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Case report

Sertoli–Leydig cell tumor of the ovary: A diagnostic dilemma

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ABSTRACT

Background: Sertoli–Leydig cell tumors are rare sex-cord stromal tumors of the ovary that can present with a variety of histological elements, which may complicate diagnosis and treatment.
Case: A 40-year-old female presenting with pelvic pain is found to have a large complex right adnexal mass and elevated alpha-fetoprotein. The mass was diagnosed as a Sertoli–Leydig cell tumor with heterologous elements including carcinoid and hepatoid components. She was treated with surgical resection followed by adjuvant chemotherapy and remains clear of disease.
Conclusion: Prognostic indicators for Sertoli–Leydig cell tumors include degree and type of heterologous element differentiation. Thorough characterization of such elements is crucial for adequate diagnosis and treatment.

1. Introduction

Sertoli–Leydig cell tumors (SLCTs) are rare tumors, accounting for less than 0.5% of all ovarian cancers (DiSaia and Creasman, 1997). The varying histopathology and differentiation of this tumor present difficulties with proper diagnosis and development of optimal treatment regimens. The prevalence of Sertoli–Leydig tumors with hepatoid differentiation is exceedingly uncommon with few published case reports, resulting in an additional diagnostic dilemma. We report the case of a Sertoli–Leydig cell tumor found in a 40-year-old female with intermediate differentiation and heterologous elements including endometrioid and hepatoid differentiation with alpha-fetoprotein expression.

2. Case

The patient is a 40-year-old female with a past medical history of morbid obesity (body mass index 54.3 kg/m^2), abnormal uterine bleeding status post-endometrial ablation, and extensive abdominal surgeries, including three cesarean sections and repair of a large ventral hernia with mesh, who presented to the emergency department with a chief complaint of progressive left lower quadrant abdominal pain over a period of five years. On abdominal computed tomography (CT) and ultrasound imaging, she was found to have a 13 cm complex right adnexal mass. Diagnostic studies showed an isolated elevation of the serum alpha-fetoprotein tumor marker. She was taken to the operating room where initial exploration noted no evidence of disseminated disease but, due to extensive adhesions from her prior surgeries, prolonged adhesiolysis was performed, including resection of a portion of small bowel densely adherent to the previously placed abdominal wall mesh. Once visualized, the right adnexal mass was excised, with frozen section noting ovarian neoplasm, favor malignant, with suspicion for mucinous components. The left ovary was also grossly abnormal in appearance, so it too was removed. Given the suspected mucinous tumor, additional procedures performed included omentectomy and appendectomy. Lymphadenectomy was not performed given the mucinous histology. Final pathology, however, noted a moderately differentiated Sertoli–Leydig cell tumor with heterologous elements, including liver tissue demonstrating alpha-fetoprotein expression, confined to the right ovary [Fig. 1]. Benign pathology was noted on the left ovary.

Shortly following surgery, the patient's serum alpha-fetoprotein level returned to normal. She received 2 cycles of carboplatin and paclitaxel, which was poorly tolerated and met with significant side effects. She was admitted following cycle 1 for intractable nausea and was noted to have chronic Helicobacter pylori infection on esophagogastroduodenoscopy. Following cycle 2, she was treated for possible shingles and continued to have significant abdominal pain and nausea. Subsequent to multiple emergency room visits, she had a CT scan showing no evidence of recurrent or residual disease as well as no additional acute findings. In light of her poor tolerance to the medications and favorable findings at time of surgery, the decision was made in conjunction with the patient to discontinue chemotherapy. To date, she has remained without evidence of disease for 20 months.

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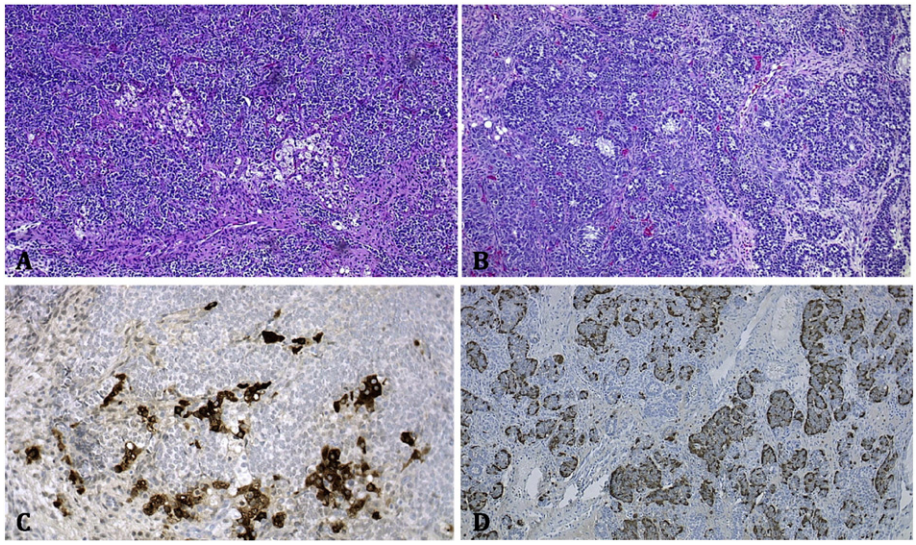

Fig. 1. Immunohistochemical staining of Sertoli–Leydig cell tumor. (A): Sertoli–Leydig cell tumor, intermediate grade with hepatoid differentiation. (B): Area of carcinoid tumor. (C): Immunohistochemical stain alpha-fetoprotein (AFP) positive in the area of hepatoid differentiation. (D): Immunohistochemical stain chromogranin positive in the carcinoid tumor.

3. Discussion

Ovarian sex cord-stromal tumors are a heterogeneous group of ovarian tumors that comprise only 1.2% of all primary ovarian cancers (DiSaia and Creasman, 1997). Sertoli–Leydig cell tumors (SLCTs), also called androblastomas, are a subset of ovarian sex cord-stromal tumors that constitute less than 0.5% of all ovarian tumors (DiSaia and Creasman, 1997). SLCTs are characterized as well differentiated, intermediately differentiated, and poorly differentiated, with the degree of differentiation corresponding to patient prognosis (Chen et al., 2014; Young and Scully, 1985). These tumors most often occur in young women 20 to 30 years old, are unilateral, confined to the ovary, and large (Young and Scully, 1985). Though frequently characterized by the presence of androgen production, only 30% of patients display virilization or defeminization on presentation (Young and Scully, 1985). Specifically, classic endocrine manifestations are rarely seen in SLCTs of retiform type or those with heterologous elements (Chen et al., 2014). Instead, these tumors are highly variable in their proportions of Sertoli cells, Leydig cells, and/or fibroblastic cells, and patients most often present with abdominal pain or distention (Chen et al., 2014). Pure Sertoli cell tumors are usually estrogenic and on occasion secrete renin resulting in hypertension and hypokalemia. In contrast, pure Leydig cell tumors are androgen secreting, though reports of these are rare (Oliva et al., 2005). Approximately 20% of Sertoli–Leydig cell tumors contain heterologous elements such as gastrointestinal epithelium, carcinoid, cartilage and skeletal muscle (Oliva et al., 2005).

Common Sertoli–Leydig cell tumor immunohistochemical expression includes negative staining for epithelial membrane antigen and positive staining for inhibin and caltretinin (Weng et al., 2013). Although rare, alpha-fetoprotein (AFP) has been reported in approximately 30 cases of SLCTs (Sekkate et al., 2013). AFP is a plasma protein produced by the yolk sac and fetal hepatocytes during development. It is closely coupled to cellular division and the degree of cell differentiation (Sung et al., 2013). As such, elevated levels of serum AFP are often associated with hepatocellular carcinoma, neuroblastoma, endodermal sinus (yolk sac) tumors, and carcinomas involving endodermally derived organs including the lung, esophagus, stomach and pancreas (Sung et al., 2013). It has additionally been noted in teratomas, though the association is likely due to a component of endodermal sinus tumor present in the teratoma. Likewise, it has been associated with Wilms' tumor, which is also notable for the presence of hepatoid cells (Young and Scully, 1985).

The differential diagnosis of Sertoli–Leydig cell tumors with hepatoid components and alpha-fetoprotein expression includes granulosa cell tumors, female adnexal tumor of probable wolffian origin (FATWO), endometrioid carcinoma, hepatoid carcinoma of the ovary, serous carcinoma, and endodermal sinus tumor [Table 1]. Improper diagnosis due to the homogeneity of these tumors has led to the utilization of immunohistochemical stains to distinguish tumors with similar cell types (Weng et al., 2013). SLCTs can sometimes be differentiated from granulosa cell tumors through the absence of Call-Exner bodies on microscopic analysis. In addition, granulosa cell tumors often do not present with heterologous elements (Sekkate et al., 2013). FATWOs can be distinguished from SLCTs by the absence of heterologous elements and endocrine disturbance in addition to the microscopic presence of a mixture of closely packed tubules and sieve-like growth of various sized cysts with diffuse spindle or polygonal cells (Chen et al., 2014). Endometrioid tumors have immunohistochemical staining positive for EMA and CK7 while their neoplastic glands are negative for inhibin and caltretinin (Chen et al., 2014), which is in contrast to SLCTs. Hepatoid carcinoma of the ovary (HCO) can similarly present as a large pelvic mass with elevated serum AFP and hepatoid cells; however, on microscopic evaluation, HCO forms a characteristically solid sheet of uniform cells with abundant eosinophilic cytoplasm, distinct borders, and centrally located nuclei with prominent nucleoli (Sung et al., 2013). SLCT differs from serous carcinoma in that no serous tumors have been found positive for AFP production, as in this case. AFP producing endodermal sinus tumors (EST) present similarly as pelvic masses in young women. They display elevated serum AFP levels and contain hepatoid cells, however, ESTs display characteristic papillary cells termed Schiller–Duval bodies, which were absent in this specimen (Young and Scully, 1985).

The heterogeneous nature of SLCTs makes determining prognostic outcomes difficult. However, histological assessment defining the degree of differentiation is informative. Metastatic disease is rare in well-differentiated subtypes of SLCTs as compared to the intermediate and poorly differentiated subtypes (Young and Scully, 1985). The presence of heterologous elements and retiform pattern is more common with intermediate and poorly differentiated subtypes, conferring an additionally poor prognosis. Tumor stage based on extraovarian spread and rupture or spillage of the tumor presents a greater risk of metastasis, in addition to larger tumor size. Corresponding to the degree of differentiation, prognosis correlates most meaningfully with tumor stage at time of presentation (Chen et al., 2014; Young and Scully, 1985).

Table 1
Differential diagnosis of Sertoli–Leydig cell tumor with heterologous elements and positive alpha fetoprotein staining including various tumor distinguishing characteristics (AMH: Anti Mullerian hormone, AFP: Alpha Fetoprotein, CEA: carcinoembryonic antigen, HPL: human placental lactogen, WT-1: Wilms' tumor 1, EMA: epithelial membrane antigen, PLAP: placental alkaline phosphatase).

	Sertoli–Leydig cell tumor (SLCT)	Granulosa cell tumors	Female adnexal tumor of probable wolffian origin (FATWO)	Endometrioid carcinoma	Hepatoid carcinoma of the ovary (HCC)	Endodermal sinus tumor (EST)	Serous carcinoma
Age	2–75 years Avg 25	15+ years Avg 53 Recur 20 years later	18–81 years Avg 50	26–87 years Avg 51	42–78 years Avg 62	Young Avg 17	45–57 years (low-grade) 55–65 years (high-grade)
Tumor characteristics	Unilateral Solid/cystic Avg 16 cm	Unilateral Solid/cystic Avg 10 cm	Unilateral Solid/cystic 1–20 cm	Bilateral (25–40%) Solid/cystic Avg 11 cm	Solid (+/− cystic, hemorrhagic, necrotic), large	Solid/cystic Fleshy Necrotic Avg 15 cm	Bilateral Solid
Tumor markers	Testosterone	Inhibin A&B Estradiol AMH	None	CA-125	AFP CA-125	AFP Alpha-1-antitrypsin	CA-125
Tumor type	Sex-cord stromal tumor	Sex-cord stromal tumor	Wolffian–Mesonephric origin	Epithelial	Epithelial vs yolk sac	Germ cell neoplasia	Epithelial
Heterologous elements	Gastrointestinal Liver Skeletal muscle cartilage Hepatoid	No	No	No	Hepatoid	Hepatoid Gastrointestinal	No
Microscopic characteristics	Sertoli, leydig and fibroblastic cells. Retiform pattern with elongated, irregularly shaped tubules and cysts containing papillae	Various cell patterns including macrofollicular, trabecular, solid and insular. Steroid-type cells, Call-Exner bodies, areas with interstitial hemorrhage	Mixture of closely packed tubules and sieve-like growth of various sized cysts with diffuse spindle or polygonal cells	Non-cystic, villoglandular pattern, glandular confluence of stromal disappearance	Solid sheet of uniform cells with abundant eosinophilic cytoplasm, distinct borders, and centrally located nuclei with prominent nucleoli	Various patterns including reticular or microcystic, polyvesicular. Presence of Schiller–Duval and hyaline bodies	Extensive papillae with psammona bodies, glandular complexity, variable fibrous stroma or stromal invasion
Immunostaining	Testosterone Estradiol Cytokeratin AFP (hepatoid) CD99 Alpha-inhibin Cytokeratin AMH Progesterone receptor Androgen receptor Vimentin	Alpha-inhibin Vimentin Calretinin CD99 Smooth muscle actin Desmoplakin	CD10 CAM5.2 Vimentin Variable EMA Caltretinin Inhibin	Keratin CEA HPL EMA CK7 Inhibin Caltretinin	Focal AFP Polyclonal CEA Cytokeratin	Keratin AFP (yolk sac, hepatic or intestinal epi in teratomas) CD10	p53 WT1 CA-125 Mesothelin CK5/6 D2-40
Negative stains	EMA PLAP CEA CA19-9 CA125 S100	EMA	Mucin B72.3 CEA S100 Alpha-inhibin				AFP

Though the malignant potential of SLCTs is approximated at 10–30%, the risk of recurrence for SLCTs, specifically those with hepatoid differentiation and heterologous elements is approximately 40 to 50% in published case reports. As such, the presence of noted poor prognostic indicators influences the use of adjuvant chemotherapy.

Management for SLCTs can include fertility-sparing surgery for stage IA/IC patients who desire future childbearing. Otherwise, complete surgical staging combined with adjuvant chemotherapy is standard treatment. Combination chemotherapy regimens for SLCTs have been generalized from recommendations for other sex cord-stromal tumors (SCSTs), most often adult granulosa cell tumors. However, the optimal treatment algorithm is unknown given the rarity of SCSTs and has evolved from vincristine, doxorubicin and cyclophosphamide (VAC) to bleomycin, etoposide and cisplatin (BEP) (Brown et al., 2005). Though the platinum-based chemotherapy is widely used for sex cord-stromal tumors given the overall response rate, the side effect profile for bleomycin limits its utility and the relapse rate can also exceed 40 to 50% (Chen et al., 2014). As such, a study by Brown et al. in 2005 suggested an alternative regimen utilizing taxanes with or without a platinum agent, for the treatment of SCSTs. The study showed sensitivity of SCSTs, specifically granulosa cell tumors, to taxane chemotherapy with similarly efficacy to BEP and the potential for a more durable response with less toxicity (Brown et al., 2005).

Our patient was treated with carboplatin and paclitaxel given concerns about pulmonary toxicity and because the patient's personal obligations precluded inpatient hospitalization for treatment. At this point, she has remained without evidence of disease recurrence. Thorough evaluation of her histopathology was crucial given the uncommon nature of disease, and underscores the need for accurate diagnosis of rare tumors as the appropriate adjuvant treatment in these cases, which is ultimately tied to patient outcome; may vary.

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