Case report

Ganglioneuroblastoma arising in a Mature Cystic Teratoma of Ovary: Report and Literature review of an uncommon neoplasm

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1. Introduction

A 29-year-old female patient with a history of back pain (x 1 year) and amenorrhea (x multiple years), was brought to the ER with worsening pain. A 7.8 cm complex right ovarian mass with calcifications was identified on the CT scan, along with increased levels of testosterone and mildly elevated levels of AFP on serological evaluation. Right salpingo-oophorectomy, partial omentectomy, and peritoneal staging biopsies were performed. Histologic examination of the solid areas of the right ovary showed spindled cells with Schwannian features along with single and clustered ganglion cells (both positive for synaptophysin and chromogranin A), and of the cystic areas showed mature tissue elements like skin, skin appendages, and adipose tissue. No N-MYC amplification was identified with FISH testing. A diagnosis of Ganglioneuroblastoma arising within a mature cystic teratoma was made. We present the second reported case, in English literature, of this entity arising in an ovarian teratoma and discuss its differential diagnostic considerations. Due to its rarity, this tumor may pose a diagnostic challenge for Pathologists and a management conundrum for Gynecological oncologists.

2. Clinical presentation

A 29-year-old nulligravida female with a one-year history of back pain managed with over-the-counter medication presented to the emergency room with worsening pain. There was no history of accompanying nausea, vomiting, diarrhea or constipation, fever, early satiety, or unintentional weight loss or gain. She had a significant history of amenorrhea for many years. Clinical examination showed a high BMI of 50.7 and hirsutism. A non-contrast computed tomographic scan of the abdomen and pelvis identified a 7.8 cm right complex ovarian mass with calcifications, mild retroperitoneal lymph node enlargement, splenomegaly, and hepatomegaly. Corresponding pelvic ultrasound showed a complex mass with shadowing and calcifications, concerning for a teratoma in the right ovary. Serological evaluation showed an elevated testosterone level (276) and mildly elevated alpha fetoprotein (11.2). The levels of CA-125, CEA, and beta-HCG were normal. Given her hirsutism, amenorrhea, and elevated levels of testosterone, the clinical concern included a tumor with a Sertoli-Leydig component.

A robotic assisted right salpingo-oophorectomy was planned for fertility preservation, with a possible hysterectomy and contralateral salpingo-oophorectomy, if needed, based on intraoperative findings. Intraoperatively an irregular, lobulated, predominantly solid right adnexal mass was identified, with adhesions to the omentum, with no other obvious nodules in the pelvis or extrapelvic peritoneum. As such only partial omentectomy and peritoneal staging biopsies were performed.

3. Gross and microscopic pathology

The right adnexum weighed 160 g and consisted of a 9.1 × 7.5 × 5.0 cm ovary and a 3.5 × 0.4 cm fimbriated fallopian tube. The ovary had a smooth external surface with adhered omentum, focally. Cut sections of
the ovary showed a multiloculated cyst, measuring 1.5 cm, and filled with sebaceous material admixed with hair. A solid, 6.0 cm mural nodule was identified adjacent to the cyst wall, and had a uniform, fleshy, brown to grey cut surface. No hemorrhage or necrosis was identified within this component. The fallopian tube was grossly unremarkable.

The hematoxylin and eosin-stained sections showed various mature tissue elements in the cyst wall, including skin and skin appendage, and adipose tissue. The adjacent brown-grey nodule (Fig. 1A) showed a nodular proliferation of bland spindled cells with Schwannian features (Fig. 1B), admixed with singly present and clustered ganglion cells (characterized by large nuclei, prominent nucleoli, and cytoplasm with granules (Fig. 1C), and scattered “immature appearing” neuroblastic cells (Fig. 1D) that had round, darkly staining nuclei, and scant cytoplasm. Immature neuroepithelium and rosettes were not identified. Mitoses were scant to absent.

Immunoperoxidase stain for synaptophysin was positive in the spindled neural elements (Fig. 2A1) and ganglion cells (Fig. 2A2), both of which were also positive for chromogranin-A (Fig. 2B). Rare ganglion cells were also positive for NeuN (Fig. 2C), which was negative in the immature neuroblastic appearing cells. All components were negative for glial fibrillary acidic protein (GFAP), S100 and, CD34. MIB1 proliferation index was less than 5 % in all components. No N-MYC amplification was identified on fluorescent in-situ hybridization testing of the tumor.

Right fallopian tube, peritoneal biopsies, and omentum were negative for gliomatosis and metastatic immature teratoma. There are currently no staging criteria for a somatic neoplasm arising in an ovarian teratoma; however, provided the neoplasm was confined to the ovary, for clinical purposes, if the AJCC, 8th Ed staging parameters for ovarian malignancies were to be used, the tumor stage would be pT1a.

4. Discussion

Mature Cystic Teratoma, the most common germ cell neoplasm of the ovary, is usually detected incidentally in asymptomatic patients or may present with pain due to torsion, or rupture. Histologically, majority of these tumors contain differentiated and mature elements from multiple germ cell layers, including skin, bone, teeth, cartilage, respiratory epithelium, and mature glial and ependymal tissue, while some can be monodermal, such as struma (mature thyroid follicles). Putatively, due to the acquisition of oncogenic mutations, benign and malignant somatic neoplasms have been reported to arise in mature teratomas (Desouki et al., 2015) in 1 to 2 % of cases. These neoplasms include carcinoid (most commonly), squamous carcinoma, mucinous adenocarcinoma, carcinoma of thyroid origin, and rarely, tumors of glial origin. Teratomas that have immature neuroepithelium are considered “immature teratomas”, and are a distinct entity, separate from somatic neoplasms involving mature teratoma, as discussed later.

Ganglioneuroblastoma is a peripheral neuroblastic tumor and likely arises from neural crest progenitors in the ovarian teratoma. The Shimada classification system (Shimada et al., 1999) classifies peripheral neuroblastic tumors into three categories, based on their differentiation/maturity. These tumors include (A) Neuroblastoma that are characterized by dominant nests of immature neuroblasts with hyperchromatic nuclei, high N:C ratio, rosette formation, and paucity of Schwannian stroma, (B) Ganglioneuroblastoma are an intermediate tumor, characterized by intermixed neuroblasts and ganglion cells at various stages of maturation (intermixed type), or nodular regions of dense neuroblastic nests (nodular type), along with the increasing amount of schwannian stroma, and (C) Ganglioneuroma characterized by an abundance of stroma with well-differentiated ganglion cells and absence of neuroblastic cells. This classification system is based on the biological behavior of these tumors, when they occur as somatic neoplasms, usually along the distribution of the sympathetic chain. While Neuroblastoma, the most immature form has an unfavorable prognosis, ganglioneuroma is essentially benign and has a favorable prognosis. Ganglioneuroblastoma with intermixed morphology (as in the presented case) tends to have a favorable prognosis, unlike their nodular counterparts. N-MYC amplification, a marker of poor prognosis by
Cytogenetic studies, was not seen in our case.

The biological behavior of these tumors arising in somatic locations is predictable; however, due to their rarity in the ovary as a secondary neoplasm arising in a teratoma, their clinical course cannot be ascertained. The presented case, to the best of our knowledge, is the fourth case of a peripheral neuroblastic tumor involving a mature teratoma. The previously reported cases included a 23-year-old female patient with a 7.0 cm ganglioneuroblastoma arising in left ovarian teratoma (Rajendran et al., 2019), and two cases of ganglioneuroma, one measuring 8.5 cm and involving the left ovary in a 26-year-old female patient (Coy et al., 2018) and the other measuring 0.5 cm and involving right ovary in a 34-year-old patient (Marucci and Collina, 2006). While, like our case, none of the previously presented cases had any extra-ovarian disease or implants or gliomatosis, we did not have any follow-up information on previously reported cases. Our patient had no clinical evidence of disease, 3 months after her initial presentation. Elevated levels of testosterone, amenorrhea, and hirsutism in our patient, were not reported in any of the other reported cases. These are likely unassociated with the tumor and may also be due to a high body mass index related metabolic syndrome.

Histopathological differential diagnoses for gangliocytic tumors within the ovary, include immature teratoma, glial neoplasms, such as glioblastoma multiforme (Kim et al., 2018), and ependymoma (Garcia-Barriola et al., 2000), and mature non-neoplastic glial and cerebellar elements (Ishida et al., 2014).

Immature teratoma is characterized by rosettes, pseudo-rosettes, and immature neuroepithelial tubules. These are classified as low grade (grade 1) or high-grade (grades 2 and 3), respectively based on the presence of 1 or more than 1 foci of immature neuroepithelium in a 40x light microscopy examination field (Norris et al., 1976). The morphological features of an immature teratoma are usually characteristic and immunohistochemistry has a limited role in its diagnosis. In challenging cases, S100 (positive) and GFAP (positive) can be used to highlight immature neuroepithelium. As noted, ganglioneuroblastoma tends to be negative for GFAP, and S100 may be focally positive depending on the component. Unlike the indeterminate biological behavior of peripheral neuroblastic tumors, the behavior of immature teratomas depends on their grade and stage. Low-grade and low-stage (FIGO-IA) immature teratoma can be managed surgically alone and have a very low risk of recurrence, while the high-grade tumors, depending on the patient’s age and particularly when high-stage, require adjuvant chemotherapy (Alwazzan et al., 2015) and have a higher risk of recurrence as immature implants or gliomatosis.

Glioblastoma, such as glioblastoma multiforme, akin to their central nervous system counterparts have foci of hypercellular mature glial tissue with significant cytological atypia, glomeruloid vascular / endothelial proliferation, pseudopalisading necrosis, and high MIB1 proliferation. These tumors, consistent with their glial origin, are positive for GFAP. High-grade gliomas of the ovary are extremely rare neoplasms as well, with only seventeen reported cases in English literature. In presented cases, the biological behavior ranged from no recurrences after a long follow-up in a stage IA, surgically managed tumor (den Boon et al., 1999) to need for aggressive chemotherapy in conventionally high stage or ruptured tumors (Kim et al., 2018). Ependymoma of the ovary can be identified by the presence of true-rosettes and expression of GFAP, and in the published cases had a good prognosis, even in the tumors with a high stage at presentation (Garcia-Barriola et al., 2000).

Presence of mature cerebellar and neural tissue and other common benign neoplasms such as carcinoma or paraganglioma within the ovary may rarely be confused with a ganglioneuroblastoma. Review by one or more pathologists with expertise and/or experience in gynecological pathology, and assistance with appropriate immunoperoxidase stains are helpful in the reliable distinction of these differentials.

In summary, we present the second case of ganglioneuroblastoma and the fourth case of peripheral neuroblastic tumor arising in a mature cystic teratoma of the ovary. All presented cases had tumors confined to the ipsilateral ovary; however, no long-term follow-ups were available to ascertain their potential for locoregional or distant recurrence.
CRediT authorship contribution statement

Nikita Shah: Data curation, Writing – original draft. Karolina Kilowski: Data curation, Writing – original draft. Robert Holloway: Writing – review & editing. Charanjeet Singh: Writing – original draft, Writing – review & editing, Data curation.

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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