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Pure large-cell neuroendocrine carcinoma of the ovary with a somatic BRCA1 mutation: The first reported case and the review of the literature

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Abstract

Pure large-cell neuroendocrine carcinomas of the ovary are extremely rare, so there is a lack of molecular information on this type of cancer. Herein, we presented a pure primary large-cell neuroendocrine carcinomas of the ovary in a 72-year-old female with a pathogenic somatic mutation at the c.5332+1g>a splice site of the BRCA1 gene and with no TP53 mutation. She was uneventful 32 months after the operation and chemotherapies. To the best of our knowledge, this is the first report of a BRCA1 somatic mutation in the ovary large-cell neuroendocrine carcinomas. Testing BRCA1/2 mutations in patients with large ovarian cell neuroendocrine carcinomas might provide an opportunity for their future target treatments. It would expand our understanding.

Keywords

Pure large-cell neuroendocrine carcinoma, rarity, ovary, gene sequencing, target treatment

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Introduction

Neuroendocrine neoplasms are uncommon invasive carcinomas in the ovary. In addition, neuroendocrine neoplasia is very poorly understood.[1] Thus far, only 25 cases of pure primary ovarian large-cell neuroendocrine carcinoma (LCNEC) have been reported in English literature.[1–8] To the best of our knowledge, only one reported case had a confirmed BRAC2 germline mutation through molecular testing.[2] In the present study, we introduce another unique case of pure large-cell neuroendocrine carcinoma (pLCNEC) of the ovary, which is the first one reported with the BRAC1 somatic mutation. We also summarize the clinicopathological features, immunohistochemical staining, molecular characteristics, differential diagnosis, and possible targeted treatment based on the molecular changes according to the existing literature.

Materials and methods

Case history

A 72-year-old female was admitted to our hospital for 3 months of anorexia and vague abdominal pain. Enhanced computed tomography of the head, chest, and abdomen showed a 5.8 × 5.0 cm mass in the pelvis with obvious uneven enhancement. A malignant tumor was suspected. There were no other abnormalities in other parts of the body. Tumor markers in blood including carcinoembryonic antigen, CA125, carbohydrate antigen 72-4 (CA 72-4), estradiol, chorionic gonadotropin, alpha-fetoprotein, sugar chain antigen CA19-9, human epididymis protein 4, testosterone, and postmenopausal risk ovarian malignancy algorithm (ROME) index[9] were all within the normal range.

Laparoscopic total hysterectomy, bilateral adnexectomy, abdominal paraaortic lymphadenectomy, and greater

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omentum resection were performed. During the operation, the tumor was found in the left adnexal area adhered to the abdominal wall, and enlarged lymph nodes were seen beside the abdominal aorta. No abnormalities were found in the uterus, right appendage, appendix, and greater omentum. There was also no effusion in the abdominal cavity.

Morphology and immunohistochemistry

Represented samples were taken from the resected uterus, bilateral adnexa, paraaortic lymph nodes, and the greater omentum. They were routinely processed.

The immunohistochemical antibodies were all ready to use and were processed using the automatic immunohistochemical staining machine (Aliya ®Automatic Stainer) according to standardized protocols. The primary antibodies used were attached in Supplemental Material 1.

Next-generation sequencing (NGS)

We provided the tumor formalin fixed paraffin embedded (FFPE) tissue samples and the patient's blood to the KingMed Diagnostics company to do NGS after obtaining the patient's informed and signed consent. The panel consisted of 52 genes believed to be closely related to ovarian cancer (Supplemental Material 2).

Review of the literature

The PubMed and Google Scholar databases were searched for relevant articles using the following keywords: "ovary and/or large-cell neuroendocrine carcinoma," "large gynecological cell neuroendocrine carcinoma," "large-cell neuroendocrine carcinoma and molecular," and "non-small-cell neuroendocrine carcinoma of the ovary." Only articles written in English were included. The abstracts of these articles were read, and detailed information about each pure primary LCNEC of the ovary was recorded from the full-length articles.

Results

Morphology and immunohistochemistry

The laparoscopic surgical specimens obtained from total hysterectomy, bilateral adnexectomy, paraaortic lymphadenectomy, greater omentum, and appendix were received and examined. The left accessory was cut into pieces, revealing a pile of gray-white to gray-red tissue measuring approximately $6 \times 5 \times 4$ cm in size, which was fragile. Extensive sampling of the tumor was performed, and no nodules or obvious abnormalities were found in the uterus, right accessory, greater omentum, and appendix. One of the lymph nodes, measuring approximately 3 cm in length, had a gray and fine-cut surface.

Microscopically, the left ovary was replaced by tumor cells. The tumor cells exhibited a solid and/or nestling arrangement, forming islands, trabeculae, and gland-like patterns. Geographic tumor necrosis was observed. The tumor cells were medium to large in size, with scattered giant cells visible. The nuclei were large, characterized by rough chromatin, prominent nucleoli, and a high number of mitotic figures (30/10HPF). The cytoplasm of the tumor cells was abundant, appearing eosinophilic or transparent (Figure 1(a) and (b)). Tumor cells were also identified in one of the lymph nodes. No other abnormalities were found in the other resected organs.

Immunohistochemically, the tumor cells showed diffuse expression of broad-spectrum CK, CK7, CD56, syn, chromogranin A (CgA), INI-1, RB1, and SMARCA4. Wild-type expression of P53 was observed, and the Ki67 proliferation index was approximately 60%. The tumor cells were negative for CA125, Pax8, GATA3, p63, P40, p16, CK5/6, SALL4, PLAP, epithelial membrane antigen (EMA), estrogen receptor (ER), progesterone receptor (PR), vimentin, CK20, and PD-L1 (Figure 1(c) and (f)).

NGS findings

The quality control parameters for the sequencing analysis were as follows: for tissue tDNA, the average sequencing depth was 3040.95×, and the ratio of bases with a sequencing depth greater than 500× was 97.68%. For the peripheral blood gDNA, the average sequencing depth was 645.31×, and the ratio of bases with a sequencing depth greater than 20× was 98.26%.

The analysis identified the presence of the BRCA1 exon20 c.5332 + 1G > A mutation, which had a mutation rate of 74.7% at a sequencing depth of 1668×. In addition, a copy number neutral loss of heterozygosity (cnLOH) was observed in BRCA1. No other abnormalities were detected in the analysis.

The treatment and outcome of our present patient

The patient was diagnosed with primary left ovarian pure LCNEC, with evidence of tumor cells present in the vessels and on the surface of the ovary. Metastatic carcinoma was also observed in one lymph node adjacent to the abdominal aorta. No tumor cells were detected in other organs. The pathological tumor stage was determined as pT1c-N1aM0, corresponding to FIGO (International Federation of Gynecology and Obstetrics) stage IIIA1.

Following the surgery, the patient underwent six cycles of chemotherapy with docetaxel (90 mg) and carboplatin (400 mg). Mild myelosuppression was experienced by the patient at the beginning of the chemotherapy, but it resolved without requiring treatment. After the chemotherapy regimen, no tumor recurrence was detected in the patient's pelvic

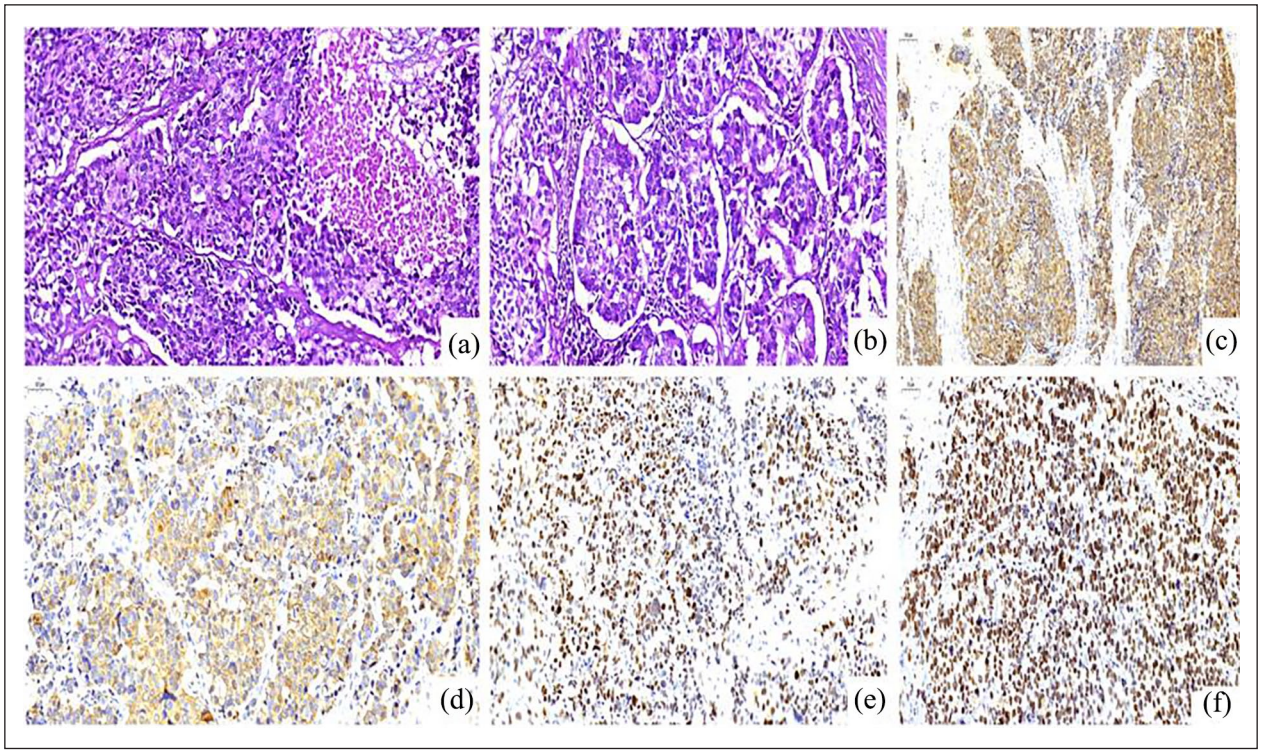

Figure 1. Morphology and immunohistochemical feature of pLCNEC. (a) The classical histological features of LCNEC of polymorphism, ample cytoplasm, and geographic necrosis (HE). (b) Organoid, rosette-like, gland-like structures of the tumor (HE). (c) Strong expression of chromogranin (IHC). (d) Expression of pan-CK (IHC). (e) Preserved retinoblastoma (RB) protein expression (IHC). (f) Preserved SMARCA4 expression (IHC).
Abbreviation: pLCNEC: pure large-cell neuroendocrine carcinoma of the ovary; HE: hematoxylin and eosin stain; IHC: immunohistochemical stain.

and abdominal cavities. At present, which is 32 months post-operation, the patient remains in good condition without any signs of recurrence or metastasis.

Review of the literature

After conducting a comprehensive literature review, a total of 25 cases of pure primary LCNEC were identified in English language publications.[2–5] The average age of the patients was 70 years, ranging from 27 to 77 years, with a mean age of 55 years. It is worth noting that only two cases underwent gene examination, and one of them was reported to have a germline BRAC2 mutation.

Most of the patients underwent surgical intervention and/or chemotherapy as part of their treatment. The outcomes varied among the cases, with 5 out of the 25 patients succumbing to cancer, while four others passed away due to complications unrelated to the cancer itself.

Discussion

Pure LCNEC of the ovary is exceptionally unconventional. Previous reports of LCNEC in the ovary have primarily been associated with other epithelial carcinomas or teratomas.[2–6] To date, including our case, only 26 cases of pure LCNEC of the ovary have been reported.

The diagnosis of LCNEC relies heavily on the morphological and immunohistochemical characteristics of the tumor. These features include the presence of neuroendocrine tumor structures such as organoid, trabecular, palisading, and/or rosette formations. The tumor cells typically exhibit vesicular chromatin, prominent nucleoli, abundant eosinophilic cytoplasm, and brisk mitotic activity (usually more than 10 mitoses per 2 mm^2), three times the diameter of lymphocytes, which is the distinguishing morphology differentiated LCNEC from small-cell neuroendocrine carcinoma. In addition, necrosis is often observed in LCNEC cases.[1] The presented case in this study exhibited the typical morphological features consistent with LCNEC.

Immunohistochemical analysis of the LCNEC tumor cells revealed positive staining for at least one of the neuroendocrine markers, such as CgA, syn, NSE, and CD56. Conversely, the tumor cells were typically negative for PAX8, WT1, vimentin, ER, PR, and EMA. The p53 protein exhibited a wild-type pattern, while the nuclear stains for SMARCB1/INI-1 and SMARCA4 were retained.[1–8]

Based on the above-mentioned histopathological and immunohistochemical features, the final diagnosis of our

case here was fully consistent with the diagnosis of pure LCNEC of the ovary.

Immunohistochemical stains can also provide useful information on whether patients are suitable for targeted therapies. Expression of HER2 and PD-L1 in cancer cells has been associated with favorable outcomes in certain patients.[10] Unfortunately, in our case, the two markers were negative.

The main differential diagnosis of LCNEC is high-grade serous carcinoma. In LCNEC, the neuroendocrine markers typically exhibit positivity, with at least one marker showing diffuse staining.[1] Although neuroendocrine markers can also be positive in some high-grade serous carcinoma of the ovary, their expression was often focal, and high-grade serous carcinoma can also express WT-1 and mutated type p53.[7–11] In challenging cases, the morphological characteristic of LCNEC should be given primary consideration for an accurate diagnosis.

pLCNEC in the ovary is not common. To the best of our knowledge, only 25 cases have been reported in English literature. Molecular examination has been limited in these cases, with only two cases undergoing gene analysis. One showed heterozygous germline mutation of BRCA2 exon 17, c.7976G>A, p.(Arg2659Lys), and a deleterious somatic mutation in TP53, c.600delT, p.(Leu201Cysfs*46); the other showed pathogenic mutations in telomerase reverse transcriptase (TERT) and TP53, without BRCA1/2 mutations.[2,6] In the present case, BRCA1 exon 20 c.5332 + 1G>A splice site mutation and cnLOH were found. The c.5332 + 1G>a splice site mutation of the BRCA1 gene is predicted to affect normal splicing and result in loss of protein function. The cnLOH observed in the gene copy number variation analysis may contribute to the development of ovarian cancer.[12,13]

Molecular studies on LCNEC in other parts of the body are also limited. Kim et al.[14] did gene sequencing in 467 cases of lung LCNEC and categorized the tumors into SCLC-LCNEC (TP53/RB1 co-mutated) and NSCLC-LCNEC (wild type for TP53 or RB1). Rekhtman et al.[15] found TP53 (78%), RB1 (38%), STK11 (33%), KEAP1 (31%), and KRAS (22%) in LCNECs, classifying them into SCLC-like (TP53+RB1 co-mutation/loss), NSCLC-like, and other SCLC-type subtypes.

Yaghmour et al.[16] studied 46 cases of neuroendocrine tumors of the ovary and 58 cases of small-cell carcinoma of the lung using NGS and Sanger sequencing (a 47-gene panel) and revealed that TP53 mutations in 25% of small-cell carcinoma (1/4) patients, BRCA2 mutations in 50% of small-cell carcinoma (1/2) patients. There were no LCNEC in their series. Our case had no TP53 or RB1 mutation.

In the case of multiple tumors occurring simultaneously, gene analysis can help determine their common origin by identifying a common molecular profile. In addition, gene mutations can aid in selecting targeted therapies or predicting prognosis. TP53 mutations have been associated with poor prognosis and early recurrence, while patients with BRCA gene mutations may benefit from Poly(ADP-Ribose) Polymerase 1 (PARP) therapy.[17] Our patient had a good prognosis which may be due to the lack of p53 mutations. However, further comprehensive studies are needed to deepen our understanding of these molecular characteristics and their clinical implications.

Surgical removal of the tumor is the primary treatment option for eligible patients with pure LCNEC of the ovary. Chemotherapy regimens commonly include paclitaxel, platinum, docetaxel, carboplatin, or cisplatin.[2–8] However, previous studies have reported poor treatment responses and dismal prognoses in LCNEC cases.[3,4] It has been observed that different molecular profiles of LCNEC tumors may respond differently to chemotherapy regimens. For example, patients with RB1 wild-type tumors showed worse response to paclitaxel + etoposide regimen compared to GTP regimen (platinum + gemcitabine or taxanes) (overall survival was 5.6 vs 9.6 months).[18]

Despite the historically poor prognosis associated with LCNEC, it is interesting to note that among the 26 reported cases of pLCNEC, only 20% of patients died of progressive cancer within 2–20 months. This suggests potential better prognoses in these cases, but further research is needed to investigate the factors influencing the outcomes of pLCNECs.

The presence of BRCA1/BRCA2 mutations in LCNEC tumors may provide a therapeutic target for clinicians, as these tumors may exhibit sensitivity to platinum-based chemotherapy and PARP inhibitors.[19] Patients with BRCA1/BRCA2 germline or somatic mutations, like the case described, could potentially benefit from targeted and more precise therapies. Our patient did not receive target treatment because of her uneventful course.

Conclusions

Pure LCNEC of the ovary is unusual. In our case, BRCA1 exon 20 c.5332 + 1G>A splice site mutation and cnLOH were found, and no TP53 or RB1 mutation existed. The patient had a relatively good prognosis in 32 months and seemed better than their counterparts in other parts of the body. It is unknown whether the patient's better prognosis is due to the lack of p53 mutations or the different location of the tumor. Thorough molecular characteristics, biological behavior, and optimal treatment options are needed.

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Code availability

None.

Data availability

All data generated or analyzed for the present study are included.

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Ethics approval

The study has been conducted according to the guidelines of the local ethical committee. Informed consent was obtained from the patient.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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Supplemental material

Supplemental material for this article is available online.

References

1. Talia KL and Ganesan R. Neuroendocrine neoplasia of the female genital tract. *Surg Pathol Clin* 2022; 15(2): 407–420.
2. Herold N, Wappenschmidt B, Markiefka B, et al. Non-small cell neuroendocrine carcinoma of the ovary in a BRCA2-germline mutation carrier: a case report and brief review of the literature. *Oncol Lett* 2018; 15(4): 4093–4096.
3. Tsuyoshi H, Yashiro K, Yamada S, et al. Role of diagnostic laparoscopy in patients with large cell neuroendocrine carcinoma of the ovary with cancerous peritonitis: case report and review of the literature. *J Ovarian Res* 2019; 12(1): 95.
4. Yang X, Chen J and Dong R. Pathological features, clinical presentations and prognostic factors of ovarian large cell neuroendocrine carcinoma: a case report and review of published literature. *J Ovarian Res* 2019; 12(1): 69.
5. Doğanay M, Cengaver N, Kızılkanat KT, et al. Pure large cell neuroendocrine carcinoma of ovary: a rare clinical entity. *J Exp Ther Oncol* 2019; 13(1): 55–58.
6. Vande Berg A, Segers K, Van de Vijver K, et al. Serous tubal intraepithelial carcinoma-like and pagetoid tubal metastasis of an ovarian large cell neuroendocrine carcinoma: peculiar metastatic growth patterns of a rare tumor. *Int J Surg Pathol* 2021; 29(3): 281–283.
7. Gupta P, Bagga R, Rai B, et al. Primary pure large cell neuroendocrine carcinoma of the ovary: histopathologic and immunohistochemical analysis with review of the literature. *Int J Clin Exp Pathol* 2021; 14(9): 1000–1009.
8. Veras E, Deavers MT, Silva EG, et al. Ovarian nonsmall cell neuroendocrine carcinoma: a clinicopathologic and immunohistochemical study of 11 cases. *Am J Surg Pathol* 2007; 31(5): 774–782.
9. Karlsen MA, Sandhu N, Høgdall C, et al. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. *Gynecol Oncol* 2012; 127(2): 379–383.
10. Eichhorn F, Harms A, Warth A, et al. PD-L1 expression in large cell neuroendocrine carcinoma of the lung. *Lung Cancer* 2018; 118: 76–82.
11. Karpathiou G, Matias-Guiu X, Mobarki M, et al. Ovarian neuroendocrine carcinoma of metastatic origin: clues for diagnosis. *Hum Pathol* 2019; 85: 309–312.
12. Saita C, Aruga T, Adachi M, et al. Germline variant of BRCA1 c.5332G>A has clinical features of hereditary breast and ovarian cancer syndrome. *Int Cancer Conf J* 2021; 11(1): 12–16.
13. Gorringe KL, Ramakrishna M, Williams LH, et al. Are there any more ovarian tumor suppressor genes? A new perspective using ultra high-resolution copy number and loss of heterozygosity analysis. *Genes Chromosomes Cancer* 2009; 48(10): 931–942.
14. Kim C, McGrath JE, Xiu J, et al. Genomic and immunologic characterization of large-cell neuroendocrine carcinoma of the lung. *J Clinic Oncol* 2021; 39(15_suppl): 8535.
15. Rekhtman N, Pietanza MC, Hellmann MD, et al. Next-generation sequencing of pulmonary large cell neuroendocrine carcinoma reveals small cell carcinoma-like and non-small cell carcinoma-like subsets. *Clin Cancer Res* 2016; 22(14): 3618–3629.
16. Yaghmour G, Prouet P, Wiedower E, et al. Genomic alterations in neuroendocrine cancers of the ovary. *J Ovarian Res* 2016; 9(1): 52.
17. Sa JK, Kim J, Kang S, et al. Somatic genomic landscape of East Asian epithelial ovarian carcinoma and its clinical implications from prospective clinical sequencing: a Korean Gynecologic Oncology Group study (KGOG 3047). *Int J Cancer* 2022; 151(7): 1086–1097.
18. Derks JL, Leblay N, Thunnissen E, et al. Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome. *Clin Cancer Res* 2018; 24: 33–42.
19. Le Page C, Amuzu S, Rahimi K, et al. Lessons learned from understanding chemotherapy resistance in epithelial tubo-ovarian carcinoma from BRCA1and BRCA2mutation carriers. *Semin Cancer Biol* 2021; 77: 110–126.