Large Cell Neuroendocrine Carcinoma of the Uterine Cervix Associated with Adenocarcinoma

Ma-Lee Ko[1], Cherng-Jye Jeng[2]*, Shih-Hung Huang[3], Jenta Shen[4], Su-Chee Chen[1], Chii-Ruey Tzeng[2]

[1]Department of Obstetrics and Gynecology and [3]Department of Pathology, Cathay General Hospital, and [2]Department of Obstetrics and Gynecology, Taipei Medical University, Taipei, Taiwan, and [4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, California Pacific Medical Center, San Francisco, USA.

SUMMARY

Objective: Large cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive cervical neoplasm. In the present study, we present a 45-year-old woman with large cell neuroendocrine uterine cervical carcinoma with coexisting adenocarcinoma.

Case Report: A 45-year-old G2 P0 presented with vaginal bleeding for 7 months. On pelvic examination, a polypoid mass of the cervix was discovered. Biopsy of the lesion revealed large cell neuroendocrine carcinoma of the cervix. The patient underwent a radical hysterectomy, and then received concurrent chemotherapy and radiation therapy. She has remained disease free until the time of this writing.

Conclusion: Patients with LCNEC of the cervix have had poor prognoses; hence aggressive multimodality treatment is recommended. [*Taiwanese J Obstet Gynecol* 2007;46(1):68–70]

Key Words: adenocarcinoma of the cervix, large cell neuroendocrine carcinoma of the cervix

Introduction

Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is a very rare malignancy that is highly aggressive and usually results in unfavorable outcomes. It is considerably less common than the well-recognized small-cell neuroendocrine carcinoma of the cervix. We recently encountered a case of LCNEC of the cervix with coexisting adenocarcinoma of the cervix.

Case Report

A 45-year-old woman, gravida 2, para 0, presented with intermenstrual bleeding for 7 months. Her history was significant because of a mildly abnormal Pap smear, ASCUS, 3 years prior to this consultation. Pelvic examination revealed a 3-cm polypoid lesion protruding from the cervical os that was clinically confined to the cervix. The vagina was grossly normal and the bilateral parametria were free. The exophytic cervical mass was friable and bled easily on contact. A colposcopy-directed biopsy of the cervical lesion revealed a tumor with a trabecular pattern and prominent geographic necrosis. The tumor cells possessed a moderate amount of cytoplasm, with prominent nucleoli and large nuclei (Figure 1). There was a myriad of apoptotic cells and more than 10 mitoses per 10 high-power fields (HPF). The tumor cells stained positive for synaptophysin, chromogranin A, and neuron-specific enolase (NSE). Histology was consistent with the diagnosis of LCNEC of the cervix. Serum SCC was 1.0 ng/mL while CEA was 1.7 ng/mL. She also tested positive for high-risk HPV 18. A computed tomography (CT) scan of the pelvis showed an enlarged uterine cervix with no identifiable enlarged lymph node in

Correspondence to: Dr Cherng-Jye Jeng, Department of Obstetrics and Gynecology, Taipei Medical University, 250, Wu-Xin Street, Taipei 110, Taiwan.
E-mail: drcjjeng@tmu.edu.tw
Accepted: August 14, 2006

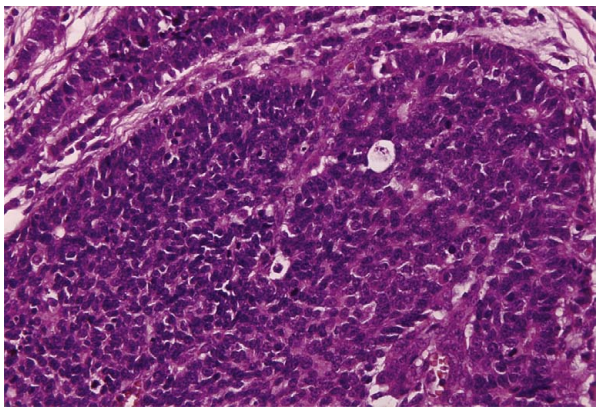

Figure 1. Histology of the cervical lesion with tumor cells possessing abundant cytoplasm, prominent nucleoli and large nuclei (hematoxylin and eosin, 400×).

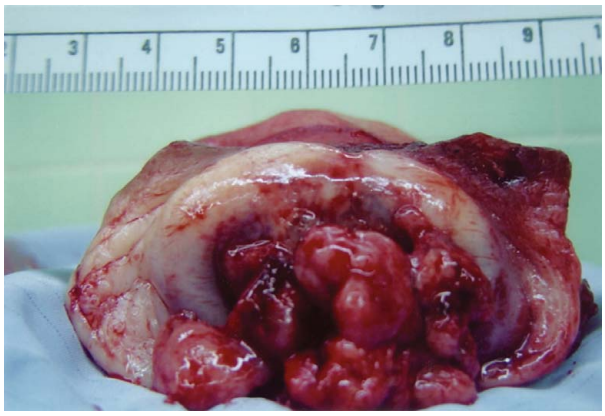

Figure 2. Cervix with the polypoid mass localized at the uterine cervix.

the abdominal or pelvic cavity. The patient underwent a radical hysterectomy, pelvic and paraarotic lymph node dissection, and transposition of bilateral ovaries (Class III radical hysterectomy). Bilateral salpingo-oohorectomy was recommended before surgery; however, the patient insisted on preserving her ovaries. Peritoneal washings were also taken for cytologic examination.

The uterus in the radical hysterectomy specimen grossly showed multiple myomas, adenomyosis, and a 3.0 × 1.09 × 0.6 cm tumor mass located at the uterine cervix (Figure 2). Pathologic examination of the cervix demonstrated LCNEC invading the inner 6 mm of the cervical wall. The parametrium, uterus, vagina, 39 lymph nodes, and peritoneal washings were free of cancer. Multiple foci of the adenocarcinoma were also noted on the cervix (Figure 3).

The patient later received postoperative radiation therapy of the pelvis (33 cGy in 24 fractions), reduced pelvis (5cGy in 4 fractions), and intravaginal brachytherapy (15cGy in 7 fractions) with concomitant weekly chemotherapy with cisplatin 40 mg/m^2 (six cycles), followed by three cycles of monthly chemotherapy with cisplatin 50 mg/m^2. Therapy was well tolerated and no relapse has been observed for 2 years.

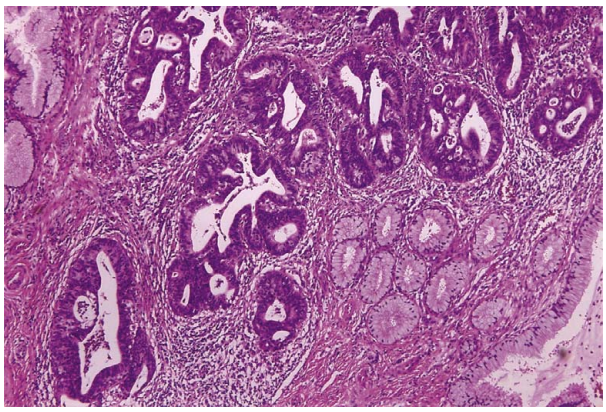

Figure 3. Histology of the well-differentiated invasive adenocarcinoma of the cervix. Note the cribriform structure in the tumor glands and desmoplastic change over the stroma (hematoxylin and eosin, 400×).

Discussion

Endocrine carcinomas are rare, accounting for nearly 5% of all cervical carcinomas. Neuroendocrine carcinomas of the uterine cervix, particularly those comprising large cells are even more uncommon, with fewer than 50 cases documented in the English literature [1–5]. Clinically, patients are younger with median age of 42 years [6].

A new classification system for neuroendocrine tumors of the cervix has been proposed by the College of American Pathologists namely: large cell, small cell, classical carcinoid, and atypical carcinoid [7]. The small cell endocrine tumors have small round cells with minimal cytoplasm, abundant mitotic figures, and extensive necrosis. The classical carcinoid has no cytologic atypia, no necrosis, and rare mitotic figures. Atypical carcinoid on the other hand possesses cytologic atypia, ≤ 10 mitotic figures/HPF and focal necrosis. Histologic criteria for diagnosis of cervical LCNEC include the presence of large cells with vesicular nuclei and prominent nucleoli, a mitotic index in excess of 10/10 HPFs, and geographical areas of tumor necrosis. Other features of these tumors include the presence of neurosecretory granules with an inconspicuous amount (< 5%) of glandular or squamous component. Tumors are argyrophylic (a neuroendocrine marker) and stain immunohistochemically with synaptophysin, chromogranin, and NSE [8].

Accurate diagnosis of cervical LCNEC is of prognostic importance. Gilks et al [2] identified 65% mortality rate within 3 years of diagnosis. Moreover, in their study of 21 stage I cervical LCNEC cases, 12 patients died of the disease after a median survival period of 16 months.

It has been suggested that viral exposure, host, and other nonviral factors may play roles in the pathogenesis of cervical cancer. According to Grayson et al [9], the integration of high-risk type HPV, in particular, type 16 and to a lesser degree type 18, was associated with LCNEC of the uterine cervix.

In this case, LCNEC of the cervix was noted to coexist with adenocarcinoma. As evident in Figure 3, adenocarcinoma with neuroendocrine differentiation was possible due to the presence of glandular structures along with the well-differentiated invasive adenocarcinoma. Such an entity has been described in other reports in the literature as divergent differentiation rather than synchronous carcinomas. Since neuroendocrine differentiation is common in invasive glandular lesions of the cervix, such as adenocarcinoma, neuroendocrine carcinomas have been postulated to arise from cervical glandular reserve cells as well as from cervical endocrine cells [6,10,11]. Hence, adenocarcinoma having both well- and poorly differentiated components, with the latter component showing that neuroendocrine differentiation is plausible.

The treatment of LCNEC of the cervix remains controversial due to the rarity of the disease. In our institution, three cycles of adjuvant chemotherapy and concurrent radiation is offered to patients with paraaortic lymph nodes positive for adenocarcinoma. However, we do not have solid evidence to support or oppose this treatment regimen. Further study is warranted.

Aggressive initial multimodality treatment with radical hysterectomy and adjuvant chemoradiation is recommended [2,7].

References

1. Walker AN, Mills SE, Taylor PT. Cervical neuroendocrine carcinoma: a clinical and light microscopic study of 14 cases. *Int J Gynecol Pathol* 1988;7:64–74.
2. Gilks CB, Young RH, Gersell DJ, et al. Large cell carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 1997;21:905–14.
3. Mannion C, Park WS, Man YG, et al. Endocrine tumors of the cervix. Morphologic assessment, expression of human papillomavirus, and evaluation for loss of heterozygosity on 1p, 3p, 11q, and 17p. *Cancer* 1998;83:1391–400.
4. Wistuba II, Thomas B, Behrens C, et al. Molecular abnormalities associated with endocrine tumors of the uterine cervix. *Gynecol Oncol* 1999;72:3–9.
5. Yun K, Nam-Pyo C, Glassford GN. Large cell neuroendocrine carcinoma of the uterine cervix: a report of a case with coexisting cervical intraepithelial neoplasia and human papillomavirus 16. *Pathology* 1999;31:158–61.
6. Savorgaonkar PR, Hale RJ, Muttan J, Monning V, Buckley CH. Neuroendocrine differentiation in cervical carcinoma. *J Clin Pathol* 1996;49:139–41.
7. Albores-Saavedra J, Gersell D, Gilks CB. Terminology of endocrine tumors of the uterine cervix: results of a workshop sponsored by the College of American Pathologists and the National Cancer Institute. *Arch Pathol Lab Med* 1997; 121:34–9.
8. Dikmen Y, Kazandi M, Zekioglu O, Ozsaran A, Terek MC, Ehran Y. Large cell neuroendocrine carcinoma of the uterine cervix: a report of a case and review of the literature. *Arch Gynecol Obstet* 2004;270:185–8.
9. Grayson W, Taylor LF, Allard U, Tiltman AJ. Detection of human papillomavirus u\in large cell neuroendocrine carcinoma of the uterine cervix: a study of 12 cases. *J Clin Pathol* 2002;55:108–14.
10. Chan JK, Tsui WM, Tung SY, Ching RC. Endocrine cell hyperplasia of the uterine cervix: a precursor of neuroendocrine carcinoma of the cervix? *Am J Clin Pathol* 1989;92: 825–30.
11. Cui S, Lespinasse P, Cracchiolo B, Sama J, Kreitzer MS, Heller DS. Large cell neuroendocrine carcinoma of the cervix associated with adenocarcinoma *in situ*: evidence of common origin. *Int J Gynecol Pathol* 2001;20:311–2.