Large cell neuroendocrine carcinoma of the endometrium: a report and review of the literature

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ABSTRACT

Large-cell neuroendocrine tumor of the endometrium is a rare tumor type which is difficult to diagnose. Our routine tissue sampling is often non-productive and these tumors can be mistaken for other poorly differentiated carcinomas. Sites of metastatic disease sometimes confuse the identification of the primary organ, and histological diagnosis requires a choice of neuroendocrine biomarkers. In addition, there are no published diagnostic criteria for LCNEC of the endometrium and diagnostic criteria must be translated from the WHO classification of tumors of the lung. Once a diagnosis is reached, there are no large series to direct treatment. Consensus opinion appears to favor surgery for early stage disease followed by chemotherapy with etoposide and platinum-based agents. While there are many hurdles to overcome, the proper diagnosis of LCNEC of the endometrium is of utmost importance in a disease characterized by rapid progression and poor prognosis. We examine a case of large cell neuroendocrine tumor of the endometrium with rapid progression over a period of two months which precluded her planned chemotherapy.

1. Introduction

Large cell neuroendocrine tumor of the endometrium is a rare malignancy with an aggressive course that often proves difficult to diagnose and treat. Data regarding this malignancy is limited to case reports and there is no definitive recommendation regarding therapy. We discuss the case of a 56 year-old who was diagnosed with large cell neuroendocrine tumor of the endometrium with rapid progression of disease.

2. Case presentation

A 56 year-old, Caucasian female, BMI 48, initially presented to Gynecologic Oncology as a referral secondary to post-menopausal bleeding and pelvic pain. At the time of initial evaluation CT and TVUS results were available demonstrating a 17 cm complex left adnexal mass, an enlarged uterus measuring 16 cm with thickened endometrial echo of 13 mm, and pulmonary densities in bilateral lung bases. Endometrial biopsy obtained at the time of initial evaluation was inadequate for evaluation. A serum Ca-125 level was obtained which was elevated at 130 U/mL. Additional noteworthy labs included a leukocytosis of 31,000 and hypercalcemia at 13 mg/dL. Repeat imaging 7 days later revealed new and enlarging lung metastasis as well as multiple new liver lesions.

Ultrasound guided biopsy of a liver lesion was performed revealing a well-differentiated neuroendocrine tumor, grade 2, versus atypical carcinoid, most likely GI in origin. Patient was referred for gastroenterology consultation and underwent upper and lower endoscopy. These studies revealed no obvious neoplasia with negative antral biopsies. Initial plan for therapy included neo-adjuvant chemotherapy utilizing etoposide and cisplatin but the patient continued to experience significant pelvic and abdominal pain. A decision was made to proceed with palliative hysterectomy with excision of the left adnexal mass. The patient underwent exploratory laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. Abdominal examination was notable for disease involving the omentum, nodularity of the liver, and visible disease consuming the uterus. Pelvic evaluation was notable for disease involving both ovaries, extension along left infundibulopelvic ligament, and extension into vesico-uterine and recto-vaginal spaces. Extensive disease spread to the vagina was noted, as well as, disease of the right labia majora that was not present at the time of preoperative evaluation eight days prior. It was felt that the 15 cm complex mass visualized in the left adnexa was, in part, the result of torsion of that ovary although both adnexa contained obvious malignancy. Postoperative pathology reports revealed stage IVB large-cell neuroendocrine carcinoma of the uterus with stage IA, grade 1.

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endometrioid adenocarcinoma of the ovary (Figs. 1 and 2).

Two weeks after the initial procedure the patient was readmitted secondary to dyspnea from her advanced pulmonary disease. Imaging revealed no evidence of pulmonary emboli, but worsening lymphadenopathy with an increase in the size and number of pulmonary and liver metastasis. The decision was made, in conjunction with patient’s family, to focus on maximum supportive care. The patient’s functional status quickly decompensated and she required increasing doses of pain medications to provide adequate comfort care. Approximately 4 days after the patient’s second hospital admission she expired due to respiratory failure and consumptive carcinomatosis.

3. Discussion

Most of what is known about large-cell neuroendocrine tumors (LCNEC) comes from the study of lung malignancies; but even so, LCNEC account for only 3% of lung cancers. According to the WHO classification of pulmonary tumors, LCNEC is defined as large-cell carcinoma with neuroendocrine morphology (nesting, trabeculae, rosettes) expressing the neuroendocrine biomarkers synaptophysin, chromogranin A and/or CD56 (Hiroshima and Mino-Kenudson, 2017). Neuroendocrine tumors (NET) in gynecological organs are more common in the cervix and ovary and rarely in the endometrium. NETs of the endometrium include low-grade carcinoid tumors, high-grade small-cell neuroendocrine tumors (SCNEC), and LCNEC. The majority of these are SCNEC tumors (Matsumoto et al., 2016). A literature review demonstrates that approximately 20 cases of large-cell neuroendocrine tumor of the uterus have been described with variable diagnostic patterns and clinical courses. These cases have been summarized in the table below (Table 1). Of note, 8 (40%) cases reported are from Japan, and only 3 cases (15%), including this report, are published from institutions located within the United States.

4. Presentation

The average age of reported cases of LCNEC is 62.6 (age range 40–88 years old). 75% of reported cases presented with abnormal or post-menopausal bleeding. This is consistent with the average age of onset and most common presenting symptom for uterine cancer in general (Noone et al., 2018).

5. Diagnosis

The recommended method of endometrial sampling in cases of abnormal uterine bleeding, an endometrial biopsy using a pipelle, has been reported with sensitivity greater than 80% (Dijkhuizen et al., 2000). However, endometrial biopsy may be less useful in LCNEC. In the 20 cases listed above, only one pathologic diagnosis was based on endometrial biopsy. This theme is echoed in the lung cancer literature; some resources recommend that only the suggestion of LCNEC be made on cytology or biopsy but the final diagnosis should be reserved for resected specimens (Hiroshima and Mino-Kenudson, 2017). In addition, there is no defined biomarker which might increase suspicion for LCNEC or be used to monitor response to chemotherapy. Several of the reports reviewed describe elevation of Ca-125, neuron specific enolase (NSE), and lactate dehydrogenase but there is no published sensitivity or specificity for these markers in this tumor type. NSE may be promising as it has been used as a biomarker for tumor burden, number of metastatic sites and response to treatment in small cell lung cancer or non-small cell lung cancer (Igrò et al., 2015).

There are no specific imaging findings to suggest large-cell neuroendocrine tumor of the endometrium. One review suggested MRI findings are similar to that of other poorly differentiated carcinomas, with ill-defined endometrial-myometrial border and heterogeneity of the mass indicating necrosis and hemorrhage (Mulvany and Allen, 2008). The diagnosis of LCNEC depends on immunohistochemical staining for neuroendocrine biomarkers, but this can be difficult due to cross reactivity of available biomarkers with other common tumors of the endometrium. On immunostaining, one neuroendocrine marker is sufficient for diagnosis of neuroendocrine origin (Hiroshima and Mino-Kenudson, 2017). However, tumor markers may have variable sensitivity and specificity. CD56 has been highly correlated with small-cell neuroendocrine carcinoma of the cervix but lacks specificity; as it can also be common in endometrioid carcinoma. LCNEC of the uterine cervix is more common than of the endometrium, and we know in those cases 25–38% of tumors will co-express chromogranin and synaptophysin. Neuron specific enolase (NSE) has also been suggested as a useful biomarker, but once again, has high sensitivity but low specificity (Hiroshima and Mino-Kenudson, 2017).

6. Therapy

There is limited data regarding the most efficacious therapy for large-cell neuroendocrine tumor. Most information relates to treatment of this tumor type in lung cancer. Most sources recommend surgery for early stage disease in both patients with LCNEC of the lung or cervix followed by adjuvant chemotherapy (Lee et al., 2008). Even within the lung cancer literature there are conflicting reports about the most effective regimen for treating LCNEC of the lung. Some authors favor a...
| Citation     | Age  | Presentation | Biopsy type and Pathology | Final pathology          | IHC staining                                                                 | Surgery                           | Treatment                           | Outcome                          | Stage   |
|--------------|------|--------------|----------------------------|--------------------------|-------------------------------------------------------------------------------|-----------------------------------|------------------------------------|----------------------------------|---------|
| Nguyen et al., 2013 | 40   | AUB          | D&C: sarcomatous undifferentiated carcinoma | LCNEC Synaptophysin, chromogranin A, CD56, p53, Ki-67 | TAH, BSO, omentectomy, LND                                                     | Etoposide, cisplatin              | None                               | Alive with disease 16 months after surgery | IB      |
| Nguyen et al., 2013 | 70   | PMB          | none                        | LCNEC Synaptophysin, CD56 and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Nguyen et al., 2013 | 71   | PMB          | EMB: extensive necrosis and LCNEC | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Nguyen et al., 2013 | 52   | PMB          | D&C: undifferentiated carcinoma of the endometrium | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Nguyen et al., 2013 | 73   | Abdominal pain | D&C: small cell carcinoma with extensive necrosis | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Nguyen et al., 2013 | 70   | PMB          | EMB: extensive necrosis and LCNEC | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Mulvany et al., 2018 | 52   | PMB          | None                        | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Mulvany et al., 2018 | 80   | PMB          | None                        | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Mulvany et al., 2018 | 77   | PMB          | None                        | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Mulvany et al., 2018 | 79   | PMB          | None                        | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Mulvany et al., 2018 | 88   | PMB          | None                        | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Ogura et al., 2018 | 52   | Menorrhagia  | Biopsy of frank tumor in vagina | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Yi-An Tu et al., 2018 | 51   | PMB          | EMB: extensive necrosis and LCNEC | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
| Yi-An Tu et al., 2018 | 78   | PMB          | EMB: extensive necrosis and LCNEC | LCNEC Synaptophysin, chromogranin A, CD56, and epithelial membrane antigen (EMA).   | TAH, BSO, omentectomy, LND                                                     | Etoposide and cisplatin           | NED (No evidence of disease) 6 months after chemotherapy | Death 6 months postoperative, renal failure | IVC     |
small cell carcinoma (SCC) treatment regimen with etoposide and platinum-based therapy. Some favor a non-small cell carcinoma approach with a platinum-based drug and gemcitabine (Derks et al., 2017). The SCC regimen of etoposide and cisplatin is generally preferred in LCNEC of the cervix with an 83% recurrence free survival reported at 3 years (Zivanovic et al., 2009). This correlates with the treatments described in the 20 case reports published. Of the 10 cases with chemotherapy regimens reported, 7/10 received or had planned to receive a SCC regimen of etoposide and cisplatin and 3/10 received irinotecan and cisplatin.

For our patient, neo-adjuvant chemotherapy with etoposide and cisplatin was planned due to advanced stage disease. This plan of care was changed due to rapidly progressive disease in an effort to achieve symptom control. There were no published case reports utilizing neo-adjuvant chemotherapy for uterine LCNEC. However, published data support neo-adjuvant therapy for small-cell neuroendocrine carcinoma of the cervix (Lee et al., 2008) in which 16% of cases received neo-adjuvant chemotherapy prior to surgical and/or radiation therapy. It would appear neo-adjuvant therapy for such an aggressive cancer should be considered if the patient’s performance status allows. This may provide the opportunity for improved quality of life over a short time frame while allowing consideration of further treatment options.

7. Prognosis

Much of what we know about prognosis of LCNEC of the endometrium must be inferred from what is known of other gynecologic neuroendocrine cancers. A retrospective review of SCC of the uterine cervix revealed the estimated 3-year progression free survival (PFS) was 22% with overall survival (OS) of 30%. These outcomes were much worse for patients that did not receive systemic chemotherapy as part of their treatment plan (Zivanovic et al., 2009). LCNEC is often diagnosed at advanced stage with the majority of patients having widely metastatic disease. This was the case in 15/20 of the published case reports which were found to have at least stage III disease. Even for early stage disease LCNEC of the endometrium appears to have an aggressive course with rapid recurrence (Isgrò et al., 2015). Of the 20 published case reports there were 0 cases of RFS at 3 years, and only one case reported no evidence of disease at 20 months. Several cases, including our own, exhibited rapid progression of disease which precluded chemotherapy.

8. Conclusion

Large-cell neuroendocrine tumor of the endometrium is a difficult diagnosis to make. These tumors are often mistaken for poorly differentiated carcinomas. Sites of metastatic disease sometimes confuse the identification of the primary organ, and histological diagnosis requires a choice of neuroendocrine biomarkers. In addition, there are no published diagnostic criteria for LCNEC of the endometrium and diagnostic criteria must be translated from the WHO classification of tumors of the lung. There is also not a specific recommendation regarding type of tissue sample needed to make a diagnosis. Once a diagnosis is reached, the course of chemotherapy must be discussed. Due to the rarity of the diagnosis there are no large series to direct treatment. Consensus opinion appears to favor surgery for early stage disease followed by chemotherapy with etoposide and platinum-based agents. While there are many hurdles to overcome, the proper diagnosis of LCNEC of the endometrium is of utmost importance in a disease characterized by rapid progression and poor prognosis.

Conflict of Interest

Drs Jenny, Kimball, Kilgore, and Boone have no potential conflicts of interest to report.
Author contribution

CJ performed literature review and wrote the manuscript. KK, LK, and JB provided direct patient care, expertise in the field, and manuscript edits.

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