time the only therapeutic option. Probably soon a most large series of cases and new therapeutic modalities should be explored.

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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.

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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. Matsuzawa, S. Makinoda, T. Oda, K. Fujiwara, 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. 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.
[8] S. Meirmanov, M. Nakashima, T. Rogounovitch, 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. Tsunoda, T. Jobo, M. Arai, M. Imai, T. Kanai, T. Tamura, J. Watanabe, 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.Y. 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 (347) (2010) e1–e6.
[14] T.D. Jones, K.M. Kernek, X.J. Yang, A. Lopez-Beltran, G.T. MacLennan, J.N. Eble, H. Lin, C.X. Pan, M. Tretiakova, L.A. Baldridge, L. Cheng, Thyroid transcription factor 1 expression in small cell carcinoma of the urinary bladder: an immunohistochemical profile of 44 cases, Hum. Pathol. 36 (2005) 718–723.
[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, E.D. Euscher, A. Malpica, N. Sneige, E.G. Silva, M.T. Deavers, Thyroid transcription factor-1 expression in endometrial and endocervical adenocarcinomas, Am. J. Surg. Pathol. 31 (2007) 1759–1763.
[18] 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.
[19] S.M. Brennan, D.L. Gregory, A. Stillie, A. Herschtal, M. Mac Manus, D.L. Ball, Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer 15 (116) (2010) 888–895.
[20] O. Bige, B. Saatli, M. Secil, M. Koyuncuoglu, U. Saygili, Small cell neuroendocrine carcinoma of the endometrium and laparoscopic staging: a clinicopathologic study of a case and a brief review of the literature, Int. J. Gynecol. Cancer 18 (2008) 838–843.
[21] K.L. Wang, Y.C. Yang, T.Y. Wang, J.R. Chen, T.C. Chen, H.S. Chen, T.H. Su, K.G. Wang, Neuroendocrine carcinoma of the uterine cervix: A clinicopathologic retrospective study of 31 cases with prognostic implications, J. Chemother. 18 (2006) 209–216.
[22] K. Nasu, T. Hirakawa, M. Okamoto, M. Nishida, C. Kiyoshima, H. Matsumoto, N. Takai, H. Narahara, Advanced small cell carcinoma of the uterine cervix treated by neoadjuvant chemotherapy with irinotecan and cisplatin followed by radical surgery, Rare Tumors 30 (3) (2011) e6.