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Case Report
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Primary Large Cell Neuroendocrine Carcinoma of the Ovary: A Case Report and Review of the Literature

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Abstract

Objective: The Neuroendocrine Carcinoma (NEC) of ovary is a rare and aggressive tumor with tendency to present at advanced stage. The prognosis is poor even when diagnosed early. Till date only 7 cases have been published in literature. Recently we managed a case which we want to report.

Case Report: We report a 58-year-old lady with a history of hysterectomy for dysfunctional uterine bleeding 12 years back presenting with bilateral primary large cell NEC of ovary with omental and intestinal metastasis for which optimal surgical debulking was done.

Conclusion: Primary NEC of ovary is a rare tumor which is managed similar to epithelial malignancies, but the outcome is poor.

Keywords: Carcinoma; Neuroendocrine/pathology; Carcinoma; Neuroendocrine/therapy; Immunohistochemistry; Ovarian neoplasms/pathology; Ovarian neoplasms/therapy

Introduction

The neuroendocrine tumors may arise from a wide range of organs. The Neuroendocrine Carcinoma (NEC) of the ovary is now recognized as a separate histological entity and included in the World Health Organization tumor classification. The neuroendocrine cells are normally present in the epithelium of the female genital tract and hypothesized to give rise to NEC. Though rare, the clinical behaviour of NEC is usually aggressive and carry poor prognosis even when diagnosed at an early stage. In recent decades, there has been an increased diagnosis of neuroendocrine tumors, which may partly be attributed to the improved and standardized classification criteria, and increased awareness among pathologists. On extensive literature search, till date, we could find that only 40 cases of Large Cell Neuroendocrine Carcinoma (LCNEC) of the ovary are reported of which 34 cases were associated with other histologic subtypes and 7 cases were purely LCNEC. Hence we are reporting the 8th case of bilateral primary large cell neuroendocrine carcinoma of the ovary.

Case Presentation

A postmenopausal lady of 58 years of age, presented to us with one month history of abdominal discomfort and lump abdomen. She had undergone vaginal hysterectomy 12 years back for a diagnosis of dysfunctional uterine bleeding and right total hip replacement 4 yrs back. On physical examination, a pelvic mass of size 10 cm x 10 cm was palpable and prevaginal and per rectal examination confirmed it to be of pelvic origin, probably form the adnexa. The complete haemogram, routine biochemical tests and chest radiograph were reported normal. Her serum CA 125 was 59.2 U/ml (0-35U/ml). The contrast enhanced computed tomography (CECT, Figure 1) revealed a lobulated soft tissue density lesion of size 10.4 cm x 8.7 cm on the right side and an enhancing soft tissue density lesion of size 4.5 cm x 4.1 cm on left side. A diagnosis of bilateral ovarian neoplasms probably malignant was made and she was planned for exploratory laparotomy with intraoperative consultation followed by staging laparotomy if malignant. On exploration, there was a free fluid of 500 ml which was collected for cytology. There was an irregular multinodular lesion in the right ovary of size 10 cm x 10 cm which was adherent to terminal ileal mesentery, pouch of Douglas, urinary bladder and vaginal vault and another mass in left ovary measuring 4 cm x 5 cm. There was a 1 cm x 2 cm sized surface deposit over the terminal ileum. The right ovarian mass excised and sent for frozen section analysis, which was reported as poorly differentiated malignancy (Figure 2). Hence a staging laparotomy consisting of excision of the left ovarian mass, bilateral pelvic and paraaortic lymph node dissection, infracolic omentectomy, random peritoneal biopsies and excision of the ileal nodule were done. The final histopathological diagnosis was reported as

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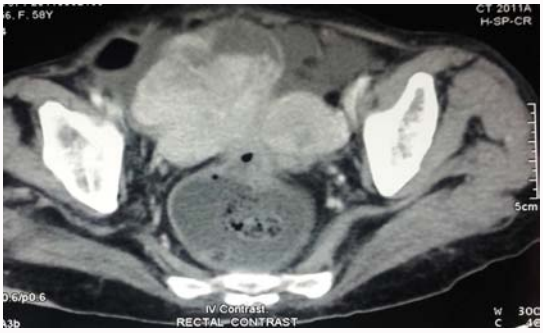

Figure 1: CECT abdomen and pelvis showing bilateral adnexal tumors.

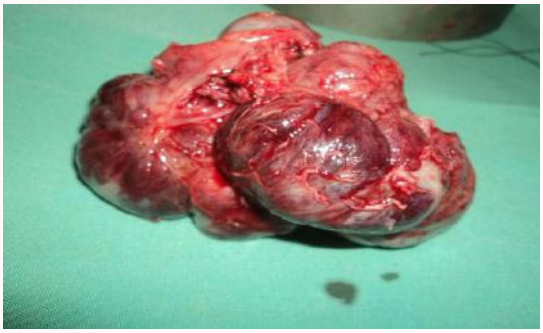

Figure 2: Postoperative image.

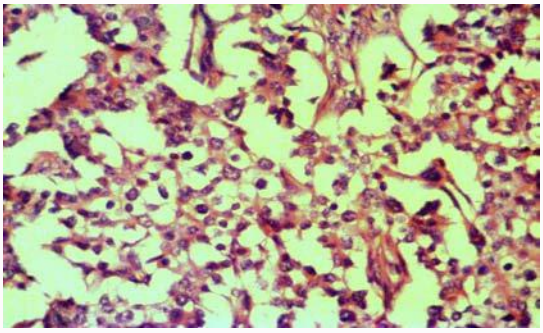

Figure 3: Photomicrograph showing presence of large round to pleomorphic cells with round to mild pleomorphic vesicular nucleus, open chromatin, prominent chromocentres, some with speckled chromatin and scant eosinophilic cytoplasm (H&Ex40).

primary bilateral neuroendocrine carcinoma – large cell type with metastasis to the omentum and ileum (FIGO, Stage IIIB, Figure 3). On confirmatory immunohistochemistry (IHC) of the tumor tissue of ovaries and ileal deposit, the tumor cell was diffusely positive for synaptophysin and chromogranin and negative for inhibin alpha, CK 7 and CK 20 (Figure 4 and 5). To rule out a more common possibility of intestinal origin IHC with CDX2 was done, which was negative. Postoperative she was discharge by 10th postoperative day without any complications and referred to Medical Oncology services for further treatment.

Discussion

The histogenesis of neuroendocrine tumors is unknown and there have been several hypotheses, First, the neuroendocrine cells are present in the epithelium of benign, borderline and malignant tumors of the female genital tract. Second, primitive endocrine cells may differentiate into endocrine and other cell types. Third, ovarian

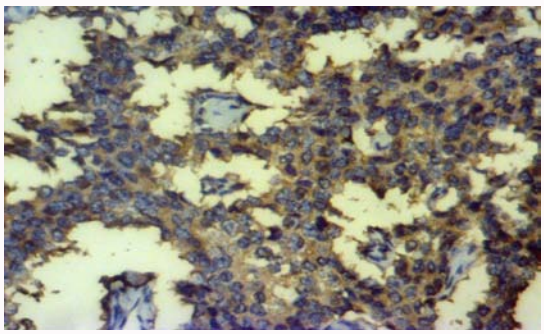

Figure 4: Showing diffuse moderate cytoplasmic positivity for Chromogranin (IHC x 40).

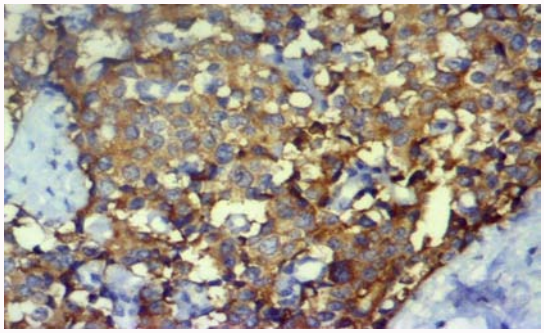

Figure 5: Showing diffuse moderate cytoplasmic positivity for synaptophysin in tumour cells.

neuroendocrine tumors may develop from non-neuroendocrine cells, which activate genes promoting neuroendocrine differentiation. These cells can produce biologically active amines and peptides which act as neurotransmitters, hormones, or paracrine regulators [1]. On extensive literature search we found that most of the reported NECs are associated with either teratoma or epithelial tumor, such as serous or mucinous tumors [2]. Our case is rare in that it was a pure primary bilateral NEC of large cell type. The World Health Organization (WHO) defines LCNEC as a tumour with a large nucleus and a tendency to have neuroendocrine differentiation, and it includes ovarian LCNECs as miscellaneous tumors [3]. The neuroendocrine tumors are commonly classified as well differentiated neoplasms (carcinoid and atypical carcinoid) and high grade neuroendocrine carcinoma (small cell and large cell types).

The reported age range is between 22 to 76 years, most common clinical manifestation being pain abdomen followed by distension or mass and postmenopausal bleeding. Most of the LCNCs are partly cystic and solid, measuring 9 cm to 30 cm in size. These tumors are often aggressive, metastasizing early, resulting in poor survival. The diagnosis often requires IHC analysis with markers such as chromogranin A, synaptophysin and CD56 to confirm the diagnosis. The most common sites of metastases are the regional nodes, liver, bone and lungs. On rare occasions, these tumors may also spread to contra lateral ovary, thyroid and breast [2,4]. The preoperative diagnosis of NEC is rarely possible. The CA-125 is a tumor antigen found in 75% to 83% of epithelial ovarian cancers [5] is rarely elevated in NEC. Ngan et al. [6] have reported that 5-Hydroxyindole Acetic Acid (5-HIAA) is markedly increased in NEC of the ovary and it can be used as a sensitive tumor marker. The more commonly used radiologic studies such as CECT and Magnetic Resonance Imaging (MRI) are not useful for the differential diagnosis of NC from other

ovarian tumors [4,7,8]. where as radionuclide studies with special isotopes may be more useful. The 68 Gallium DOTANOC PET/CT scan has been used in the diagnosis and staging, response assessment, and differentiation from other tumors, including benign lesions [9]. One of the important differentials in our case was metastatic NEC more commonly from gastrointestinal tract. The diagnostic clues include younger age, bilateralism, multifocal nodularity and several histological features such as cystic degeneration and necrosis, cribriform pattern, vascular invasion and surface involvement. The immunohistochemical staining with CDX2 may be a useful marker to distinguish primary NEC of ovarian origin from small intestinal metastasis [10-11].

The management of NEC of ovary is similar to that of epithelial cancers and consist of surgical staging with complete removal of tumor with negative margins. The surgery may range from fertility sparing to radical debulking depending on patient age, desire and stage. In a study reported by Veras et al from the MD Anderson Cancer Centre the long-term survival was 22-68 months with standard surgery followed by adjuvant platinum-based chemotherapy [12]. If the tumors are not responsive to the standard platinum based chemotherapy, second-line chemotherapy regimens, such as cisplatin/etoposide, cisplatin/vinblastine, cisplatin/docetaxel, should be considered. In cases of local recurrence, a combination of chemotherapy with aggressive surgery and adjuvant radiation therapy may be useful. Compared to the epithelial ovarian malignancies, the prognosis is worse, dependent on histologic subtype.

In conclusion, the LCNC of ovary is a rare and aggressive tumor. The rarity of LCNCs makes it difficult to formulate general consensus on the standard therapy. In all ovarian malignancies, a differential of NEC should be kept in mind. Though rare, its incidence is increasing and it needs aggressive management.

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