Large cell neuroendocrine carcinoma of the ovary: a case report and a brief review of the literature

Eun Young Ki, Jong Sup Park, Keun Ho Lee, Seog Nyeon Bae and Soo Young Hur*

Abstract

Large cell neuroendocrine carcinoma (LCNC) of the ovary, or ovarian undifferentiated non-small cell carcinoma of neuroendocrine type, is a rare entity that is frequently associated with ovarian surface epithelial tumors. Few cases have been reported in the literature. LCNC is an aggressive tumor with tendency to present at advanced stages and to cause death after a short postoperative duration. We report three cases of LCNC diagnosed histopathologically. Immunohistochemically, the tumor cells were positive for chromogranin A, NSE, CD56, and pancytokeratin. The patients were treated postoperatively with combination chemotherapy. Due to the rarity of LCNC, the general consensus on standard therapy is not established. Although most patients are at stage I, the biological aggressiveness and poor prognosis of the tumors have been reported in previous reports despite extensive surgery and chemotherapy.

Keywords: Ovary, Neuroendocrine carcinoma, Non-small cell, Large cell

Background

Ovarian neoplasms associated with hormone production and secretion include sex-cord-stromal and germ cell tumors [1]. Another tumor showing endocrine features is small cell carcinoma, which is divided into hypercalcemic and pulmonary types [2]. According to the World Health Organization (WHO), undifferentiated non-small cell carcinoma of neuroendocrine type is synonymous with large cell neuroendocrine carcinoma (LCNC) [3,4]. LCNC is a rare cancer, and 27 cases have been reported in the literature so far [2-7]. The clinical behaviors of LCNC are aggressive and show poor prognosis despite being diagnosed in the early stages [2,8,9]. Most of the reported LCNCs are associated with teratoma or epithelial tumor, such as serous and mucinous tumors [10-12].

We report three cases of large cell neuroendocrine carcinoma of the ovary with a literature review.

Case presentation

Case 1

A 77-year old woman visited our clinic with a 1-month history of abdominal distension and discomfort. She had been diagnosed with coronary artery disease prior to this presentation. Physical examination showed ascites and firm/fixed mass in the suprapubic area. In the left supraclavicular area, nodular masses were palpable, raising suspicion of metastatic lymph nodes. Computed tomography (CT) revealed a huge heterogenous soft tissue mass in the pelvic cavity. Chest CT showed an extensive, conglomerated soft tissue density in the left supraclavicular area. The CA125 value was 124 u/ml. She underwent an exploratory laparotomy. At operation, a 15-cm ovarian mass was found to adhere to the uterus, bladder, rectum, and small intestine. About 500 ml of ascites was noted. The uterus, pelvic mass, and neck masses were removed, and there were large amounts of intraoperative bleeding. The pathologic diagnosis of the ovarian mass was undifferentiated non-small cell neuroendocrine carcinoma of the ovary. Immunohistochemical staining was negative for synaptophysin, but positive for chromogranin A and NSE (Figure 1). The pathologic examination revealed that the neck mass had malignant cells with massive necrosis. The cytologic evaluation of the ascites showed malignant cells. She received 1 session of etoposide 100 mg/m² for 2 days along with 1 session of carboplatin 300 mg/m² at 14 days after operation. She died of septic shock after 45 postoperative days.
Figure 1 Microscopic pictures. (a) Neuroendocrine carcinoma low-power field shows solid sheets (H&E, ×40). (b) Cells with larger vesicular nuclei: prominent nucleoli, and mitotic activity (H&E, ×400). (c) Chromogranin A is expressed in a neuroendocrine carcinoma (×400). (d) Pancytokeratin is expressed in a neuroendocrine carcinoma (×400). (e) NSE is expressed focally in a neuroendocrine carcinoma (×400). (f) CD56 is expressed in a neuroendocrine carcinoma (×400).
cells of the diffuse neuroendocrine system, which in turn originates from endocrine cells in the peripheral nervous systems as well as several endocrine organs. These cells can produce biologically active amines and peptides which can act as neurotransmitters, hormones, or paracrine regulators. Neuroendocrine cells are present in normal epithelium of the female genital tract [10]. It has been shown that primitive endodermal cells have the potential to differentiate into both endocrine and other cell types and that ovarian neuroendocrine tumors may develop from non-neuroendocrine cells through activation of genes that promote neuroendocrine differentiation [12].

In general, the incidence of epithelial ovarian cancer increases in older patients (age >50 years), but the LCNC can be developed in premenopausal and postmenopausal women, ranging from 22 to 76 years. Similarly, in our report the age of patients ranged from 58 to 77 years, and mean age was 67.3 years. Clinical symptoms at initial presentation are variable. The most common clinical manifestation was abdominal pain in 7 cases [3,13], followed by abdominal distension (n = 4) [14-17], and an abdominal palpable mass (n = 3) [3,5,16], abdominal bloating (n = 3) [3], abdominal discomfort (n = 1) [2], postmenopausal vaginal bleeding (n = 1) [3], and dysarthria due to brain metastasis (n = 1) [8]. In our report, abdominal distension, abdominal discomfort, and urinary frequency occurred in one case each. The urinary frequency may have been due to compression of the bladder by the huge ovarian mass. Most of the LCNCs are partially solid or partially cystic, with size ranging from 9 and 30 cm (mean size, 16.6 cm) [2,3,8,14,17]. In this report, the mean size of the mass was 13 cm, and the mass was also partially solid or cystic.

The histogenesis of neuroendocrine tumors is unknown. The following hypotheses have been proposed. First, neuroendocrine cells have been presented in the normal epithelium of benign, borderline, and malignant tumors of the female genital tract. These cells serve as an origin of neuroendocrine tumors of the ovary. Second, primitive endocrine cells can differentiate into endocrine and other cell types. Third, ovarian neuroendocrine tumors may develop from non-neuroendocrine cells, which activate genes promoting neuroendocrine differentiation [12,18].

CA125 is a tumor antigen found in 75 to 83% of all epithelial ovarian cancers [19]. Serum CA125 levels correlate with cancer stages or responses to treatment. A rise in CA125 levels usually precedes tumor progression or recurrence. Therefore, CA125 can be used to monitor epithelial ovarian cancer. In LCNC, serum CA125 levels are not specific to clinical courses. Table 1 shows reported serum CA125 levels in previous studies. The CA125 levels range from 5.7 to 917 u/ml. Some authors have reported other tumor markers. Ngan et al. [9] have reported that 5-hydroxyindole acetic acid (5-HIAA) markedly increase in neuroendocrine carcinomas of the
Figure 2 A photograph of an ovarian mass. It is composed of solid and cystic lesions.

Table 1 Clinicopathologic review, adjuvant treatment, CA125 levels, and follow-up periods of reported cases

| Author                  | Mean age (years) | Chief complaint                                      | Adjuvant treatment                                      | CA125 (u/ml) | Follow-up periods (months) |
|-------------------------|------------------|------------------------------------------------------|---------------------------------------------------------|--------------|---------------------------|
| Lindboe et al. [2]      | 64               | Abdominal discomfort, nausea                         | Cisplatin + Bleomycin + Etoposide                       | 380          | 9                         |
| Shakuntala et al. [14]  | 40               | Abdominal distension                                 | Cisplatin + Etoposide                                   | 280          | 6                         |
| Hinde et al. [15]       | 54               | Abdominal distension                                 | Carboplatin + Paclitaxcel                               |              | 8                         |
| Dundr et al. [8]        | 73               | Dysarthria, difficulty in verbal expression because of brain metastasis | Carboplatin + Paclitaxcel                              | 94           | 12                        |
| Tsuji et al. [17]       | 46               | Abdominal distension                                 | Carboplatin + Paclitaxcel                               | 914          | Died after 4 months postoperatively |
| Aslam et al. [13]       | 76               | Abdominal pain                                       | None                                                    | Within the normal range | Died postoperatively     |
| Chenevert et al. [16]   | 53               | Abdominal mass                                        | Carboplatin + Paclitaxcel                               | 80           | Died after 3 months postoperatively |
|                         | 53               | Abdominal distension                                 | Carboplatin + Etoposide                                 | 5.7          | Died after 7 months postoperatively |
| Behnam et al. [5]       | 27               | Pelvic mass                                           | Carboplatin + Paclitaxcel                               |              | 10                        |
| Veras et al. [3]        | 22 to 63 [46.7]  | 6: abdominal pain                                    | None                                                    |              | Mean survival: 12         |
|                         | 11 cases         |                                                       |                                                         |              | Mean follow-up periods: 28 |
| Ki et al.               | 77               | Abdominal distension                                 | Carboplatin + Etoposide                                 | 124          | Died after 1.5 months postoperatively |
|                         | 58               | Abdominal discomfort                                 | Carboplatin + Paclitaxcel                               | None         | Died after 17 months postoperatively |
|                         | 67               | Urinary frequency                                    | Carboplatin + Paclitaxcel                               | 71.8         | 5                         |

3: abdominal bloating
1: pelvic mass
1: postmenopausal bleeding
A combination of platinum and paclitaxel has been used in combination chemotherapy regimens, such as platinum, chromogranin A, NSE, CD56, and pancytokeratin. Our specimens were immunohistochemically positive for differentiation when other stains are negative [3,5,15,16,18]. Specificity and may not be conclusive for neuroendocrine differentiation. These biphasic tumors can usually be distinguished from LCNC by identifying non-neuroendocrine components [3,5,12]. Immunohistochemistry is important to diagnose neuroendocrine carcinoma. The most commonly used non-hormonal immunohistochemical markers are chromogranin A, synaptophysin, cytokeratin, and CD56. NSE and Leu-7 lack specificity and may not be conclusive for neuroendocrine differentiation when other stains are negative [3,5,15,16,18]. Our specimens were immunohistochemically positive for chromogranin A, NSE, CD56, and pancytokeratin. There is no standard treatment of LCNC. Various combination chemotherapy regimens, such as platinum, paclitaxel, etoposide, and bleomycin have been used in previous studies. The survival periods varied among the groups. A combination of platinum and paclitaxel has most frequently been used with shorter survival.

**Conclusion**

LCNC is rare, shows aggressive behaviors and poor responses to treatment. Due to the rarity of LCNCs, general consensus on the standard therapy has not yet been established. Although patients with LCNC are at stage I, their survival rates are relatively low due to biological aggressiveness despite extensive surgery and chemotherapy. We reported three cases of advanced or early LCNC with a brief review of the literature.

**Consent**

Written informed consent was obtained. The study was approved by the Institutional Review Board of our hospital (KC14ZISE0113).

**Abbreviations**

S-HIAA: 5-hydroxyindole acetic acid; AUC4: 4-hour area-under-the-curve; CT: computed tomography; H&E: hematoxylin and eosin; LCNC: large cell neuroendocrine carcinoma; MRI: magnetic resonance image; WHO: World Health Organization.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

EYK wrote the initial draft. SYH and JSP performed the surgery and helped collect clinical information. SYH, KHL and SNB designed the study and made the manuscript of this paper. All authors have read and approved the final manuscript.

**Received:** 21 March 2014 **Accepted:** 3 October 2014

**Published:** 15 October 2014

**References**

1. Eichhorn JH, Young RH, Scully RE: Primary ovarian small cell carcinoma of pulmonary type. A clinicopathologic, immunohistologic, and flow cytometric analysis of 11 cases. *Am J Surg Pathol* 1992, 16:526–538.
2. Lindboe C: Large cell neuroendocrine carcinoma of the ovary: case report and review of the literature. *APMS* 2007, 115:169–176.
3. Veras E, Deavers MT, Silva EG, Malpica A: Ovarian nonsmall cell neuroendocrine carcinoma: a clinicopathological and immunohistochemical study of 11 cases. *Am J Surg Pathol* 2007, 31:774–780.
4. Khurana KK, Torres N, Silva EG: Ovarian neuroendocrine carcinoma associated with a mucinous neoplasia. *Arch Pathol Lab Med* 1994, 118(10):1032–1034.
5. Behnam K: Primary ovarian undifferentiated non-small cell carcinoma, neuroendocrine type. *Gynecol Oncol* 2004, 92(1):372–375.
6. Hiratsawa T: Ovarian neuroendocrine carcinoma associated with mucus carcinoma and teratoma. *Nihon Rinsho* 2004, 62(5):973–978.
7. Eichhorn JH, Lawrence WD, Young RH, Scully RE: Ovarian neuroendocrine carcinomas of non-small-cell type associated with surface epithelial adenocarcinomas. A study of five cases and review of the literature. *Int J Gynecol Pathol* 1996, 15(4):503–514.
8. Dundr P, Fischerová D, Povýsil C, Cibula D: Primary pure large-cell neuroendocrine carcinoma of the ovary. *Pathol Res Pract* 2008, 204(2):133–137.
9. Ngan HY, Collins RJ, Wong LC, Chan SY, Ma HK: The value of tumor markers in a mixed tumor, mucinous and neuroendocrine carcinoma of the ovary. *Gynecol Oncol* 1989, 35:272–274.
10. Eichhorn JH, Young RH: Neuroendocrine tumours of the genital tract. *Am J Clin Pathol* 2001, 115(1):504–512.
11. Chen KTK: Composite large-cell neuroendocrine carcinoma and surface epithelial-stromal neoplasm of the ovary. *Int J Surg Pathol* 2001, 8(2):169–174.
12. Collins RJ, Cheung A, Ngan HYS, Wong LC, Chan SYW, Ma MK: Primary mixed neuroendocrine and mucinous carcinoma of the ovary. *Arch Gynecol Obstet* 1991, 248:139–143.
13. Aslam MF, Choi C, Khulpatnea N: Neuroendocrine tumour of the ovary. *J Obstet Gynaecol* 2009, 29(4):446–449.
14. Shakkunta PN, Devi KU, Shobha K, Bafna UD, Geratshahree M: Pure large cell neuroendocrine carcinoma of ovary: a rare clinical entity and review of literature. *Case Rep Oncol Med* 2012, 2012:120727–120731.
15. Fatemi Hinde E: Rare tumors of ovary: case report and literature review. *Open J Pathol* 2012, 02(03):61–64.
16. Chenevert J, Bassette P, Plante M, Tetu B, Dubé V: Mixed ovarian large cell neuroendocrine carcinoma, mucinous adenocarcinoma, and teratoma: a report of two cases and review of the literature. *Pathol Res Pract* 2009, 205(9):657–661.
17. Tsuj T, Togami S, Shintomo N, Fukamachi N, Douchi T, Taguchi S: Ovarian large cell neuroendocrine carcinoma. *J Obstet Gynaecol Res* 2008, 34(4 Pt 2):726–730.
18. Choi YD, Lee IS, Choi C, Park CS, Nam JH: Ovarian neuroendocrine carcinoma, non-small cell type, associated with serous carcinoma. *Gynecol Oncol* 2007, 104(3):747–752.
19. Bost RC Jr, Klug TL, Schaetzl E, Lavin P, Niloff JM, Greber TF, Zurawski VR Jr, Knapp RC: Monitoring human ovarian carcinoma with a combination of CA 125, CA 19-9, and carcinoembryonic antigen. *Am J Obstet Gynecol* 1984, 150:553–559.

**doi:**10.1186/1477-7819-12-314

Cite this article as: Ki et al.: Large cell neuroendocrine carcinoma of the ovary: a case report and a brief review of the literature. *World Journal of Surgical Oncology* 2014 12:314.