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Primary ovarian neuroendocrine neoplasia with concurrent large epithelial borderline ovarian tumor, coexistent with non-malignant pleural effusion and multiple uterine fibroids: a case report and review of the literature

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Abstract

Background Neuroendocrine neoplasms are a group of neoplasms often originating from the neuroendocrine cells in the gastrointestinal tract, pancreas, and respiratory tract. Neuroendocrine neoplasms rarely occur in female reproductive organs and less than a hundred cases of ovarian high-grade lesions have been reported in the literature so far. Fewer still are cases reported in the literature associated with a borderline epithelial tumor in the same ovary. Owing to the rarity of the condition, there is a lack of specific guidelines for staging, and optimal management of these tumors.

Case presentation We are reporting a case of primary ovarian neuroendocrine neoplasm in association with an epithelial borderline tumor. She is a 50-year-old Filipino woman who presented with nonspecific symptoms. Initial imaging revealed a large mass with suspicion of widespread metastasis. However, further imaging and laparotomy revealed early-stage neuroendocrine neoplasm, a large borderline epithelial tumor, with no evidence of pulmonary metastasis, despite having pleural effusion. She was lost to follow-up, presented again after a year with evidence of residual disease/metastasis, and was treated with chemotherapy.

Discussion and conclusion The case posed significant difficulty owing to a lack of typical symptoms at presentation, nonmalignant changes in lungs in imaging, and therapeutic challenges due to the noncompliance of the patient. This report highlights the importance of considering the combination of borderline tumors of the ovary with neuroendocrine carcinoma as a possible differential diagnosis in ovarian tumors, the use of imaging and specific bio-markers for early identification, timely treatment, and follow-ups.

Keywords Neuroendocrine neoplasms, Ovarian neoplasm, Primary ovarian neuroendocrine tumor, Ovarian NET, Gynecological NEN, Borderline mucinous tumor of the ovary

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Introduction

Neuroendocrine neoplasms (NENs) are a group of neoplasms often originating from the neuroendocrine cells in the gastrointestinal tract, pancreas, and respiratory tract from the tracheobronchial system. NENs arise from the endocrine cells derived from the neuroectoderm, neural crest, and endoderm [1, 2]. These are rarely seen in other organs and are very rare in the female reproductive tract [3–5]. According to the World Health Organization's (WHO) updated classification guide (fifth edition) for gynecologic NEN, well-differentiated low-grade (grade [G] 1 and G2) lesions are termed neuroendocrine tumors (NETs; carcinoids) and poorly differentiated high-grade (G3) lesions are called neuroendocrine carcinomas (NEC) [6]. Among the female reproductive tract tumors, primary NENs constitute only $\leq 2\%$. The most common site of gynecological NENs is the cervix ($>50\%$); these NENs are typically aggressive and poorly differentiated [5, 7, 8]. Only 16% of gynecological NENs have primary ovarian origin [9, 10].

Carcinoid tumors are commoner; they are low-grade and limited to the ovary [11]. They are of insular, trabecular, strumal, and mucinous types. Well-differentiated NETs are characterized by pale eosinophilic cytoplasm with round to ovular nuclei, inconspicuous nucleoli, and fine to coarsely granular chromatin described as "salt and pepper" [11, 12]. NECs are further classified as small-cell, large-cell, combination small-cell, and combined large-cell NECs [9]. Approximately 90 cases of small- and large-cell ovarian carcinomas are reported in the literature so far [11, 13–16]. The tumor cells in NECs are pleomorphic, contain irregular nuclei, and have a high mitotic index, necrosis, and a few secretory granules in the cytoplasm [11, 12].

Ovarian carcinoids can be primary or metastatic, and the former is more common. The median age at diagnosis is 55 years (17–83 years) [17]. Carcinoid tumors usually present with facial flushing, diarrhea, and abdominal cramping, called carcinoid syndrome [18]. The primary ovarian carcinoids can be associated with germ cell tumors of the ovary such as dermoids, which usually leads to poor prognosis [11, 19, 20]. However, primary NEC associated with a borderline mucinous ovarian tumor in the same ovary has not been previously reported. When in close proximity, tumors can be collision or composite. While collision shows clear geographic polarization, with no admixture or transition of the two neoplastic components, composite tumors are multidirectional differentiation of a single neoplasm [21]. Despite the characteristic histology, the diagnosis requires immunohistochemistry for confirmation. The most commonly used biomarkers for NENs are synaptophysin, chromogranin A, CD56, CD57, and synaptic vesicle protein 2 (SV2). However, as no specific biomarkers are highly accurate in diagnosing and determining the prognosis, a combination of imaging studies and circulating biomarkers are used to obtain further information on tumor behavior [11]. The staging of these tumors is done using either the International Federation of Gynecology and Obstetrics (FIGO) system or the American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) staging systems for ovarian cancers. The management of NECs includes surgery and chemotherapy as per the staging.

Through this report, we present a case of primary high-grade NEN (NEC) of the ovary in collision with a borderline epithelial tumor, presenting diagnostic challenges due to the associated large borderline mucinous tumor, nonmalignant pleural effusion, and a lack of typical symptoms at presentation. There were therapeutic challenges due to the non-availability of standard guidelines for the management of gynecological NENs and the non-compliance of the patient.

Case report

A 50-year-old Filipino female working as a domestic help presented to the outpatient department of the hospital in March 2022 with abdominal pain, a history of weight loss, and irregular vaginal bleeding for 2 months. On further questioning, she revealed fatigue, and on-and-off diarrhea for the past month. There were no other complaints.

Her menstrual history showed that she had menarche at the age of 12 years and had regular cycles of 28–30 days with 4–5 days of bleeding, without any intermenstrual or postcoital bleeding. Her last normal menstrual cycle was 2 months back. She had had irregular vaginal bleeding for the preceding 2 months since then. She was married with two children born vaginally. She is not known to have any gynecological illnesses such as fibroids and had not received any treatment for any gynecological problems. She had not received the human papillomavirus vaccine and had been following her cervical cancer screening with normal results. She did not report any chronic medical illnesses, surgery, or allergies. Her family history was negative for any gynecological or familial cancers. She denied any long-term medication, habituations, or addictions. She had not been sexually active for the last 14 years after separation from her husband.

On examination, she was conscious, cooperative, alert, and well-oriented to person, place, and time with normal mood and behavior. She had mild conjunctival pallor, but no icterus, cyanosis, or clubbing. There was no pedal edema or enlarged lymph nodes. The thyroid gland was normal to palpation. The respiratory system examination showed a respiratory rate of 22 breaths per minute and evidence of free fluid in the right pleural cavity.

The abdomen was distended and soft to palpation, with a large non-tender cystic mass arising from the pelvis. The bowel sounds were normally heard. Speculum examination showed cervicitis and revealed a large adnexal mass on the left side and a bulky uterus with restricted mobility. The examination of other systems revealed no abnormality. Imaging and other investigations were ordered, as the symptoms suggested a possible malignant etiology. The imaging revealed pleural effusion. Further imaging revealed a possible ovarian malignancy with suspicion of pulmonary metastasis (Figs. 1, 2). A thoracocentesis was done, but the fluid was negative for malignant cells (Table 1).

A staging laparotomy was done by total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy on 22 March 2022. Intraoperative findings showed an enlarged left ovary with a large complex multicystic mass containing mucinous and serous fluid. The size was 20 cm × 20 cm, and it was adherent to the left ureter, fallopian tube, and the small intestine posteriorly, weighing approximately 2245 g. Slightly hemorrhagic ascitic fluid around 600 mL. Her enlarged right ovary measured 5 × 5 cm, with a endometriotic cyst adherent to the posterior peritoneum and cecum. She had an enlarged 10-week size uterus with multiple fibroids. The appendix, omentum, and other visceral surfaces looked normal.

The histopathology report showed chronic cervicitis, an enlarged uterus, proliferative endometrium, and a benign endometrial polyp. There were multiple intramural leiomyomas with focal degenerative changes. The right ovary showed a hemorrhagic cystic corpus luteum and an unremarkable right tube. The left ovarian capsule had ruptured in two areas, but the surface was not involved. There were solid and cystic areas in the left ovary. The solid area showed an NEC of 6.5 × 4.2 cm, and the cystic area revealed a large mucinous borderline tumor of 23.0 × 18.0 cm, without any evidence of stromal invasion.

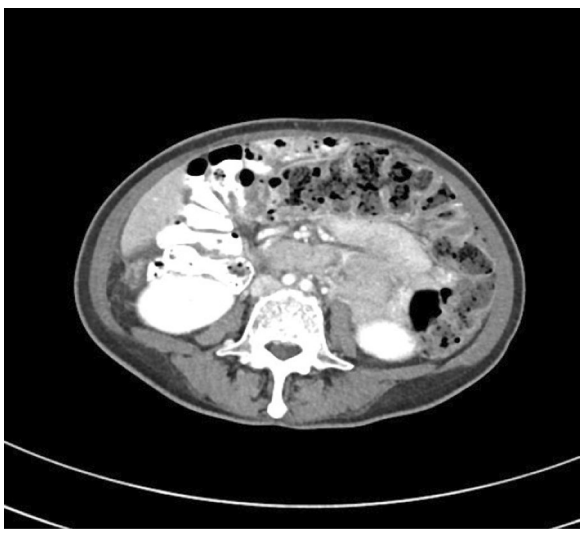

Fig. 1 Computed tomography scan of the pelvis. A large, hypodense cystic mass with multiple septations and solid components is seen within the abdomen, appearing to be arising from the left adnexa. It measures 19 × 22 × 9 cm in size. It is displacing and compressing the bowel loops. The right ovary is enlarged in size measuring of 4.6 × 4 cm

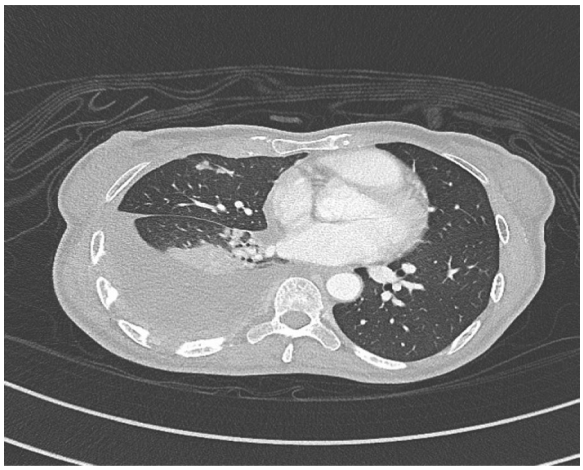

Fig. 2 Computed tomography scan of the lungs. Patchy ground-glass densities are seen in the peri-broncho-vascular region in the right lung. Pulmonary nodules in the anterior segment of the right upper lobe and small fissural-based nodules are seen at the level of the anterior basal segment of the right lower lobe likely to be granulomas. Fibroatelectatic changes are seen in the middle lobe. No traction bronchiectasis or honeycombing was seen. No enlarged lymph nodes are seen in the mediastinum and bilateral hilar regions. Minimal pleural effusion on the right side, but no pleural effusion on the left side. No evidence of pericardial effusion

The left fallopian tubal surface involvement was not identified (Figs. 3, 4, 5). The immunohistochemistry and tumor markers further confirmed the tumor to be NEN (Table 2). There was no evidence of malignancy in the omental biopsy, and the regional lymph nodes were not involved. The pleural effusion resolved after drainage and did not recur. The report stated the high-grade tumor showed an organoid pattern of mild pleomorphic cells with vesicular nuclei, coarse chromatin (salt and pepper type), and many mitotic figures. Differential diagnosis includes NEN or sex cord stromal tumor or high-grade epithelial carcinoma. Cancer staging is presented below:

- Cancer staged: staging form: ovary; AJCC V7-clinical; FIGO Stage IA (T1a, N0, M0)
- Cancer staged: staging form: ovary; AJCC V7-pathologic; FIGO Stage IA (T1a, N0, cM0)

Table 1 Imaging results

Serial number	Date	Investigation	Findings	Comment
At initial presentation				
1.	14/03/2022	Chest X-ray	Large right pleural effusion with near total underlying collapse of the right lung.	Thoracocentesis was done, and cytology was negative for malignant cells.
2.	15/03/2022	CT of the chest	Pulmonary nodule measuring 5.6 × 5 mm in size is seen in the anterior segment of the right upper lobe. Fibroatelectatic changes are seen in the middle lobe. Minimal right pleural effusion.	Nodule suspicious of metastatic nodule. Chest drainage catheter in place.
3.	14/03/2022	CT of the CAP and neck	Pulmonary nodule in the anterior segment of the right upper lobe. Large amount of pleural effusion.	Node suspicious for metastasis. Requires follow-up.
4.		CT of the abdomen and pelvis	Large mass with solid and cystic areas most likely arising from the left adnexa and reaching up to hepatic flexure of the colon, causing the displacement of the bowel loops, mild left hydro-nephrosis, hydroureter, and mild ascites. Enlarged right ovary. Solid lesion at the superior lateral wall of the uterus, likely representing a subserosal fibroid.	Features are suggestive of a malignant ovarian tumor.
Follow-up after 1 year				
5.	23/02/2023	CT of the abdomen	Multiple recurrent and metastatic abdominal deposits.	ECOG 0–1. Malignant neoplasm of ovary (CMS HCC).
		CT of the chest	Moderate right-sided pleural effusion with multiple right-sided subpleural metastatic deposits.	
Second follow-up				
	23/03/2023	CT of the chest	Persisting moderate pleural effusion with diffuse right pleural thickening and multiple enhancing pleural nodules.	
Third follow-up				
	08/05/2023	Ga68 DOTATOC scan	Focal somatostatin overexpression in the left pelvic region in the projection of the surgical clips. Marked right pleural effusion with marginal intercostal somatostatin overexpression and focal somatostatin overexpression in the right lung. Focal somatostatin overexpression the right midthoracic rib with corresponding sclerotic changes.	Possible residual disease. - Metastasis - Bone metastasis
Fourth follow-up				
	16/06/2023 (after four cycles of cisplatin/etoposide)	CT scan	Persisting large complex pelvic mass. Persisting moderate right pleural effusion with right lung pulmonary nodule and diffuse pleural thickening multiple enhancing pleural nodules. Decreasing size and enhancement of the omental/peritoneal/umbilical/right lower anterior abdominal wall/pelvic and right inguinal lymph nodes.	Residual/metastatic disease. Partially responding to chemotherapy.

Table 1 (continued)

Serial number	Date	Investigation	Findings	Comment
Fifth follow-up				
	01/09/2023 (after eight cycles of cisplatin/etoposide)	CT scan	Mild increase in the amount of right moderate pleural effusion and underlying passive lung atelectasis. Mild increase as regards both the size and numbers of right pulmonary and pleural nodules. Newly developed heterogeneously enhancing soft tissue mass density seen along the lower right chest wall likely metastatic. Increasing in terms of both the size and enhancement of the multiple soft tissue density metastatic peritoneal/omental deposits as well as soft tissue deposits in the umbilicus and right lower abdominal wall. - Persisting large irregularly shaped soft tissue density pelvic mass adherent to adjacent bowel loops.	Non-responder to cisplatin/etoposide. She was switched to second-line chemotherapy with FOLFIRI.

CAP chest–abdomen–pelvis, *CMS* Centers for Medicare and Medicaid Services, *CT* computed tomography, *FOLFIRI* leucovorin calcium (folinic acid)/fluorouracil/irinotecan hydrochloride, *HCC* Hierarchical Condition Categories

- Cancer staged: staging form: Surveillance, Epidemiology, and End Results (SEER) Summary Staging—SEER Summary: localized (localized)

Oncology multidisciplinary meeting was done, and the pathologic tumor stage was changed from pT1a to pT1c1 and the FIGO stage from IA to IC1 (surgical spill present) for the left ovarian NEC. The case was discussed in the multidisciplinary team, and she was referred to oncology for systemic chemotherapy. However, the patient did not report for chemotherapy and was lost to follow-up.

The patient again presented in February 2023 to the emergency department with abdominal pain. She was diagnosed with recurrent metastatic NEC, given the previous diagnosis and imaging findings (Figs. 6, 7; Table 1). The patient was started on chemotherapy with cisplatin/etoposide (Table 1) and continued eight cycles until Sept 2023. There was an inadequate response to the chemotherapy, so second-line treatment with leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride (FOLFIRI) was started. From the time of follow-up until December 2023, she had responded to five cycles of treatment with evidence of remission and symptomatic improvement.

Discussion

NENs are uncommon tumors of the female genital tract, and are rare in the ovaries. Very few cases of ovarian NEC have been reported in the literature and fewer in association with a mucinous borderline tumor and coexistent nonmalignant pleural effusion. When two tumors are in close proximity, they can be due to collision or composite in nature [21]. Owing to the development and widespread use of various diagnostic technologies, the incidence of NENs has been gradually increasing in recent years.

Classification of ovarian NENs

The 2014 WHO classification of tumors did not include a separate classification for ovarian NENs. The broad categorization consisted of carcinoid tumor (at least four subtypes), small-cell NEC of the ovary of pulmonary type (SCCOPT), small-cell NEC of the ovary of hypercalcemic type (SCCOHT), large-cell NEC, and rare tumors such as paragangliomas and pheochromocytomas [5]. In the new 2020 WHO classification, all ovarian NET are included as carcinoid tumors, and SCCOPT was incorporated in the small-cell NEC (not a separate category) [6]. However, it can be argued that SCCOHT needs to be considered a separate, non-NEN-related entity in view of the pathologic markers and molecular subclassification [22–26].

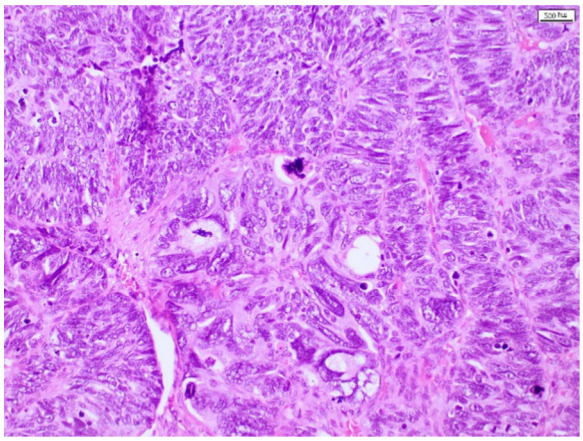

Fig. 3 Nested and trabecular pattern tumor composed of pleomorphic cells with scanty cytoplasm and prominent nucleoli and many atypical mitotic figures present (hematoxylin and eosin 200× original magnification)

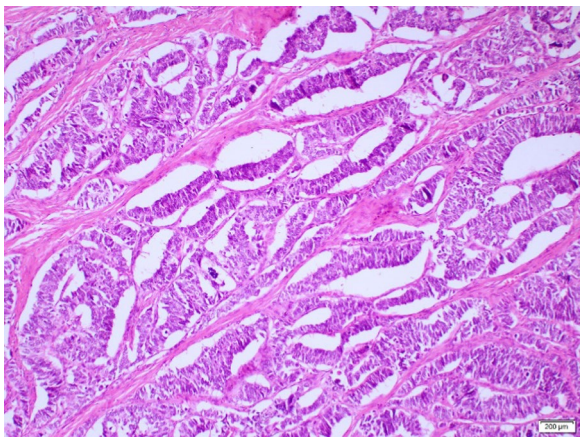

Fig. 4 Showing mostly trabecular pattern of tumor cell arrangement of the same tumor (hematoxylin and eosin 100× original magnification)

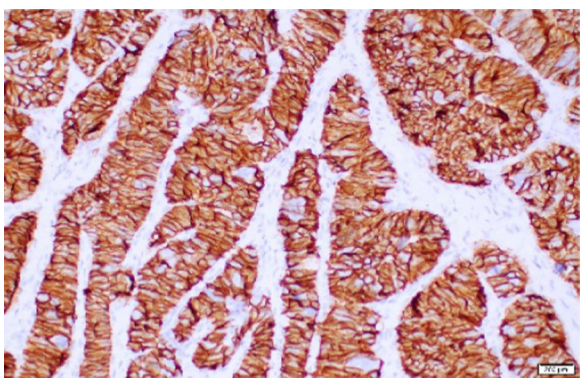

Fig. 5 CD56 immunomarker is diffuse-membranous-positive in the tumor cells; 100× original magnification

Table 2 Tumor markers and immunohistochemistry

Date	Investigation	Findings
15/03/2022	CA 125	622.0 (high) (normal < 35 U/mL)
	CA 19-9	12.9 (normal < 39 U/mL)
28/04/2022 Immunohistochemistry	Ki-67	90%
	CD56 Chromogranin Synaptophysin TTF-1	Positive in NEN cells Chromogranin at 67 U/L
	CEA CDX2 PAX8	Positive in the adjacent mucinous borderline tumor Negative in the NEN cells
	Calretinin Inhibin	Negative in tumor cells

NEN neuroendocrine tumor, *CA* carcinoma antigen, *Ki-67* antigen Kiel 67, *TTF-1* thyroid transcription factor-1, *CDX2* caudal-type homeobox 2, *PAX8* paired-box gene 8, *CEA* carcinoembryonic antigen

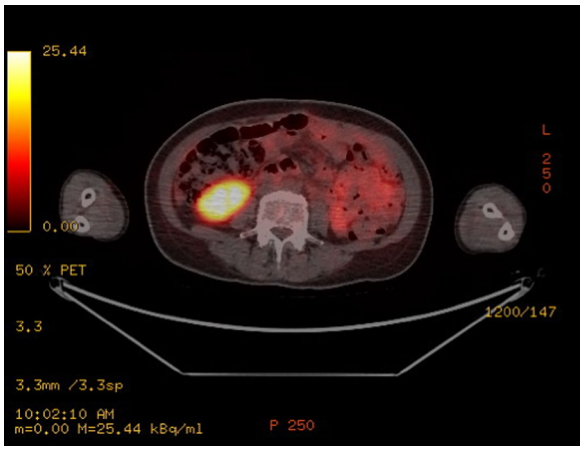

Fig. 6 Positron emission tomography. Focal somatostatin overexpression in the left pelvic region in the projection of the surgical clips, raising the possibility of residual disease

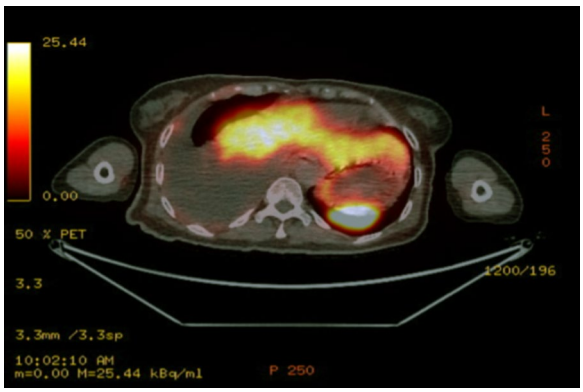

Fig. 7 Marked right pleural effusion with marginal intercostal somatostatin overexpression and focal somatostatin overexpression in the right lung, all together suspicious of metastatic disease

The large-cell ovarian NECs are aggressive tumors with a median survival of less than a year [11, 14, 15]. Very rarely, the NECs are combined with the other germ cell and ovarian epithelial tumors of the ovary [27, 28]. Only about 30% of patients with ovarian NETs show clinical symptoms such as facial flushing, diarrhea, and abdominal cramping. The differential diagnosis of NET in the ovary includes germ cell tumors, sex cord and granulosa cell cancers, other gynecologic cancers, and metastatic neoplasms [29]. It is important to differentiate the NET from NECs in the ovary. While it is much explored in gastrointestinal and pancreatic NENs, the guidance is unclear and overlapping in ovarian NENs. The classification of NEC in our patient was based on distortion of organoid features, somatostatin expression, mitotic figures, and the presence of coagulative necrosis. A highly unique feature of this case was identifying epithelial and NEN tumors in collision, in the absence of typical symptoms of carcinoid syndrome. Although there was suspicion of pulmonary metastasis at presentation, the pleural fluid was negative for tumor cells, and effusion resolved after drainage. In the absence of other evidence of metastasis, the computed tomography (CT) findings can suggest infection, which could have subsided with therapy given for laparotomy. She developed metastasis, most probably due to noncompliance to chemotherapy, as evidenced by imaging results after a year. Furthermore, the metastatic disease did not respond to primary chemotherapeutic agents.

Diagnosis and the role of biomarkers in NENs

Most of the ovarian NETs originate from one tissue type (monodermal subtype) of teratomas. The resulting tissue can be thyroid tissue (struma ovarii), neuroendocrine tissue (carcinoid), or a combination of both (stromal carcinoids) [30]. They have characteristic histology but require additional immunohistochemistry for confirmation of diagnosis. Many biomarkers such as synaptophysin, chromogranin A, SV2, and insulinoma-associated protein 1 (INSM1) are used for NENs. Strumal carcinoids stain positively with neuroendocrine markers (carcinoid component) and thyroglobulin and thyroid transcription factor (TTF1; thyroid component). The Ki-67 proliferation index in primary ovarian carcinoid tumors of insular, trabecular, and strumal types is usually less than 1% [31]. The expression of somatostatin receptors on the NEN cell surface in well-differentiated tumors enables diagnostic imaging (positron emission tomography [PET])/CT) and therapeutic procedures [32]. However, as no specific biomarkers are highly accurate in diagnosing and determining the prognosis, a combination of imaging studies

Table 3 Biomarkers for ovarian NENs

				References
Immunohistochemistry	Ki-67	90%; mucinous cyst was border-line without stromal invasion.	Ki-67 antigen is overexpressed in malignant ovarian epithelial tumors. The higher expression signifies an aggressive tumor and a poorer prognosis.	[34, 38]
	Chromogranin A	Positive in NEN cells.	It is a nonspecific marker and can be increased in non-neoplastic conditions such as inflammation. However, it is sensitive to rectal and ovarian NEN at higher levels (cut off 84–87 U/L).	[11, 39]
	CD56	Positive in NEN cells.	An immunological marker for various types of ovarian tumors such as granulosa cell tumors, Sertoli-stromal cell tumors, large and small cell NECs, and ovarian NETs. Can differentiate neoplastic tumors from normal ovarian follicles.	[40]
	Synaptophysin	Positive in NEN cells.	A common marker of neuroendocrine differentiation used in combination with other markers for diagnosing NENs. Positive results are associated with better or poorer prognosis in NENs at different sites.	[41]
	TTF-1	Positive in NEN cells.	TTF-1 is used in the diagnosis of lung and thyroid carcinomas. May be positive rarely in serous and endometroid ovarian carcinoma.	[42]
	• CEA • CDX2 • PAX8	Positive in the adjacent Mucinous borderline tumor. Negative in the NEN cells.	CEA is a nonspecific serum biomarker that is elevated in various malignancies, including mucinous ovarian cancer. CDX2 and PAX8 are positive in epithelial tumors and differentiate epithelial from metastatic tumors. - PAX8 positivity indicates primary NETs in the thyroid.	[43] [44]
	Calretinin inhibin	Negative in tumor cells.	Calretinin is positive in sex cord stromal tumors and is associated with a hyperandrogenic state. Inhibin is a tumor marker for mucinous and granulosa cell tumors.	[45] [46]
	INSM1	Not done in our patient.	Equally or less sensitive but more specific for NETs than other markers such as synaptophysin and chromogranin.	[47, 48]

NET neuroendocrine tumor, *CA* carcinoma antigen, *TTF-1* thyroid transcription factor-1, *CDX2* caudal-type homeobox 2, *PAX8* paired-box gene 8, *INSM1* insulinoma-associated protein 1

and circulating biomarkers can be used to obtain further information on tumor behavior [11]. A summary of those are described in Table 3. Ki-67 positivity depicts the differentiation of NETs according to previous classification. Ki-67 of < 20% shows NET-G1 and G2, while over 20% is seen in NET-G3 and NEC (NET G3 with still organoid histology or NEC without organoid histology [33, 34]. In our case the tumor had no organoid histology with 90% positive Ki-67. In addition, somatostatin receptor subtype 2A (SSTR2A) expression is the basis of somatostatin receptor functional imaging (e.g., Ga 68-DOTATATE), and is useful for evaluating the presence and extent of disease [35]. It is useful in the distinction of NET (usually strongly positive) from NEC (only one-third are positive, with expression typically weaker than in NET) and for assisting in treatment decision-making for patients [36, 37]. It is also effective in locating the site of an unknown primary in patients with NEC who present with metastatic NEC but no known primary tumor [37].

Treatment and prognosis of ovarian NENs

Primary ovarian NENs are rare tumors. Hence, there are no universally agreed-upon parameters for guiding the treatment or predicting the prognosis of these tumors. Surgical treatment in the form of hysterectomy with bilateral salpingo-oophorectomy along with debulking is usually recommended [9]. Lymphadenectomy provides prognostic information, as stage is associated with survival, but has not proven to lower the mortality [49, 50]. While somatostatin inhibitors such as octreotide or lanreotide can be used in carcinoids, aggressive multi-agent chemotherapy and potentially adjuvant radiotherapy may improve survival in NECs [13, 51]. Ovarian NECs are largely reported in the literature as isolated cases, with no specific treatment guidelines. Genetic and infectious agents have been implicated in the etiology of diseases [52, 53]. NENs have been studied in association with microbiome and multiple endocrinal neoplasia (MEN-1) by various studies. However, this has not been explored for our patient [54, 55].

A recent study involving 431 women with NENs identified age, AJCC stage, treatment, and histological type as independent prognostic factors of ovarian NECs. The overall survival and cancer-specific survival were reported to be better for early-stage cases treated with surgery alone, as compared with the advanced stages where more comprehensive treatment is administered to improve survival [56]. Metastatic ovarian NECs are typically associated with a poor prognosis. Although our patient presented with an early-stage disease at first,

noncompliance with follow-up resulted in metastasis and a poor response to etoposide/cisplatin. Currently, she is responding to the chemotherapy and following up regularly. This is in contrast to a recent case report showing that, despite extensive metastasis at presentation, the patient responded well to a combination of surgical resection and etoposide and cisplatin [18]. Another case series of three patients with primary ovarian NENs showed a poorer prognosis of small-cell carcinoma diagnosed early in the disease than a carcinoid, signifying the aggressive nature of NECs [31].

The limitations of this report are that it is a single report, the case is still under follow-up till the time of preparation of the manuscript, and the final outcome is awaited. However, the strengths are the rarity of the case, unusual presentation, diagnostic challenges, inclusion of images of diagnostic procedures and histology depicting the findings, involvement of a multidisciplinary team from the beginning in all stages of management, and a review of the literature to help in decision-making about the diagnosis and management of such cases.

Conclusion

Although primary NENs are rare in ovaries, early diagnosis, staging, and commencement of treatment lead to higher survival rates. This case report highlights the importance of considering the combination of borderline tumors with NENs as a possible differential diagnosis in ovarian tumors, the use of imaging, and specific biomarkers for early identification, timely treatment, and follow-ups. It also depicts the effective use of second-line chemotherapeutic agents in case of non-responders. Further studies are necessary to determine the best possible management of gynecologic NENs in women.

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Author contributions
Mariam Mohsin (MM), Rajani Dube (RD), Dina Hamza (DH), Mavra Ali (MA), and Heena Garg (HG) contributed to this research in the following roles: MM, RD, and DH designed the study, collected the patient data, and coordinated the research. RD and MM wrote the manuscript. MA, HG, and DH edited the manuscript and coordinated with the other authors. All authors have read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
It was reviewed by institutional review board. Medical Research Section, Dubai Scientific Research Ethics Committee has also reviewed the proposal and exempted it from further need for ethical approval because of written consent from the patient for a single case report, in line with the policy of the committee.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
None.

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