Case report

Mixed neuroendocrine/Non-neuroendocrine neoplasm (MiNEN) of gastrointestinal lineage arising in an ovarian mature cystic teratoma

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1. Introduction

Mature cystic teratoma (MCT) is an encapsulated germ cell tumor composed of well differentiated derivations from at least two of the three germ cell layers. Malignant transformation of ovarian MCT is rare, occurring in only 1–2% of cases. It is commonly seen in postmenopausal women, with squamous cell carcinoma representing the most common type of malignancy. Adenocarcinoma and neuroendocrine tumors arising from MCT are unusual and are exceedingly rare as a synchronous event.

Here, we are reporting a case with a unique occurrence of mixed well differentiated neuroendocrine and non-neuroendocrine neoplasm (MiNEN) arising in the background of MCT in a young woman.

2. Informed consent statement

A written informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Case report

A 20-year-old nulligravida presented with left lower quadrant abdominal pain and cramping. On CT, she had complex bilateral adnexal masses. The right mass (5.9 cm) had a homogeneous echogenic appearance while the left (7.3 cm) had well circumscribed borders with cystic and solid components. The uterus and cervix were unremarkable. She was initially taken to the OR at an outside hospital by a general gynecologist who removed the left fallopian tube and de-torsed the ovary but did not feel comfortable with performing a cystectomy and thus she was sent to the University for further management. She was then taken to the operating room with gynecologic oncology for bilateral cystectomy as patient strongly desired to retain as much normal anatomy as possible given her young age. Of note, the operative report from the general gynecologist noted that grossly, the ovaries were consistent with benign dermoid cysts and thus no further tumor markers were obtained. She then underwent bilateral ovarian cystectomy with gynecologic oncology where intra-operatively the findings were consistent with benign dermoid cysts and thus no further tumor markers were obtained. She then underwent bilateral ovarian cystectomy with gynecologic oncology where intra-operatively the findings were consistent with benign dermoid and a complete abdominal and pelvic survey were performed without evidence of concerning findings/metastatic disease were found and thus no intra-operative frozen section analysis was obtained. Grossly, the right ovarian cyst was received as disrupted tissue fragments; further sectioning showed friable material and hair. The left adnexal cyst was received intact; sectioning revealed a solid, ill-defined mass with an adjacent cyst containing friable material and hair (Fig. 1).

Microscopic examination of solid areas of the left adnexal mass showed predominantly monotonous round cells arranged in nests and rosettes, surrounded by cleft-like spaces with inconspicuous nucleoli. Cells had stippled nuclear chromatin and scant cytoplasm, morphologically consistent with a well differentiated neuroendocrine tumor.

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Adjacent areas showed rare, malignant glands with extracellular mucin dissecting the densely fibrous stroma. This observation warranted more sampling of the tissue. The additional sections showed additional malignant glands with extracellular mucin pools, that confirmed the diagnosis of adenocarcinoma (Figs. 2C-2D). Areas of transition from the neuroendocrine component to the adenocarcinoma component were also noted. This mixed tumor was 70% well differentiated neuroendocrine tumor and 30% adenocarcinoma. Sections from the cystic areas exhibited mature teratomatous components. Immunohistochemically, tumor cells of the neuroendocrine component showed strong and diffuse immunoreactivity with synaptophysin (Fig. 3A) and focal, patchy immunoreactivity with chromogranin (Fig. 3B), and a Ki-67 proliferation index of up to 10% (Fig. 3C). Tumor cells of the adenocarcinoma component were positive for Cytokeratin7, Cytokeratin 20 and CDX2 (Figs. 3D-3F). SATB2 was strongly positive in both the neuroendocrine and the adenocarcinoma components (Fig. 3G). Mucicarmine stain highlighted the extracellular mucin (Fig. 3H). The given immunohistochemical profile supported the diagnosis of both components arising from gastrointestinal lineage of the teratoma. Based on morphology and immunohistochemical stains, the left ovarian cyst was diagnosed as a mixed neuroendocrine/non-neuroendocrine neoplasm (MiNEN) arising in the background of MCT. The right ovarian cyst showed mature cystic teratoma, negative for malignancy.

Given the final pathology, the patient had a consult with a medical oncologist specializing in neuroendocrine tumors and it was recommended that she undergo a Dotatate PET/CT which showed a focus of dotatate activity in the central pelvis adjacent to a partially calcified left adnexal fat density structure suspicious for residual neuroendocrine tumor. Another possible focus of dotatate activity was noted in the
superior left hepatic lobe concerning for possible neuroendocrine involvement, but follow-up liver MRI was normal with no lesions. She also underwent a colonoscopy which was within normal limits.

After the bilateral cystectomy, the patient developed recurrent episodes of diarrhea, flushing, nausea and vomiting. She presented to the emergency department once for these symptoms with unremarkable work-up. These symptoms were attributed to carcinoid-like syndrome.

Recommendation was made to proceed with laparoscopic complete cystectomy.

Fig. 3a. Diffuse strong immunoreactivity with synaptophysin in neuroendocrine component (3A: 200X).

Fig. 3b. Focal and patchy Immunoreactivity with chromogranin in neuroendocrine component (3B: 400X).

Fig. 3c. Ki-67 proliferation index 10% in neuroendocrine component (3C: 400X).

Fig. 3d. Cytokeratin 7 (CK7) strongly staining in adenocarcinoma component (3D: 400X).

Fig. 3e. Cytokeratin 20 (CK20) partial staining in adenocarcinoma component (3E: 400X).

Fig. 3f. CDX2 positive staining in adenocarcinoma component (3F: 400X).
Neuroendocrine neoplasms of the ovary are rare and were recently reclassified by the World Health Organization of tumors of the female genital tract (WHO) (Classification, 2020). “Carcinoid” tumor is still acceptable terminology for ovarian well differentiated ovarian neuroendocrine tumors. Poorly differentiated ovarian neuroendocrine neoplasms are neuroendocrine carcinomas; these are exceedingly rare and only a few cases have been reported in the literature (Eichhorn et al., 1992). A subset of ovarian neuroendocrine carcinomas are mixed tumors which include a non-neuroendocrine carcinoma component, like MiNENs described in digestive and extra digestive sites. This case calls for the inclusion of the concept of MiNEN in the spectrum of gynecological neuroendocrine neoplasia analogous to its counterparts in the digestive and extra digestive locations. To the best of our knowledge, the term MiNEN was employed in the gynecologic pathology literature once earlier, in a report of a mixed ovarian carcinoma composed of high grade endometrioid carcinoma and large cell neuroendocrine carcinoma arising in the background of endometriosis (Maraglino et al., 2022). Another case was reported in the literature by Pavithra et al (Ayyanar et al., 2021) as synchronous colonic adenocarcinoma and well differentiated neuroendocrine tumor arising in a mature cystic teratoma of the ovary in a postmenopausal woman. Even though the author did not use the term MiNEN, this case closely resembled our current case and MiNEN could apply to this case as well.

MiNENs consist of two components, an epithelial, non-neuroendocrine component (most commonly adenocarcinoma; less commonly squamous cell carcinoma, acinar cell carcinoma, adenoma, and others) and a neuroendocrine component, each constituting at least 30% of the tumor. The neuroendocrine component is mostly high grade and demonstrates a high mitotic index. About 5% of MiNENs show low grade neoplasms, combining adenomas with G1/G2 (de Mestier et al., 2017). Our case is unique since it represents a well differentiated neuroendocrine tumor and mucinous adenocarcinoma of gastrointestinal lineage arising in the background of MCT of the ovary.

It is important to differentiate the gastrointestinal-type adenocarcinoma arising along with neuroendocrine tumor from a primary mucinous adenocarcinoma of the ovary. The former belongs to the germ cell category with somatic malignant transformation while the latter is of Mullerian type surface epithelial origin. Well differentiated neuroendocrine tumors are relatively chemo-resistant compared to primary epithelial ovarian cancers. Special AT-rich sequence binding protein-2 (SATB2) is selectively expressed in the lower gastrointestinal tract mucosa and has been identified as a sensitive marker for colorectal adenocarcinomas. SATB2 has gained interest as a relatively specific marker of colorectal differentiation, with potential applications including determining origin of metastatic adenocarcinomas of unknown primary and distinguishing primary ovarian mucinous adenocarcinomas from colorectal metastases. In addition, a study by Zhongwu Li et al (Li et al., 2015) has identified SATB2 as a sensitive marker for hindgut well-differentiated neuroendocrine tumors, although it is not entirely specific. In our case, positive SATB2 staining in both neuroendocrine and the adenocarcinoma components along with CDX2 positivity in the adenocarcinoma component strongly supported the hypothesis that this neoplasm represented gastrointestinal lineage of the teratoma, excluding the possibility of a primary ovarian mucinous (Müllerian) adenocarcinoma. Careful morphologic analysis and extensive sampling of specimens in combination with ancillary immunohistochemical stains are crucial in diagnosing these rare neoplasms. The final MiMEN diagnosis was only confirmed upon the examination of several additional sections. This exercise highlighted the need for adequate sampling of these tumors.

The other reported cases with a synchronous neuroendocrine tumor include the following: a case of mucinous cystadenocarcinoma and a stromal carcinoid tumor with synchronous cervical cancer Kanthan et al., 2020, a case of malignant papillary thyroid carcinoma in the...
setting of struma ovarii and a carcinoid tumor Cagino et al., 2020, and a case of stromal carcinoid tumor, papillary thyroid carcinoma in the setting of struma ovarii, and mucinous adenocarcinoma Hinshaw et al., 2012. In these cases, the patients were 48, 62, and 74 years old with MCTs that were 10 cm or greater on pre-operative imaging. The patient with the synchronous cervical cancer was treated with exploratory laparotomy, Hartmann’s operation, hysterectomy and bilateral salpingo-oophorectomy. Re-operation for full staging was recommended, but the patient declined, and she was then treated with adjuvant chemotherapy and radiation Kanthan et al., 2020. The other two patients were treated with surgery alone including hysterectomy with bilateral salpingectomy and either unilateral or bilateral oophorectomy followed by close surveillance Cagino et al., 2020, Hinshaw et al., 2012. All patients were alive and disease free when the case reports were published Kanthan et al., 2020, Cagino et al., 2020, Hinshaw et al., 2012. Of note, there has been one additional case report of a combined mucinous adenocarcinoma, goblet cell carcinoid, and typical carcinoid tumor within a MCT arising within the mesentery Shin et al., 2015.

Our case is significant for the literature since it highlights the diagnosis of MiNEN in the female genital tract and emphasizes the need of extensive sampling of even benign cystic teratomas. It is different from the previously reported cases given the patient’s young age and lack of risk factors for malignant transformation. Given this, she was initially treated with bilateral cystectomy as is standard of care for patients with bilateral MCTs. However, when considering further management for this patient, fertility preservation was a factor that was not present in previously reported cases, so decision was made to proceed with unilateral oophorectomy.

CRediT authorship contribution statement

Sandhyarani Dasaraju: Conceptualization, Writing & Editing. Khalid Amin: Conceptualization, Visualization. Molly E. Klein: Supervision, Editing, Validation. Colleen Rivard: Methodology, Data Curation. Jordan Mattson: Methodology, Data Curation. Sarah Davidson: Methodology, Data Curation. Mahmoud A. Khalifa: Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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