Large cell neuroendocrine carcinoma of the uterine corpus metastatic to brain and lung: Case report and review of the literature

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Summary

Neuroendocrine carcinoma of the uterine corpus is a rare aggressive tumor with a similar unfavorable outcome to that of the cervix. The large cell type is considerably rarer than the small cell neuroendocrine carcinoma of the uterine corpus. We report a case of a 52-year-old woman who presented with a large cell neuroendocrine tumor of the uterine corpus with very aggressive clinical behavior, cerebral and pulmonary metastases six and four months after initial diagnosis and adjuvant radiotherapy, respectively. Despite successful surgical extirpation of the cerebral metastatic lesion she did not respond to chemotherapy and died four months after disease recurrence.

Key words: Large cell neuroendocrine carcinoma; Uterine corpus; Cerebral metastasis.

Introduction

Neuroendocrine tumors are defined as tumors arising from endocrine cells with neurosecretory characteristics. These tumors have also been termed as "carcinoid" to describe tumors of epithelial cells with clear cytoplasm and organoid growth pattern [1]. Poorly differentiated neuroendocrine tumors more often tend to behave aggressively therefore recognition of these tumors are of great importance as the therapeutic approach may be changed accordingly [2]. Primary neuroendocrine tumors of the female genital tract have been described in many organs, including the cervix, endometrium and ovaries [3, 4]. Among these, neuroendocrine carcinoma of the endometium is the least common [4]. However, large cell neuroendocrine carcinoma of the endometrium has not been described.

A case of a 52-year-old woman with large cell neuroendocrine tumor of the uterine corpus with very aggressive clinical behaviour is reported.

Case

A 52-year-old multiparous woman presented with perimenopausal uterine bleeding described as a history of abnormal bleeding for six months. Except for a euthyroid goiter of ten years' duration, her medical history was unremarkable. She had been smoking two packets of cigarette per day for more than 30 years. Her father died of lung cancer.

The uterus was slightly enlarged and soft on bimanual palpation. Colposcopic examination revealed no gross abnormality of the cervix or vagina. Histologic examination of tissue obtained from the subsequent endometrial curettage demonstrated undiffentiated carcinoma of the endometrium. The patient underwent total hysterectomy with bilateral salpingo-oophorectomy. There was no evidence of extrauterine disease detected at the time of surgery. The chest X-ray, abdominal sonography and computerized tomographic scanning failed to show any metastatic lesions.

Macroscopic examination revealed a polypoid tumor of the corpus uteri 5 x 3 x 3 cm in diameter. Microscopically, infiltration of more than one half of the myometrium and vascular invasion were seen. Histologically, tumor cells with diffuse and trabecular growth patterns, polygonal and spindle cells with hyperchromatic nuclei and some prominent nucleoli were observed in all tissue sections (Figure 1). Tumor necrosis, mitotic figures, gland-like stuctures and pseudorosettes in some focuses were also observed (Figure 2). The ovaries were histologicaly normal. The cervical and isthmic areas were uninvolved.

Immunohistochemically, tumor cells stained strongly positive for neuron-specific enolase (NSE) and synaptophysin (Figure 3) and negative for chromogranin. The final pathologic diagnosis was appropriate for large cell neuroendocrine carcinoma of the endometrium.

Four months after receiving adjuvant radiotherapy, she presented with unilateral headache, visual symptoms and loss of balance. On neurologic examination, confusion and disorientation were observed. The patient also exhibited right hemiparesis, right homonymous hemianopsia and a positive Babinsky sign on the right side. Cranial computerized tomography scanning revealed hematoma on the left parieto-temporal lobe, with a slight shift to the right of the cranial component, and metastatic lesions of the left frontal and left parieto-occipital lobe. Cranial magnetic resonance imaging revealed multiple lesions of which the largest was found to be at least 3 x 4 cm in diameter on the left parietal lobe. The patient also had multiple metastatic lesions on anterior-posterior chest X-ray. Bone marrow aspiration biopsy and review of the other systems were negative for malignancy.

The patient was referred to the neurosurgical department where she underwent a craniotomy and extirpation of the

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Fig. 1

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Fig. 3

Figure 1. — Tumor cells around necrotic tissue with a polygonal and large appearance (Hematoxylin & eosin x 10).

Figure 2. — Large neoplastic cells showing pseudorosette formation (in the center) (Hematoxylin & eosin x 16).

Figure 3. — Synptophysin positivity in tumor cells (anti-synaptophysin x 16).

metastatic lesion without any complications. Histologic examination of the tissue obtained from craniotomy revealed foreign body granulation tissue, with a few suspected degenerative metastatic tumoral cells. She was scheduled for combined radiotherapy and chemotherapy with cisplatin and etoposide, and died three months after the beginning of therapy.

Discussion

Neuroendocrine tumors have been recognized for many years, beginning when Oberndorfer coined the term "carcinoid" in 1907 to describe tumors of epithelial cells with clear cytoplasm and organoid growth patterns [1]. In the past these tumors have been also termed as argyrophil cell carcinoma, small cell carcinoma and small cell variants of squamous cell carcinoma [5]. A simplified classification includes: small cell carcinoma displaying small round or fusiform cells with scant cytoplasm; carcinoid tumors displaying noduler, trabecular, or cord-like structures; atypical carcinoid tumors with more cellularity and cytologic atypia; and large cell neuroendocrine carcinoma with poor differentiation [6, 7].

Neuroendocrine neoplasms can be of variable malignancy potential, depending on the level of cellular differentiation and on the degree of nuclear anaplasia. Low-grade neuroendocrine tumors such as carcinoids are generally not a diagnostic problem. By contrast, poorly differentiated neuroendocrine tumors produce significant diagnostic difficulties. For the diagnosis of these tumors, the presence of neurosecretory granules, as determined by ultrastructure or immunostains, still seems to be the single most important feature. We used the criteria proposed by the Collage of American Pathologists for the classification of neuroendocrine tumors of the cervix [5]. The tumor cells were three or five times the size of erythrocytes. Tissue sections stained strongly with NSE, and synaptophysin and were negative for chromogranin. Tumors are considered as neuroendocrine only if the accompanying squamous or glanduler component, if present, is minor or inconspicuous (5% of tumor). If more than one-tenth of the tumor exhibits squamous differentiation, it should be regarded as a mixed tumor with a component of squamous cell carcinoma [8]. The biologic behavior of neuroendocrine carcinoma is very aggressive. While most patients have low-stage tumor at the time of diagnosis, the outlook is poor and distant metastases and recurrent disease are common [9].

The original endocrine cells with neurosecretory function are most frequently found in the digestive tract and lungs. They may be also found in the female genital tract [4], where most are uterine small cell carcinomas or ovarian carcinoids. Primary ovarian carcinoids are divided into insular, trabecular, strumal, and mucinous types; most are benign. Carcinoids metastatic to the ovary are more aggressive, and most arise in the gastrointestinal tract. Sporadic mucinous cystic tumors with neuroendocrine cells have been associated with Zollinger-Ellison

syndrome. Frank neuroendocrine carcinomas of the ovary include small cell carcinoma and large cell neuroendocrine carcinoma, each with a poor prognosis and often associated with a conventional surface epithelial tumor. Such carcinomas also occur in the endometrium and cervix. Uterine carcinoids are rare if strict criteria are applied. Small cell neuroendocrine carcinomas also occur rarely in the vagina and vulva [4].

Neuroendocrine tumors of the uterine cervix are more common than that of the uterine corpus. Histogenetically, neuroendocrine carcinoma of the endometrium probably stems from neuroendocrine cells of the normal endometrium. An alternative theory is neuroendocrine metaplasia of the mullerian epithelium [10]. Neuroendocrine carcinoma of the endometrium can be divided into carcinoid, small cell and large cell types [4]. The endometrial small cell type is more commonly seen [11-19]. Huntsman *et al.* [11] and Van Hoeven *et al.* [12] reported 16 and ten cases, respectively, of small-cell carcinoma of the endometrium with very aggressive clinical behavior and poor prognosis. They also found that these tumors may commonly be mistaken for a homologous-type mesodermal mixed tumor. In extensive review of the English literature we were not able to find any reported case of large cell neuroendocrine tumor of the uterine corpus (endometrium). However, reported cases of large cell neuroendocrine tumors of the cervix were shown to exhibit histopathologic features and clinical behavior similar to that of the present case [20-25]. Remtula *et al.* [20] reported five cases of large cell neuroendocrine tumors of the uterine cervix diagnosed microscopically and immunohistochemically. On histopathological examination, all five tumors were reported to exhibit features of a high-grade poorly differentiated malignant neoplasm with ulceration and extensive tumor necrosis including trabecular and organoid growth patterns. Also, all five neoplasms showed strong immunoreactivity for MNF116, while their endocrine nature was confirmed by staining for synaptophysin in all cases. None of the tumors showed positive staining for chromagranin A. These cases were found to have a biologic aggressive nature with very unfavorable prognosis.

In the present case, tissue sections stained strongly with NSE, and synaptophysin and were negative for chromogranin. The antigen NSE is found in neurons, normal cells in the neuroendocrine system and tumors with neuronal or neuroendocrine differantiation. It has also been demonstrated in non-neuronal normal and neoplastic tissues. Therefore NSE is not a specific marker for neuroendocrine differentiation. However, it is a useful screening tool in detecting cells with neuroendocrine features [26]. Synaptophysin, a transmembrane protein found in the presynaptic vesicles of neural cells, has been found to show variable positivity in neuroendocrine tumors [27]. Chromogranin A belongs to a family of acidic glycoprotein chromogranin and it is used for the distinction of neuroendocrine neoplasms in poorly differentiated neuroendocrine carcinomas of any origin [28].

In the present case, clinically the tumor exhibited a high risk of recurrence and very aggressive behavior similar to its small-cell variant and large cell neuroendocrine carcinoma of the cervix.

In conclusion, neuroendocrine carcinomas of the endometrium are particularly aggressive tumors. Since the incidence of these tumors is extremely low, sufficient clinical data is lacking. However, given the aggressive nature of these tumors which resembles that of small cell variants and that of large cell neuroendocrine carcinomas of the cervix, accurate diagnosis is of great importance so that appropriate and aggressive therapy is given promptly without delay. In the series of large cell neuroendocrine carcinoma of the cervix reported by Remtula et al. [20] three of five patients presented with advanced-stage cervical carcinoma, in which two of them had evidence of metastases. Treatment response and long-term survival proved to be disappointing as three of the five patients died in less than six months. Due to the low incidence of these tumors, optimal therapy has not been delineated; however, because of a high propensity to reccurrence and distant metastasis, multimodality therapy including combination chemotherapy (cisplatin and etoposide) is warranted. Neoadjuvant or adjuvant chemotherapy should be combined with radiation therapy and surgery even in early stages [29-31].

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