

## Large cell neuroendocrine carcinoma of the ovary: A pathologic entity in search of clinical identity

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**Core tip:** Large cell neuroendocrine carcinomas of diverse organs are rare. A brief overview of characteristics, diagnosis and treatment of this tumor type when occurring in the ovary is provided in this editorial.

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### Abstract

Large cell neuroendocrine carcinoma (LCNEC) of the ovary is a rare diagnosis and only a few dozen cases have been reported in the literature. It is characterized by large pleomorphic cells with large round or oval nuclei, presence of mitoses and staining for neuroendocrine (NE) markers such as chromogranin A, synaptophysin, neuron specific enolase. This editorial gives a brief overview of this histologic type of ovarian carcinomas. LCNEC of the ovary is a pathologic entity that may not be diagnosed purely on clinical grounds due to the similarity of its clinical features with those of the more common epithelial ovarian cancers. Nevertheless the diagnosis is worth-making from a practical point of view in order to consider treatments tailored towards the NE component if it is dominant or it becomes dominant during the natural evolution of the disease. Establishment of an international tumor registry with an accompanying tumor tissue bank of ovarian LCNEC could be a means of obtaining further knowledge on clinical characteristics and advance research on this rare entity. This will further inform on treatment strategies and could identify future molecular treatment targets.

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### INTRODUCTION

Large cell neuroendocrine carcinoma (LCNEC) of the ovary is a rare diagnosis and only a few dozen cases have been reported in the literature. It is characterized by large pleomorphic cells with large round or oval nuclei, presence of mitoses and immunohistochemical staining for one or more neuroendocrine (NE) markers such as chromogranin A, synaptophysin, neuron specific enolase or CD56<sup>[1]</sup>. LCNEC was first described in the lung and, although initially classified as a variant of large cell carcinoma (which is a non-small cell carcinoma), was noticed to behave more similarly to small cell carcinomas<sup>[2]</sup>. Similar neoplasms have been described arising from uterine body and cervix as well as other organs such as stomach, gallbladder, kidney, urinary bladder, prostate and parotid glands<sup>[3-8]</sup>. Rare metastatic cases with an unknown primary have been reported<sup>[9]</sup>. In most cases a concomitant epithelial ovarian component is present while presentation with pure large cell NE histology is less common<sup>[10,11]</sup>.

Presentation of LCNEC of the ovary is similar to the usual presentation of epithelial ovarian cancer with an abdominal mass, pain or distention and the diagnosis of

**Table 1 Summary of basic characteristics of ovarian large cell neuroendocrine carcinoma**

Pathologically distinct entity from epithelial ovarian cancers
Clinically similar presentation with common epithelial ovarian cancers
Often co-exists with non-neuroendocrine components
Several lines of data argue for a common origin of neuroendocrine and epithelial components (common co-existence, monoclonality analysis, neuroendocrine features arising in epithelial prostate cancer following treatment)
Treatment; suggested to be addressing the epithelial component except if neuroendocrine component is clearly dominant

a tumor is confirmed after radiologic evaluation (Table 1). Many of the cases are stage III or IV but earlier cases are often reported. Metastatic sites include the abdominal cavity and liver, typical of epithelial ovarian cancer, while other sites such as lung, brain and bone have been reported less commonly<sup>[10,12]</sup>. Thus a more diverse metastatic pattern in LCNEC of ovary compared to epithelial cancers is encountered. This is also exemplified in the skin metastasis seen in the accompanied case report. In some cases with available information metastatic deposits are solely of NE histology<sup>[12]</sup>.

Diagnostic pathology shows large cells usually with significant pleiomorphism, large nuclei with coarse and granular chromatin, prominent nucleoli, often significant mitotic activity and palisading with rosette formation. Immunohistochemistry confirms the diagnosis with positivity for one or more of the standard NE markers. Almost all cases evaluated have elevations of Ca-125 tumor marker. The great majority of cases have an adjacent epithelial ovarian cancer component, most often endometrioid and more rarely serous<sup>[13]</sup>. Of note the epithelial component often, but not always, expresses NE markers despite its differing morphology<sup>[1,13]</sup>. The pathologist needs to be alert to the diagnosis and include LCNEC in the differential diagnosis of undifferentiated carcinomas of both the ovary and the endometrium<sup>[14]</sup>.

Prognosis of LCNEC of the ovary is difficult to ascertain because of the rarity of the disease, the small number of reported cases and the lack of systematic population based studies or registry data. These shortcomings in addition to pathologic diagnosis inconsistencies prevent a solid data-based prognostication in comparison with epithelial ovarian cancer. The experience of many authors is that LCNEC of the ovary is more aggressive than epithelial ovarian cancer and may not respond as well to chemotherapy<sup>[13]</sup>. Nevertheless others have observed LCNEC to display chemosensitivity similar to other epithelial ovarian cancers<sup>[1,15]</sup>.

Pathogenesis could be an informative element for prognosis but most importantly for therapy. The fact that the great majority of ovarian LCNEC are diagnosed as part of a biphasic tumor combined with epithelial elements implies that the two components have a common cellular origin and represent two divergent clones of the same neoplastic process. Indeed a monoclonality analysis using human androgen receptor analysis disclosed a com-

mon origin of the two components in a case of composite LCNEC and mucinous epithelial ovarian carcinoma<sup>[16]</sup>. Similarly monoclonality was shown by the same authors in a case of composite LCNEC and cervical adenocarcinoma<sup>[17]</sup>. Thus, based on both the fact of common concurrence with epithelial components and the monoclonality studies, it appears that ovarian LCNEC and the even more rare endometrial LCNEC<sup>[18]</sup> represent a dedifferentiated clone of an epithelial carcinoma. This reminds the case of endometrial carcinosarcomas (malignant mixed müllerian or mesodermal tumors) in which the sarcomatous component is derived from an epithelial to mesenchymal transition program during which epithelial malignant cells obtain mesenchymal morphologic and functional properties that allow them to become mobile and metastasize<sup>[19]</sup>. The case of LCNEC in the prostate may be informative for the pathogenesis of LCNEC in general, arguing also for a common origin of epithelial and NE components. LCNEC of this origin often arise after patients are on androgen repression therapy for an epithelial prostatic carcinoma and may represent a result of therapy pressure on the tumor cells<sup>[7]</sup>. According to this theory prostatic LCNEC represent clones of the initial epithelial cancer that have become dominant following endocrine therapy because of their innate resistance to it. The minority of ovarian LCNEC cases in which no epithelial component is discernible (pure LCNEC) may represent either epithelial tumors in which the totality of cancer cells have undergone NE transition or true NE tumors derived from resident NE cells. A dual origin with concomitant transformation of epithelial cells and NE cells may be true in the exceedingly rare case of composite LCNEC and serous ovarian cancer<sup>[20]</sup>.

Regarding therapy, these pathogenic considerations imply that the optimal first line treatment for mixed epithelial and LCNEC ovarian tumors should be against the epithelial component. In case of pure LCNEC or NE element preponderance or selection of the NE clone post-treatment consideration should be given to a NE type combination (platinum-etoposide).

In conclusion, LCNEC of the ovary is a pathologic entity that may not be diagnosed purely on clinical grounds due to the similarity of its clinical features with those of the more common epithelial ovarian cancers. Nevertheless the diagnosis is worth-making from a practical point of view in order to consider treatments tailored towards the NE component if it is dominant or it becomes dominant during the natural evolution of the disease. Establishment of an international tumor registry with an accompanying tumor tissue bank of ovarian LCNEC could be a means of obtaining further knowledge on clinical characteristics and advance research on this rare entity. This will further inform on treatment strategies and could identify future molecular treatment targets.

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