Case Reports in Oncology

Case Rep Oncol 2018;11:665–670

DOI: 10.1159/000493912
Published online: October 23, 2018

Case Report

Large Cell Neuroendocrine Carcinoma of the Cervix with Sequential Metastasis to Different Sites: A Case Report

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Keywords
Large cell neuroendocrine carcinoma · Cervix · Metastasis · Treatment

Abstract
Neuroendocrine carcinoma of the cervix is rare, and prognosis is very poor. Because of its rarity, effective treatment of neuroendocrine carcinoma of the cervix has not been established. It has distinct patterns of metastasis, but can be successfully treated with radical surgery and platinum-based chemotherapy. We report a 50-year-old woman who was diagnosed with large cell neuroendocrine carcinoma of the cervix and underwent radical surgery followed by adjuvant chemoradiation therapy. She experienced recurrence several times and to different sites, with sequential metastasis to the lung, breast, and retroperitoneum, but nevertheless survived more than 5 years.

Introduction

Neuroendocrine tumors (NETs) are neuroendocrine cell-derived malignancies that can occur in various parts of the body. NETs are classified into well-differentiated and poorly differentiated NETs; large cell neuroendocrine carcinomas (NECs) are categorized as poorly differentiated NETs. Neuroendocrine carcinoma of the cervix (NECC) accounts for approximately

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0.5% to 1% of cervical cancer cases, of which around 12.5% are reported to be large cell NECs [1]. Because of the rarity and aggressive behavior of NECCs, there is a lack of research on the common sites of metastasis and the optimal treatment of metastatic disease. According to previous literature, the most common treatment strategies are radical surgery and chemotherapy with etoposide and cisplatin for patients with early stage disease, and chemoradiation therapy or chemotherapy for patients with advanced disease [2–5]. We treated a woman diagnosed with large cell neuroendocrine carcinoma of the cervix (LCNCC) who underwent radical surgery and concurrent chemotherapy, after which she experienced recurrence three times sequentially in different sites after a disease-free period of 18 months.

Case Report

A 50-year-old premenopausal Korean woman (gravida 2, para 2) presented with vaginal bleeding. Her body mass index was 23.1 kg/m^2. She had a history of two Cesarean sections and no other medical or surgical history. Her family history included a sister with uterine cancer and father with liver disease. She visited a local clinic and was found to have a cervical mass upon pelvic examination, for which she underwent punch biopsy. The result was poorly differentiated carcinoma of the cervix, so she was referred to our hospital.

Tumor marker examination was normal, with squamous cell carcinoma antigen (SCC) levels of 0.6 ng/mL (normal, 0–1.5 ng/mL) and CA125 levels of 10.1 U/mL (normal, <35 U/mL). Pelvic examination revealed a 3.5-cm mass in the uterine cervix, inferiorly involving the upper 1/3 of the vaginal wall. There was no parametrial invasion, and the tumor was estimated to be stage IIA1 by the International Federation of Gynecology and Obstetrics (FIGO) staging system. Pelvic magnetic resonance imaging demonstrated a fungating enhancing cervical mass at the posterior side of the cervix destroying the posterior cervical stromal ring and inferiorly involving the upper vaginal wall (Fig. 1). Positron emission tomography-computed tomography (CT) showed no definite regional or distant metastasis.

Radical hysterectomy with bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, and bilateral salpingo-oophorectomy were performed as initial treatment. The resected specimen was 3.5 × 2.7 × 3.4 cm (Fig. 2). The histology of the surgical specimen showed large cell neuroendocrine morphology. The tumor cells were immunoreactive to the neuroendocrine markers CD56 and neuron-specific enolase (NSE). They were also partially positive for epithelial membrane antigen (EMA) and CK20. The tumor was negative for p63, CK7, and carcinoembryonic antigen. The patient had lymphovascular invasion and no parametrial invasion. No metastasis was found in the 23 lymph nodes assessed. She was finally diagnosed with LCNCC, FIGO stage IIA1. Her postoperative course was uneventful, and 28 days after surgery, 6 weeks of concurrent chemoradiation therapy with weekly cisplatin (40 mg/m^2) was started.

Duruing a regular follow-up 18 months after radical surgery, her serum CA125 level was elevated to 138.0 U/mL. Chest CT showed a suspected metastatic nodule in the right lung apex. She underwent right upper lobectomy and was diagnosed with metastasis of cervical neuroendocrine tumor 1.3 × 0.7 × 0.7 cm in size. Immunohistochemically, the tumor was positive for CD56 and negative for thyroid transcription factor-1. She received six cycles of combination chemotherapy with carboplatin (area under the curve, 5) and paclitaxel (175 mg/m^2) every 3 weeks.

Thirty months after lobectomy and 48 months after the first operation, a small mass was detected in the right breast through self-examination. Sonography-guided breast biopsy was performed on the mass, and it was diagnosed as invasive carcinoma with neuroendocrine

differentiation. The mass was positive for NSE and negative for ER and PR. She decided against radical mastectomy because there was no longer a palpable mass after the biopsy. Instead, she received six cycles of chemotherapy with the previous regimen. Afterwards, we performed breast conserving surgery with sentinel lymph node biopsy, and histologic examination showed no residual tumor.

One year after the metastasis was found in the breast, abdominal CT suggested metastasis to the adrenal gland, soft tissue in the retrorenal space, and fat layer of the right flank area. She underwent bilateral adrenalectomy, retroperitoneoscopic partial nephrectomy, and ureteroureterostomy. Histologic examination revealed poorly differentiated carcinoma, consistent with metastasis from the uterine cervix. The metastases were positive for NSE, EMA, and CD10 and negative for CD56 and PAX8. We are planning to perform adjuvant chemotherapy for this patient.

Discussion/Conclusion

NETs originate in neurosecretory cells and can occur in many organs of the body, although they are most commonly found in the lung and GI tract. Pulmonary NETs are classified as typical carcinoid, atypical carcinoid, small cell NEC, or large cell NEC [4]. The terminology for NETs of the uterine cervix was presented in 1997 at a workshop sponsored by the College of American Pathologists and the National Cancer Institute, and is similar to that used for pulmonary NETs [6].

According to the WHO classification of pulmonary tumors in 2015, large cell neuroendocrine carcinoma (LCNECs) exhibit characteristic neuroendocrine morphology with large cell size and positive immunohistochemical staining for neuroendocrine markers [4]. Histologic features of LCNEC include neuroendocrine morphology such as organoid nesting, palisading rosettes, and trabeculae; high mitotic rate (>10 per 2 mm^2); necrosis; and cytologic features such as large cell size, low nuclear to cytoplasmic ratio, and vesicular or fine chromatin. NETs are positive for neuroendocrine markers, including synaptophysin, CD56, and chromogranin, and less specifically NSE. In order to diagnose LCNCC, metastasis of cancer outside the cervix should be ruled out at diagnosis, and expression of markers that may appear in other carcinomas, such as p63, should be identified.

There are very few studies on the most common sites of NET metastasis. One study showed that NETs most commonly metastasize to the liver, although in that study, the most common primary site was the small intestine [7]. In this study, the site of metastasis differed according to the primary site. The epidemiology of metastasis in LCNCC is not yet known, and there are only a few case reports on this subject [8, 9]. According to these reports, LCNCC has an aggressive behavior, similar to that of lung NETs, such as early metastasis to the surrounding lymph nodes, lung, liver, bone, and brain [10].

The optimal treatment for NECC has not been clearly established because the disease is rare and aggressive. According to the 2011 edition of the Society of Gynecologic Oncology guidelines, etoposide/platinum-based chemotherapy is recommended for poorly differentiated NETs [2]. In 2014, the Gynecologic Cancer InterGroup reviewed the treatment of small cell NECC, and ultimately recommended chemotherapy and radical surgery for early stage patients and etoposide and cisplatin-based chemotherapy for advanced stage patients [11]. Considering the aggressive characteristics of this cancer, we performed radical surgery followed by concurrent chemoradiation therapy. This patient had multiple recurrences of LCNCC, but complete surgical resection was possible each time, and chemotherapy was also administered.

The patient has been alive for 63 months since the original diagnosis, which is much longer than expected. Her long-term survival may be related to the invasion range of the lesion and the characteristic metastasis pattern. The metastasis pattern and treatment process of this case can be useful to understand the pathophysiology of LCNCC and establish a treatment plan for LCNCC patients.

Acknowledgement

None.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

Conceptualization: Yong-Il Ji.
Writing – original draft preparation: Eunhyun Lee.
Writing – review and editing: Yong-Il Ji.
Approval of final manuscript: all authors.

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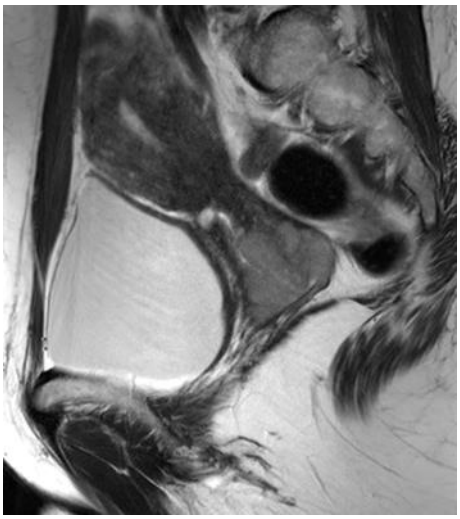

Fig. 1. Magnetic resonance image of a 50-year-old woman diagnosed with large cell neuroendocrine carcinoma of the cervix. Contrast enhanced T2-weighted sagittal image shows a fungating enhancing cervical mass.

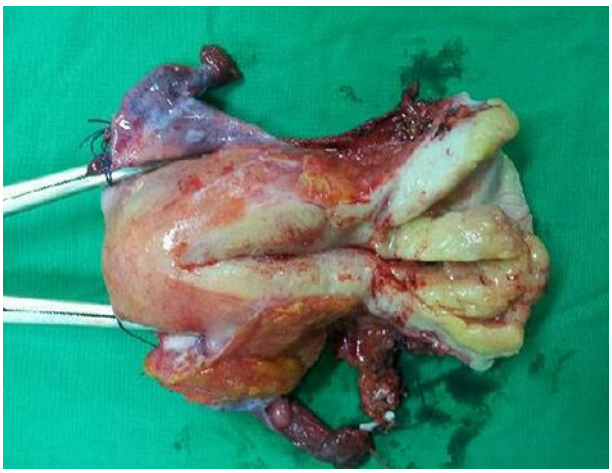

Fig. 2. A 3.5-cm neoplastic lesion resected from the cervix.