Primary Pure Large-Cell Neuroendocrine Carcinoma of the Ovary: A Rare Case Report

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Abstract

Primary pure large-cell neuroendocrine carcinoma is a rare entity with 17 cases reported till now. A 48-year-old, Para6 Live4, postmenopausal woman presented with complaints of pain abdomen, constipation for 6 months, and postmenopausal bleeding for 1 month. On per abdominal examination, an irregular, hard, fixed, and tender mass was felt in the pelvis corresponding to 32 weeks size gravid uterus. Her magnetic resonance imaging findings were suggestive of a large abdominopelvic mass of size 10.2 cm × 12.7 cm × 14.2 cm with inferior extension into the left adnexa and 3.1 cm × 2.2 cm × 2.1 cm right adnexal mass. Debulting surgery was done. The intraoperative findings were of a large abdominopelvic mass adhered to the sigmoid colon and retroperitoneal space. Histopathological and immunohistochemistry findings were suggestive of bilateral large-cell neuroendocrine carcinoma of ovaries with strong positive for Bcl2, CD56, NSE, PR, and P53. The patient was started on tablet etoposide as adjuvant treatment. After 5 months of primary surgery, contrast-enhanced computed tomography of the chest, abdomen, and pelvis revealed recurrence. She succumbed to her illness 6 months after primary surgery. Owing to its rarity and difficulty in diagnosis, it is suggested that all such cases should be registered at national level and critically analyzed to find the high risk and associated prognostic factors.

Keywords: Immunohistochemistry, neuroendocrine cancer, ovary, postmenopausal bleeding

Introduction

Large-cell neuroendocrine cancer has been recently included in the WHO classification of ovarian tumors.1] The clinical presentation is similar to epithelial ovarian cancer such as abdominal pain, distension, lump, and rarely vaginal bleeding. Radiological diagnosis preoperatively is not possible. Macroscopic picture of the tumor has both solid and cystic components. Microscopically, the tumor has large tumor cells, oval-round in shape with areas of necrosis, and increased mitosis. Its diagnosis requires confirmation by immunohistochemistry (IHC) analysis and includes positive chromogranin A, neural cell adhesion molecule, CD56, or synaptophysin.2] It has poor prognosis even if diagnosed at an early stage of the disease with high propensity of recurrence to unusual sites when compared with other types of ovarian cancers.2] There exists no standard treatment protocol also for its management. We present this case owing to the rarity of the tumor, its presentation, and treatment follow-up, so that timely detection, its diagnosis using IHC, and prognostication of the disease process can be done accordingly.

Case Report

We are presenting this case after appropriate consent from the patient and her relatives. A 48-year-old, P6 L4, postmenopausal woman presented to gynecology OPD of our hospital with complaints of pain abdomen and constipation...
Yadav, et al.: A rare case of ovarian large-cell neuroendocrine carcinoma

...for the past 6 months and postmenopausal bleeding for 1 month. She was postmenopausal for 2 years. She was a known case of hypertension and diabetes mellitus and was on treatment for the same. Owing to her signs and symptoms, she got herself investigated in private hospitals and as per the findings of bilateral adnexal masses was operated 3 months back. Due to distorted anatomy and dense bowel adhesions, laparotomy was closed without any intervention. She developed stitch line sepsis, and resuturing was done on day 15 of surgery. There was a past history of open ovarian cystectomy 8 years back. Postoperative period was uneventful. Nature of the lesion removed was not known, as her previous papers were not available with the patient. On examination, her general condition was fair, her BMI was 27.34 kg/m², and her vitals were stable. On per abdominal examination, midline vertical scar was seen extending up to the umbilicus from 2 cm above symphysis pubis and appeared to heal by secondary intention. An irregular, hard, fixed, and tender mass was felt in the pelvis corresponding to 32 weeks size gravid uterus. No free fluid was appreciated. On per speculum examination, the cervix appeared pulled up with watery discharge. Vagina was healthy. On per vaginal examination, the cervix was high up, deviated to the right. The same mass was felt. On per rectal examination, rectal mucosa was free, and no parametrium was involved.

Her baseline blood investigations were within normal limits, and her ovarian markers were CA125-31 IU/L, CEA-1.13, and CA19.9-17. Her MRI findings were suggestive of a large abdominopelvic mass of size 10.2 cm × 12.7 cm × 14.2 cm with inferior extension into the colon. The left adnexa could not be visualized separately. Right adnexal mass was seen measuring 3.1 cm × 2.2 cm × 2.1 cm abutting the posterior wall of the uterus anteriorly and pelvic mass medially. The possibilities of large left subserosal fibroid with possible sarcomatous transformation or left ovarian malignant etiology was suggested following MRI. No pelvic or para-aortic lymph nodes were enlarged.

After optimization of the patient’s medical conditions, the patient was planned for exploratory laparotomy and proceed. The procedure done was total abdominal hysterectomy with bilateral salpingo-oophorectomy with abdominopelvic mass and sigmoid resection followed by reanastomosis and diversion ileostomy. The intraoperative findings were of a large abdominopelvic mass adhered to the sigmoid colon and retroperitoneal space. Liver surface was normal-looking. Pelvic or para-aortic lymph nodes were not enlarged. Adhesiolysis of ileal loops done with the involvement of surgeons which was then followed by total abdominal hysterectomy with bilateral salpingo-oophorectomy. Resection of abdominopelvic mass (marked with green arrow) with 15 cm of the sigmoid colon (marked with black arrow) was done as it was densely adhered to the mass as in Figure 1a. This was followed by sigmoid reanastomosis and diversion ileostomy. The sample retrieved was sent for histopathology. Her estimated blood loss was 4000 ml and was given 4 units of packed cells and fresh frozen plasma. She was started on thromboprophylaxis postoperatively and was started orally from day 3. Catheter was removed when the patient started ambulating comfortably. She was discharged in a stable condition after stitch removal with follow-up advice.

The gross examination of abdominopelvic mass measured 18 cm × 12 cm × 5 cm with the attached segment of the colon. External surface of the tumor showed a capsule with the breach at multiple points. The mass showed a gray-white, firm surface with large areas of hemorrhage, and necrosis with no ovarian or fallopian tube. Microscopy from this mass revealed high-grade neuroendocrine carcinoma. Round-to-oval large cells were arranged in trabeculae manner as in Figure 1b with infiltration into the sigmoid colon serosa reaching till the muscularis propria. Lymphovascular invasion was seen into the colonic submucosa and in the ovary with mitosis of 6-8/high power field. Resected cut ends of the colon were free from tumors. Gross examination of the right ovary also showed a gray-white tumor with large areas of hemorrhage and necrosis. Microscopy sections were consistent with high-grade neuroendocrine carcinoma. IHC revealed strong positive for Bcl2, CD56, NSE, PR, and P53. Focal positivity was found for CK and EMA. The final diagnosis of bilateral high-grade neuroendocrine cancer was made. Sections from the endometrium showed progestin effect and from the cervix showed ecto-endocervicitis. Rest uterus and fallopian tubes were unremarkable.

In the follow-up of our patient, she was under palliative therapy for abdominal pain and was started on tablet etoposide 50 mg once daily for 2 weeks on-off regimen in the postoperative period following histopathological diagnosis. Review CECT (contrast-enhanced computed tomography) scan of chest and abdomen 4 months postsurgery revealed left pleural effusion with nodular deposits. Multiple variable-sized liver metastases seen with largest measuring 7.3 cm × 4.6 cm. Enlarged lymph nodes...
are seen in peripancreatic/periportal, para-aortic, bilateral internal, and external iliac regions with largest measuring 2.4 cm × 3 cm. Heterogeneous solid lesions were seen in bilateral adnexa with cystic areas of size 9.8 × 4.5 cm and 6.6 cm × 5.7 cm. Multiple peritoneal deposits and omental deposits. She succumbed to her illness after 6 months of her primary surgery.

**DISCUSSION**

Neuroendocrine tumors of the ovary include primary or metastatic carcinoid tumors which are the most common, small-cell carcinoma of pulmonary or hypercalcemic type, large-cell carcinoma, and metastatic neuroendocrine carcinoma.[1] Tumors such as teratoma, sex cord-stromal, and Sertoli–Leydig cell tumors may also show neuroendocrine differentiation.[4] Primary pure large cell neuroendocrine carcinoma is a rare entity with 17 cases reported till 2020, with our case being 18th.[4,5] Various hypothesis has been proposed behind the origin of Large cell Neuroendocrine carcinoma (LCNEC), the most important being its derivation from neuroendocrine cells through its neoplastic differentiation.[6] It has extremely high malignant potential with very poor outcomes. This tumor has the propensity to affect women of all ages ranging from 18 to 80 years.[4] The diagnosis is difficult to be made by clinical, radiological, or by any specific markers. Cancer antigen 125 is found to be raised, but out of proportion to the size of the mass, and other marker like neuron-specific enolase can be used. CA125 in our case was 31 IU/L which was considerably less when compared with the size of the lesion in our case as well. 5-Hydroxyindole acetic acid was also found to be an important marker for neuroendocrine cancers.[7] The most important tool in the definitive diagnosis is IHC. The tumor is found to be positive for NSE, chromogranin, synaptophysin, CD56, and P53. Similarly, in our case, the diagnosis was confirmed following IHC. In a study by Xiaohang Yang et al., the majority of the women presented at an advanced stage as in our case.[4] The study revealed a median survival of 10 months reflecting extremely poor prognosis of this rare variant of cancer. Among the various parameters studied related to the prognostic factors such as age, FIGO stage, residual disease post debulking, and the expression of synaptophysin is considered to be the important independent marker of disease severity.[8]

Limited data are available regarding the treatment protocol for LCNEC. Tumor debulking surgery has to be followed by chemotherapy. Various combinations have been tried in the cases reported so far such as paclitaxel–carboplatin, cisplatin–cyclophosphamide, and etoposide–cisplatin with varying results.[9] As was seen in one of the reported cases by Jehine Feki et al., 55% in the tumor mass was appreciated following etoposide–cisplatin combination.[10]

**CONCLUSION**

LCNEC is known to have a poor prognosis with early recurrence to uncommon sites. Some LCNEC has revealed favorable prognoses owing to its chemosensitivity. Hence, an attempt to recognize factors that can help improve the prognostication of this aggressive cancer should be made with the help of prospective studies.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

**Acknowledgment**

Authors would like to acknowledge Dr. O.P. Pathania, Director Professor, Department of surgery for their help in the surgery of the patient. We would also like to thank our residents, Dr. Pragati and Dr. Prerna Tayal, for their help during the surgery and postoperative management of the patient.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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