Yolk Sac Tumor of the Ovary and Extragonal Sites in Females: Lessons Learned From an Unusual Case

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Case History:

A 59 year old Egyptian woman, G4 P4, presented to her doctor in May 2008 with increasing abdominal distention, abdominal pressure and early satiety. She had various gastrointestinal symptoms including nausea, diarrhea and constipation. On examination, the abdomen was distended and there was a fluid wave. Left adnexal fullness was suspected but examination was difficult because of ascites and obesity (height 63 inches, weight 195 lbs.). A CT scan and an ultrasound of the abdomen and pelvis revealed a 6-8 cm complex mostly solid left adnexal mass suggestive of a left ovarian malignancy. A small amount of ascites was noted, and there were 3 extraovarian peritoneal masses measuring 2, 3, and 8 cm. The CA125 was elevated at 531 IU/ml and the CEA was within normal limits at 1.1 μgm/L. In July, 2008 she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, tumor debulking and placement of an intraperitoneal port. The gynecologic oncologist removed 2 liters of hemorrhagic ascites and resected a 10 cm extensively necrotic tumor that grew from the region of the left adnexa, although it did not involve the ovary or fallopian tube, to involve the anterior abdominal wall, the left side of the uterus, the anterior aspect of the bladder, the cul de sac and the small bowel mesentery. Multiple omental nodules measuring 3-4 cm were removed. Exploration of the remainder of the abdomen revealed smooth and unremarkable abdominal peritoneum, liver surfaces and diaphragms and normal appearing pelvic and para-aortic lymph nodes. She was optimally debulked.

A small clear cell carcinoma was discovered in the fallopian tube, and it was initially thought that the pelvic tumor, which was HNF-1β positive, was a metastasis from the tubal carcinoma. However, we subsequently learned that the patient had an elevated alpha-fetoprotein. We went back to the specimen and prepared additional slides and performed a panel of immunostains. The pelvic tumor was negative for CK7 and EMA, which are usually positive in clear cell carcinoma, and it showed positive staining for alpha-fetoprotein and glypican-3, which are typically positive for yolk sac tumor. Thus, we reinterpreted the tumor as an extra-ovarian yolk sac tumor.

We learned a number of things from this case, which will be discussed in this lecture:

1. Previous cases of extragonadal yolk sac tumor have been reported mainly in young women, but this case showed that such tumors can also occur in postmenopausal women.
2. It is possible that this tumor arose from the clear cell carcinoma in the fallopian tube. Rare examples of yolk sac tumors arising from endometrioid carcinomas of the ovary have been reported. Yolk sac tumor is mainly a primary germ cell tumor, but in older women the possibility of a somatic origin needs to be considered.
3. The differential diagnosis between yolk sac tumor and clear cell carcinoma can be challenging and staining for HNF-1β does not help to resolve the diagnosis since both clear cell carcinoma and yolk sac tumor are likely to be positive. In fact, we now find HNF-1β to be a useful marker for yolk sac tumor when used in an appropriate setting. A panel of immunostains needs to be used to differentiate yolk sac tumor from clear cell carcinoma.

Yolk Sac Tumor of the Ovary

Yolk sac tumor, formerly known as endodermal sinus tumor, is a malignant germ cell tumor showing differentiation into primitive endodermal structures. It is the third most common malignant germ cell tumor of the ovary and constitutes about 1% of ovarian malignancies. (Smith, Berwick et al. 2006)

Clinical Features

Yolk sac tumor occurs mainly in children and young women; the median age is 19 years. (Gershenson, del Junco et al. 1983) Rare examples have been reported in women older than 45 years of age, although other possibilities should be considered in an older patient. (Kammerer-Doak, Baurick et al. 1996) As of 2001 only 5 cases of pure yolk sac tumor of the ovary had been reported in women over the age of 50. (Oh, Kendler et al. 2001) Typical symptoms at presentation include abdominal pain, abdominal enlargement, or an abdominal mass. About 10% of patients present with acute abdominal symptoms caused by torsion or rupture of the tumor. When it is measured, most patients with yolk sac tumors have high serum levels of α-fetoprotein (AFP); as in our case, serum levels of CA-125 can also be elevated.

Yolk sac tumor appears limited to the ovary (stage I) at diagnosis in about 50% of patients. Prior to the availability of combination chemotherapy, patients with stage I yolk sac tumor had a poor prognosis, indicating that micrometastases were already present in most patients, even though the tumor appeared confined to the ovary. Of the 50% of patients presenting with visible extraovarian tumor spread, the tumor appears restricted to the pelvis (stage II) in about 10% of cases, while 40% have more widespread metastases (stage III and IV). The surgical treatment for yolk sac tumor in young women is unilateral salpingo-oophorectomy with limited debulking of extraovarian tumor. Bilateral tumors are rare, and it is not necessary to biopsy a grossly normal contralateral ovary. If they appear uninvolved, the contralateral ovary and uterus need not be removed even in patients with advanced disease.

The introduction of combination chemotherapy with VAC (vincristine, dactinomycin, and cyclophosphamide) radically changed the survival prospects for patients with yolk sac tumor. More modern chemotherapy protocols such as BEP (bleomycin, etoposide, cisplatin) as developed for testicular germ cell tumors, have further improved the results such that most patients can now be successfully treated. Overall survival for patients with all stages is now in the range of 85% (Chan, Tewari et al. 2008) to 94%. (de La Motte Rouge, Pautier et al. 2008) Patients who do not respond to chemotherapy almost always die within three years of diagnosis. (Nawa, Obata et al. 2001) The serum AFP level can be used to monitor the response to treatment and to detect tumor recurrence.

Gross Appearance
Yolk sac tumors are large, with an average diameter of 16 cm. Their cut surface is tan, white, or gray with small or large cysts and areas of hemorrhage and necrosis.

Microscopic Appearance
Numerous patterns of growth have been described, mixtures of which are present in most tumors. (Kurman and Norris 1976) The most common and distinctive patterns are the reticular, or microcystic, pattern and the endodermal sinus pattern. The reticular pattern consists of a loose meshwork of microcystic spaces lined by a single layer of flattened or cuboidal cells having clear or amphophilic cytoplasm and atypical, hyperchromatic nuclei. The endodermal sinus pattern is also known as the festoon or pseudopapillary pattern. It consists of anastomosing glands and papillae the linings of which are draped or “festooned” by columnar cells with clear or amphophilic cytoplasm and fusiform, hyperchromatic nuclei. Schiller-Duval bodies are most often associated with this pattern and are diagnostic of yolk sac tumor; they are found in about two thirds of cases. Schiller-Duval bodies are glomeruloid structures in which fibrovascular papillae lined by columnar tumor cells project into glands or cystic spaces lined by cuboidal cells. The endodermal sinus pattern often merges into the closely related alveolar-glandular pattern, in which anastomosing tubules or glands are surrounded by a myxoid or spindle cell stroma. The glands are lined by cuboidal or columnar cells that are often stratified into multiple layers or form small papillae. Glands of endometrioid or intestinal type are occasionally seen in a yolk sac tumor. In the endometrioid-like variant, which can be mistaken for endometrioid carcinoma, the glands are lined by a single layer of columnar cells that have clear supra- or subnuclear cytoplasmic vacuoles, somewhat reminiscent of the appearance of secretory endometrium. (Clement, Young et al. 1987) The intestinal pattern can mimic a primary or metastatic mucinous tumor. It consists of primitive endodermal glands lined by low columnar cells occasionally with intermixed goblet cells. (Kim, Hsiu et al. 1989) In the solid pattern there are nests or sheets of small to medium sized undifferentiated cells with a moderate amount of amphophilic or clear cytoplasm. In the polyvesicular vitelline pattern, cysts bearing a resemblance to yolk sac vesicles are lined by cuboidal, columnar, or mucinous epithelial cells. (Nogales, Matilla et al. 1978) The cysts are surrounded by myxoid immature cellular mesenchymal stroma. Rare patterns include a hepatoid pattern in which large cells resembling liver cells, with central vesicular nuclei, prominent nucleoli, and abundant granular eosinophilic cytoplasm grow in sheets or trabecula. (Prat, Bhan et al. 1982; Devouassoux-Shisheboran, Schammel et al. 1999) Extensive hepatoid differentiation may be present, but this pattern is more typically a focal microscopic finding.

<table>
<thead>
<tr>
<th>Yolk Sac Tumor Histologic Patterns</th>
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<tbody>
<tr>
<td>Microcystic (aka Reticular)</td>
</tr>
<tr>
<td>Macrocystic</td>
</tr>
<tr>
<td>Solid</td>
</tr>
<tr>
<td>Endodermal sinus (aka festoon)</td>
</tr>
<tr>
<td>Papillary</td>
</tr>
<tr>
<td>Glandular/alveolar (including intestinal, endometrioid)</td>
</tr>
<tr>
<td>Polyvesicular vitelline</td>
</tr>
<tr>
<td>Myxoid (aka myxomatous)</td>
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<tr>
<td>Parietal</td>
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Eosinophilic, PAS-positive, diastase-resistant hyaline globules are a distinctive finding in yolk sac tumors; they are most often found in the reticular and endodermal sinus patterns. The abundant PAS-positive extracellular hyaline material that is sometimes found in reticular or solid areas is thought to be indicative of parietal yolk sac differentiation. (Ulbright, Roth et al. 1986) The hyaline material contains laminin and type IV collagen and it resembles basement membrane ultrastructurally. It is worth noting that both hyaline globules and hyaline material in the stroma are present in clear cell carcinoma as well as yolk sac tumor. Small, bland, enteric glands lined by columnar and goblet cells are found in 50% of yolk sac tumors. Myxoid stroma containing spindle or stellate cells that stain with both cytokeratin and vimentin is prominent in 25% of yolk sac tumors. (Michael, Ulbright et al. 1989) These stromal cells may differentiate into mesenchymal elements such as cartilage, striated muscle, and bone, which are seen occasionally in yolk sac tumors. Stromal cells are luteinized in or adjacent to 15-20% of yolk sac tumors. Syncytiotrophoblastic giant cells are seen in rare cases.

Immunohistochemistry

Positive staining for AFP is the most characteristic immunohistochemical finding in yolk sac tumor. Positive staining of tumor cell cytoplasm, secretory material within cysts and glands, and some hyaline bodies is found in more than 75% of yolk sac tumors. However, staining is often weak and focal. (Ramalingam, Malpica et al. 2004) Other stains that are typically positive in yolk sac tumor include SALL4 and HNF-1β, (Cao, Guo et al. 2009) both of which are nuclear stains, and glypican-3, (Esheba, Pate et al. 2008; Maeda, Ota et al. 2009) which is a cytoplasmic stain. Staining for glypican-3 can also be seen in choriocarcinoma and in some teratomas. (Zynger, Everton et al. 2008) Yolk sac tumor does not stain for the primitive germ cell tumor markers OCT4 and NANOG, and staining for SOX2 is also reported to be negative. (Chang, Vargas et al. 2009) CD117 and D2-40, which show membrane staining in dysgerminoma, and CD30, which shows membrane staining in embryonal carcinoma, are negative in yolk sac tumor. (Chang, Vargas et al. 2009) I have found a simple keratin stain using antibody AE1/AE3 to be quite helpful in evaluating germ cell tumors. Yolk sac tumor is strongly positive and shows staining of the cytoplasm, while embryonal carcinoma shows a distinctive membrane pattern of staining, similar to that seen with CD30 in embryonal carcinoma. Yolk sac tumor is almost always negative for such epithelial markers as CK7 and EMA. (Ramalingam, Malpica et al. 2004) Immunohistochemical stains for human chorionic gonadotropin are negative except in rare tumors that contain syncytiotrophoblastic giant cells.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Yolk Sac Tumor</th>
<th>Embryonal Ca</th>
<th>Dysgerminoma</th>
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<tbody>
<tr>
<td>AE1/AE3</td>
<td>+, cytoplasm</td>
<td>+, membranes</td>
<td>- (dots and rims)</td>
</tr>
<tr>
<td>OCT4</td>
<td>-</td>
<td>+, nucleus</td>
<td>+, nucleus</td>
</tr>
<tr>
<td>NANOG</td>
<td>-</td>
<td>+, nucleus</td>
<td>+, nucleus</td>
</tr>
<tr>
<td>SOX2</td>
<td>-</td>
<td>+, nucleus</td>
<td>-</td>
</tr>
<tr>
<td>SALL4</td>
<td>+, nucleus</td>
<td>+, nucleus</td>
<td>+, nucleus</td>
</tr>
<tr>
<td>AFP</td>
<td>+, cytoplasm</td>
<td>-/+</td>
<td>-</td>
</tr>
<tr>
<td>Glypican-3</td>
<td>+, cytoplasm</td>
<td>-</td>
<td>-</td>
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Yolk Sac Tumor and Somatic Carcinomas

Most yolk sac tumors in females arise in the ovary in children or young adults. Rare examples have been reported in older women. Some of these have arisen in association with endometrioid carcinomas (Rutgers, Young et al. 1987; Nogales, Bergeron et al. 1996; Lopez, Malpica et al. 2003; McBee, Brainard et al. 2007) or other types of surface epithelial tumors such as mucinous neoplasms or mixed mullerian tumors. (Garcia-Galvis, Cabrera-Ozoria et al. 2008) Hybrid tumors with yolk sac components tend to be aggressive neoplasms with a poor response to chemotherapy, and a poor prognosis. (Nogales, Bergeron et al. 1996) Occasional cases have a more favorable outcome. Such neoplasms may be have somatic, rather than germ cell, origin. In our case, the presence of a synchronous small clear cell carcinoma of the fallopian tube was a confounding factor, and raises the possibility that the pelvic tumor might have originated from the clear cell carcinoma, along the lines of the ovarian and extraovarian examples that have arisen from endometrioid carcinomas. The yolk sac elements of these mixed tumors show the typical patterns of immunostaining detailed above, while the endometrioid carcinomas stain typically for epithelial tumors. In one example, the yolk sac component stained for alpha-fetoprotein, but not for CK7, EMA, CA125 or hormone receptors, which showed positive staining in the endometrioid carcinoma part of the tumor. (Abe, Furumoto et al. 2008)

Extraovarian Yolk Sac Tumor in the Pelvis

Most yolk sac tumors of the female genital tract occur in the ovaries. The most common extragonadal site is the vagina, where extraovarian yolk sac tumors arise in young children. (Young and Scully 1984; Arora, Shrivastav et al. 2002) Rare cases have been reported in the vulva, (Traen, Logghe et al. 2004) the cervix and the endometrium. (Spatz, Bouron et al. 1998) Yolk sac tumors arising in the pelvis outside of the ovary, like our case, are distinctly uncommon. (Clement, Young et al. 1988; Dede, Pabuccu et al. 2004) As of 2008, only 10 examples of pelvic yolk sac tumor had been reported. (Pasternack, Shaco-Levy et al. 2008) All previously reported examples of pelvic yolk sac tumor occurred in the usual age range for yolk sac tumor (22 months to 39 years) and exhibited typical patterns of yolk sac tumor. Two patients were pregnant at the time of diagnosis. The largest series, reported by Clement, (Clement, Young et al. 1988) et al contained only four cases, with the patients ranging in age from 17-39 years. The response to therapy has been variable, but patients treated with optimum tumor resection and chemotherapy can do well. Our case is unusual in that it occurred in a 59 year old postmenopausal women, well out of the usual age range, and it had an unusual histologic pattern. In the initial sections it grew purely in a diffuse pattern as solid sheets of malignant cells with clear or granular cytoplasm. Additional sections revealed some glands, but none of the typical patterns, such as the reticular pattern or the endodermal sinus pattern were seen, and no Schiller-Duval bodies were identified. Nevertheless, a panel of immunostains revealed the typical pattern for a yolk sac tumor, with lack of staining for CK7 and EMA and positive staining for alpha-fetoprotein, glypican-3, and HNF.

<table>
<thead>
<tr>
<th>HNF</th>
<th>+, nucleus</th>
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<tbody>
<tr>
<td>CD117</td>
<td>-</td>
<td>-</td>
<td>+, membranes</td>
</tr>
<tr>
<td>D2-40</td>
<td>-</td>
<td>-</td>
<td>+, membranes</td>
</tr>
<tr>
<td>CD30</td>
<td>-</td>
<td>+, membranes</td>
<td>-</td>
</tr>
<tr>
<td>EMA</td>
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References


