Case Report

Primary pure large cell neuroendocrine carcinoma of ovary: An extremely rare entity

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Abstract

Primary large cell neuroendocrine carcinoma of ovary is an uncommon neoplasm with an aggressive biological behaviour. These carcinomas usually occur in association with epithelial-sex cord tumours; pure form being a rarity which can pose a diagnostic difficulty. A 42 year old female presented with a large abdominal mass and pain. Computed tomography revealed a heterogeneously enhancing solid left ovarian mass. Differential diagnoses on histopathology included large cell neuroendocrine carcinoma, carcinoid tumour, hepatoid carcinoma and malignant steroid cell tumour, not otherwise specified (NOS). Positive neuroendocrine markers including CD56, chromogranin, and NSE facilitated a correct diagnosis of large cell neuroendocrine carcinoma. Primary ovarian large cell neuroendocrine carcinomas are under-recognized aggressive tumours and must be considered as a differential in undifferentiated ovarian tumours. Histologic features and a panel of immunohistochemical stains should lead to the correct diagnosis.

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Introduction

Ovarian neuroendocrine tumours are rare neoplasms, accounting for 1 % of ovarian tumours.[1] The neuroendocrine tumours of ovary are classified into the categories: carcinoid tumour, small cell carcinoma of pulmonary type, and large cell neuroendocrine carcinoma (LCNEC). Ovarian LCNEC is defined as miscellaneous tumour by World Health Organization and is synonymous with undifferentiated carcinoma of the non-small cell neuroendocrine type (NSNEC).[2]Till date, 33 cases of ovarian LCNEC have been reported.[3] Most of them are associated with epithelial-sex cord tumours with pure form being described only in 4 cases.[3-6]Aggressive biological behavior of these tumours requires them to be diagnosed as specific entity. Herein, we present this rare case of primary ovarian NSCNEC occurring in a pure form.

Case Report

A 42 year old female, gravida 2, parity 2 presented with abdominal pain and gradually increasing mass for 6 months, along with loss of appetite and significant weight loss. She had undergone hysterectomy for uterine fibroid 10 months back. On physical examination, an irregular, non-tender mass was palpable per abdomen. Vaginal vault was normal. Serum CA-125 was 203.0 U/ml. Computed tomography revealed a large 13.2x12.6x15.1 cm, heterogeneously enhancing left adnexal mass having solid component with necrotic areas. Intraoperatively, the mass was solid with irregular surface, and was adherent to omentum, sigmoid colon and anterior abdominal wall. Left ovarian mass was excised along with left salpingectomy and omentectomy. Peritoneal washings taken were negative for malignancy.

Grossly, the ovarian mass measured 24x16x12 cm and was encapsulated, gray brown, having bosselated surface. Capsule was intact. Cut surface of the mass was predominantly solid, gray white and firm in consistency (Fig 1). Large areas of necrosis were present. Microscopic examination showed a tumour arranged as solid organoid nests, trabeculae and cords separated by thin fibrovascular septae (Figs 2, 3). Glandular differentiation was noted focally. Tumour cells were large and exhibited mild to moderate pleomorphism, vesicular nuclei, prominent nucleoli, abundant amount of eosinophilic to clear cytoplasm and well defined cell borders (Fig 4). Mitotic count was 10/10 HPF. Extensive areas as well as microscopic foci of necrosis were also identified along with some areas of dystrophic calcification. Lympho-vascular space invasion was not seen. No surface epithelial or tumour component other than neuroendocrine carcinoma was identified in multiple sections examined. The left fallopian tube and omentum were free of tumour.

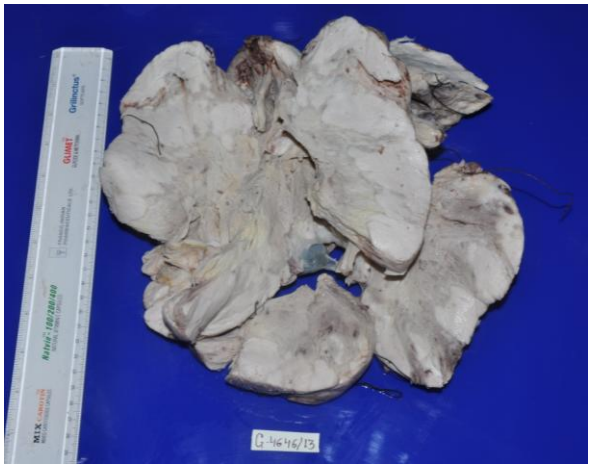

Figure 1: Cut surface of the tumor having solid grey white appearance.

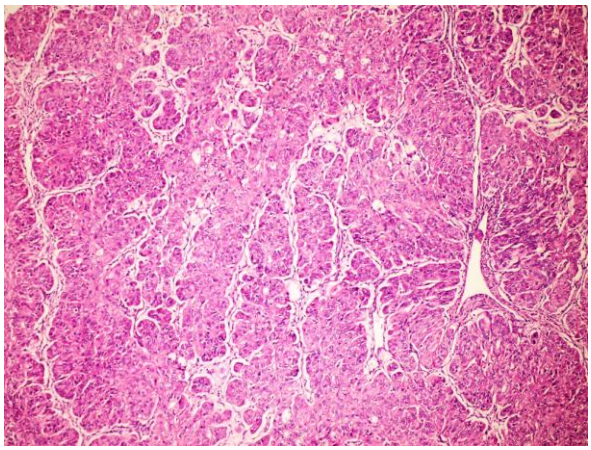

Figure 2: Organoid arrangement of the tumor cells (H&E stain, 100X)

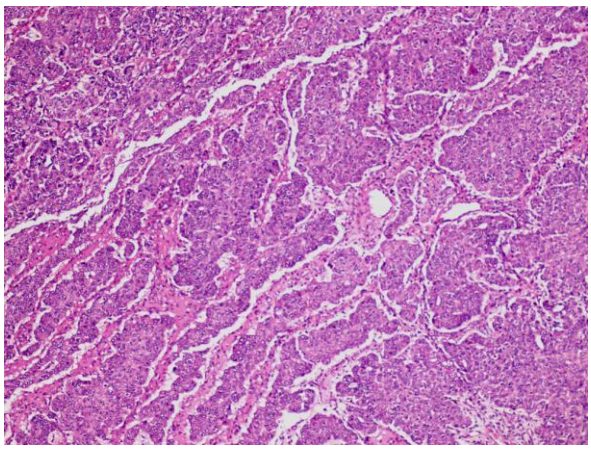

Figure 3: Trabecular arrangement of the cells (H&E stain, 100X).

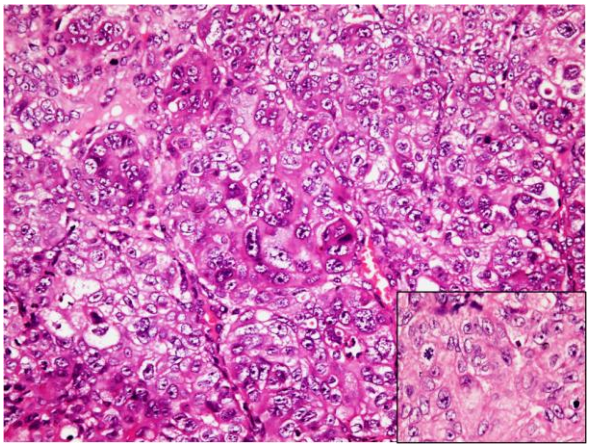

Figure 4: Higher magnification showing tumor cells with mild to moderate pleomorphism, vesicular nuclei, prominent nucleoli and high mitotic count. Inset highlights frequent atypical mitoses. (H&E stain, 400X).

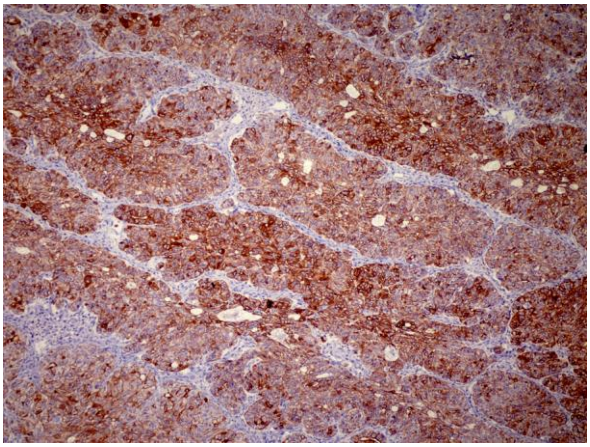

Figure 5: Diffuse strong CK7 positivity of the tumor cells (Immunostain, 100X).

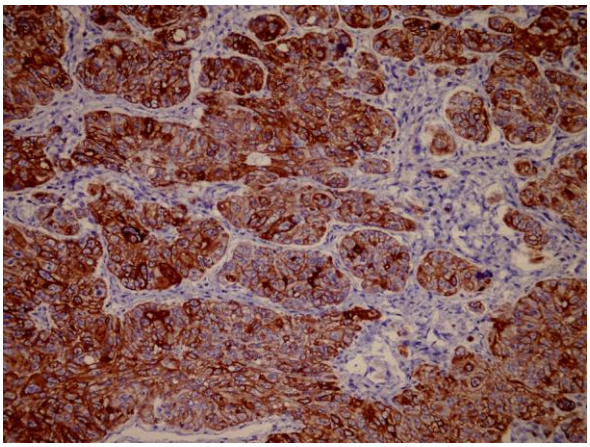

Figure 6: Tumor cells exhibiting strong CD 56 expression (Immunostain, 200X).

Immunohistochemistry (IHC) revealed diffuse strong positivity for pan-cytokeratin, cytokeratin 7 (Fig 5), CD56 (Fig 6), and neuron specific enolase while focal positivity for chromogranin. Tumour cells were negative for cytokeratin 20, α-fetaoprotein (AFP), hep par-1, inhibin and calretinin. Based on morphology and IHC findings, a final diagnosis of LCNEC was given. The case was classified as FIGO stage Ia and the patient is currently receiving adjuvant chemotherapy.

Discussion

Neuroendocrine differentiation may be expressed in a variety of ovarian tumours including surface epithelial tumours, Sertoli–Leydig cell tumours, teratomas, carcinoid tumour, small cell carcinoma of pulmonary type, and undifferentiated carcinoma of non-small cell neuroendocrine type.[7] LCNEC are quite uncommon tumours, the pure form being a rarity. These tumours can pose a diagnostic difficulty as was faced in the present case. Differential considerations in present case included LCNEC, carcinoid tumour, hepatoid carcinoma and malignant steroid cell tumour, not otherwise specified (NOS). Architectural resemblance to carcinoid tumour was present; however it was excluded on the basis of cell morphology, higher mitotic count and large areas of necrosis. Histomorphology was quite similar to that of hepatoid carcinoma, however, negative AFP and hep par 1 immunochemistry helped in its exclusion. Malignant steroid cell tumour, NOS was omitted on the basis of gross appearance, lack of nuclear atypia as well as negative inhibin and calretinin immune markers. Positive neuroendocrine markers including CD56, chromogranin, and NSE facilitated a correct diagnosis of LCNEC. A composite tumour was ruled out by examining multiple sections which did not reveal any component of surface epithelial, sex cord or germ cell tumour. Also, due to the homogenous appearance of gross specimen, it was unlikely to identify any other component on further blocking and sampling was thought to be adequate.

A more aggressive ovarian neuroendocrine tumour in the differential diagnosis is small cell carcinoma of pulmonary type. These differ from NSCNEC by their smaller cell size and less-intense immunohistochemical reactivity for cytokeratin and chromogranin.[5] The ovarian small cell carcinoma of hypercalcemic type must also be considered in the differential, especially given that many of these tumours may have a significant number of large neoplastic cells.[8]

One final but important diagnostic consideration is metastatic NSCNEC. NSCNEC has been reported to

arise in a variety of other organs including the lung, urinary bladder, cervix, and gallbladder. Pathological clues that an ovarian tumour is metastatic include bilateral ovarian involvement, multinodular growth pattern, and vascular invasion. Ultimately, clinical history will be of paramount importance in ruling out a metastatic tumour.[5]In view of large tumour size and unilateral involvement as well as lack of clinical and radiological evidence of pulmonary and gastrointestinal tumour, the present case was considered as primary in origin.

The prognosis of ovarian LCNEC is recognized to be extremely poor, and metastases almost always consist of neuroendocrine components.[2] Oshita et al.[3] documented a total 5-year survival of 34.9% in 33 LCNEC cases and also suggested that most LCNEC cases are as chemotherapy-sensitive as common ovarian cancer

Conclusion

In conclusion, LCNECs are under-recognized aggressive tumours and must be considered as a differential in undifferentiated ovarian tumours. Histologic features (i.e., a trabecular or nested growth pattern, extensive necrosis, a very high mitotic rate) and a panel of immunohistochemical stains should lead to the correct diagnosis.

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Competing Interests

None declared.

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