Serum biomarkers for evaluation of an adnexal mass for non-epithelial ovarian cancers

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adnexal mass

- An adnexal mass may be found in females of all ages, fetuses to the elderly.
- Adnexal masses occur less frequently in children and adolescents than in reproductive-age patients.

Evaluation

- The goal of the evaluation of a patient with an adnexal mass is to determine the most likely etiology of the mass.
- The evaluation is guided in large part by the anatomic location of the mass and age and reproductive status of the patient.
- As an example, a solid ovarian mass in a postmenopausal patient raises a high suspicion of ovarian cancer.

Evaluation

- The likelihood that an adnexal mass is malignant depends mainly upon one or more of the following factors:
  - Age or menopausal status
  - Risk factors
  - Imaging study findings that are consistent with malignancy
  - Laboratory results
- The age and menopausal status of the patient help to guide the process of evaluation, *with the highest proportion of malignancy found in an adnexal mass in a postmenopausal patient or a child or adolescent.*

- **fetal and neonatal ovarian cysts usually resolve spontaneously by six months of age.**

- **Children and adolescents**: when an adnexal mass is found in this patient population, there is a significant likelihood of adnexal torsion or an ovarian malignancy (approximately 10 to 20 percent) .

- Increased height velocity (may indicate the onset of puberty, which is associated with increased incidence of physiologic cysts; rarely may indicate hormone producing tumors).

children and adolescents

- The majority of ovarian tumors in children and adolescents are of germ cell origin (eg, mature teratoma, immature teratoma, gonadoblastoma, dysgerminoma .
- Approximately 35 to 45 percent of ovarian cancers in children are germ cell tumors.
- Epithelial tumors (eg, serous or mucinous cystadenoma are rare in prepubertal children.
- Sex cord-stromal tumors (eg, thecomas, fibromas, juvenile granulosa cell tumor, Sertoli-Leydig cell tumors) are rare in children and adolescents .
- They may present with isosexual or heterosexual precocious puberty.

- germ cell tumors are the most commonly encountered ovarian neoplasms in the pediatric population, followed by surface epithelial tumors and sex cord stromal tumors .

Premenopausal patients

- The great majority of adnexal masses occur in reproductive-age patients, and most of these masses are benign .
- many benign adnexal masses is associated with reproductive function (eg, follicular cysts, endometriomas).
- Pregnancy-related etiologies occur exclusively in reproductive-age patients by definition.
- Ovarian or fallopian tube cancer is less likely in premenopausal than postmenopausal patients, but the possibility of malignancy should be considered in all patients.

Postmenopausal patients

- Excluding malignancy is the main priority in postmenopausal patients with an adnexal mass (the average age of diagnosis of ovarian cancer in the United States is 63 years old) .
- Urgent conditions (eg, adnexal torsion, tubo-ovarian abscess) may also occur in postmenopausal patients, but are less common and are more likely to be associated with malignancy.
- Many of these patients will require a surgical evaluation.

Patients with an adnexal mass

- The degree of suspicion for malignancy in an adnexal mass is based upon all the available clinical information, including:
- Symptoms, P/E
- menopausal status,
- risk factors,
- Imaging
- biomarker testing
- The clinician must determine whether to proceed with surgical exploration and whether referral to a gynecologic oncologist is appropriate.

symptoms

- Nonspecific symptoms may be more common with epithelial than germ cell ovarian tumors.
- complaints of precocious puberty .
- Patients with an adnexal mass who present with symptoms or signs of estrogen excess (abnormal uterine bleeding) or androgen excess (virilization or hirsutism)

P/E

- The size, consistency, and mobility of a mass,
- a solid mass that is irregular or fixed or with posterior cul-de-sac nodularity.
- In endometriomas and tubo-ovarian abscesses :may be fixed and irregular. Posterior cul-de-sac nodularity in a premenopausal patient.
- The diagnosis of malignancy is almost certain in patients with both a fixed, irregular pelvic mass and an abdominal mass or ascites.

Imaging studies

- **Pelvic ultrasound** – Pelvic ultrasound is the imaging study of choice for the evaluation of an adnexal mass.
- less expensive than other imaging modalities and its diagnostic performance is similar .
- Both a transvaginal and transabdominal ultrasound should be obtained in most patients. Transabdominal ultrasound is better tolerated and is more helpful in visualizing abdominal processes.
- A definitive diagnosis of the type of adnexal mass can be made only with histologic evaluation, not with imaging. However, simple ovarian cysts, hemorrhagic cysts, endometriomas, and teratomas often have characteristic ultrasound features that are highly predictive of the histologic diagnosis.

Imaging studies

- ●**Magnetic resonance imaging** – MRI is used as a secondary imaging study to determine if surgical evaluation is needed in patients with ovarian masses that have an indeterminant appearance on ultrasound (eg, hemorrhagic masses in which mural clot can appear solid on ultrasound, mature teratomas with an atypical appearance, solid ovarian neoplasms) .
- ●**Computed tomography** – CT is not a primary modality for evaluation of adnexal masses. If an adnexal mass is incidentally detected on CT, further imaging with high-resolution transvaginal ultrasound is often needed to better characterize the mass. CT or MRI is used as part of noninvasive staging of patients with suspected ovarian cancer.

Ultrasonographic findings associated with malignant tumors

- Size ≥ 8 to 10 cm
- Multiple lesions
- Bilateral masses
- Solid or heterogeneous (solid components >2 cm, thick septations, papillary projections),
- metastatic
- Calcifications
- Ascites
- Increased blood flow (compared with minimal or no blood flow)

Tumor markers

- Tumor markers are molecules or substances produced by or in response to neoplastic proliferation that enter the circulation in detectable amounts.
- They indicate the likely presence of cancer, or provide information about its behavior.
- Serum biomarkers contribute to the evaluation of an adnexal mass for malignancy; however, their utility is limited.

Tumor markers

Preoperative measurement of biomarkers in patients with possible ovarian cancer has potential functions:

- diagnosis
- monitor treatment
- for post-treatment surveillance .
- may play a role in predicting whether optimal cytoreduction is feasible.

notice

- The decision whether to proceed with surgical evaluation for a patient with an adnexal mass depends mostly upon the appearance of the mass on imaging and other factors, rather than on a biomarker test.

- It is important to note that absence of elevated tumor markers does not exclude malignancy.

- Elevated platelets are a nonspecific marker of ovarian malignancy in children and adolescents and may be particularly helpful in the acute evaluation of ovarian mass with torsion (the platelet count is not typically elevated in ovarian torsion without malignancy).

Serum markers

- Germ cell and sex cord-stromal tumors may secrete hormones or other substances that can be detected preoperatively to contribute to the diagnostic evaluation.
- In many cases, however, the diagnosis of these histologic types is made only upon postoperative pathology evaluation of the ovary.

Germ cell tumors

- ✓ They mainly occur in girls, adolescents, and younger women who are often diagnosed with stage I disease; the median age at diagnosis is 16 to 20 years.
- ✓ In young women (<35 years) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors.However, pregnancy should also After be ruled out.
- ✓ Gonadal dysgenesis is a risk factor for germ cell tumors.
- ✓ Malignant germ cell tumors have an excellent prognosis.
- ✓ After appropriate treatment, 5-year survival is more than 85%.

Germ cell tumors &Tumor markers

- Tumor markers produced by tumors are as follows:
- ●**hCG** – Embryonal cell carcinomas and ovarian choriocarcinomas, mixed germ cell tumors, and some dysgerminomas.
- ●**AFP** – Yolk sac tumors, embryonal cell carcinomas and mixed germ cell tumors, and some immature teratomas ,polyembryoma carcinomas.
- most dysgerminomas are associated with a normal AFP.
- ●**LDH** – Dysgerminomas

Dysgerminoma

- Dysgerminoma, the most common malignant germ cell tumor, is the most common ovarian malignancy in children .
- The majority (82%) occur in people between 10 years and 29 years of age, with a minority (6%) in children younger than 10 years .
- **LDH** has been found to be positive in up to 95% of people with dysgerminomas .Because of the presence of syncytiotrophoblastic cells, 5% of dysgerminomas produce **HCG** .
- Approximately 70% of people present with Stage IA disease and are treated with surgical resection .
- It is bilateral in 10–15% of cases .

SCSTs

- Ovarian SCSTs are less common than tumors of epithelial cell and germ cell origin.
- . In contrast to the more common epithelial ovarian malignant neoplasms, most patients with malignant SCSTs are diagnosed with early-stage disease .
- Histology is generally low grade, lymph node metastases are rare, and prognosis is good .
- However, some neoplasms are aggressive and have a lethal outcome.

Ovarian sex cord-stromal tumors

- These tumors are often found in adolescents and young adults.

Manifestations:

- adnexal mass, abdominal pain, distention, and,rarely, torsion.
- In contrast to epithelial and germ cell tumors, however, sex cord stromal tumors frequently present with signs of hormonal production, such as hirsutism and virilization, menstrual changes,or precocious puberty.

Ovarian sex cord-stromal tumors

- These tumors are typically unilateral, 10 to 15 cm in greatest dimension, and may vary from solid, firm, and lobulated to soft and friable, often with hemorrhage and/or necrosis.
- Most patients with SCSTs present with early-stage disease; the disease is typically indolent.

Juvenile granulosa cell tumor

- Juvenile granulosa cell tumor is a malignant pure sex cord tumor predominantly occurring in people younger than 30 years.

- Juvenile granulosa cell tumor is a hormonally active estrogen-producing tumor; premenarchal females present with signs of precocious puberty, including vaginal bleeding, breast development, axillary and pubic hair, and somatic growth.
- Post-menarchal patients can present with menorrhagia or amenorrhea.There have also been reports of virilization
- Granulosa cells produce inhibin, and serum inhibin B levels might be positive.
- The majority of cases (>90%) are FIGO Stage IA and are treated with oophorectomy.

PREOPERATIVE EVALUATION AND INITIAL TREATMENT

- When an ovarian sex cord-stromal tumor is suspected, levels of inhibin, estradiol, testosterone, and AFP should be obtained.
- Inhibin levels may be elevated in granulosa cell tumors;
- inhibin B may be more predictive than inhibin A.
- Granulosa cell tumors may also present with elevated estradiol, and Sertoli-Leydig cell tumors may present with elevated testosterone or, rarely, AFP.

adnexal mass and abnormal uterine bleeding

- The differential diagnosis in patients who present with both an adnexal mass and abnormal uterine bleeding includes:
- SCSTs
- ovarian metastasis from a primary uterine cancer
- an endometrial metastasis from a primary ovarian malignant neoplasm,
- separate primary ovarian and endometrial carcinomas.

Endometrial sampling

- Endometrial sampling should be performed in premenopausal patients with an adnexal mass and abnormal uterine bleeding and in postmenopausal patients with a thickened (>4 to 5 mm) endometrial stripe on transvaginal ultrasound examination since these signs/symptoms can be due to excess estrogen production and affect management.
- ●

Endometrial sampling

- Endometrial sampling will detect endometrial hyperplasia/intraepithelial neoplasia in 25 to 50 percent of patients with granulosa cell tumors and carcinoma in 5 to 10 percent .
- In patients with thecoma, carcinoma is present in approximately 20 to 25 percent of patients, and another 15 percent have a precursor lesion.
- Theca cells produce androstenedione, a weak androgen, and granulosa cells convert the androstenedione to estradiol.

Table 4 Tumor markers and associated ovarian neoplasms

α-fetoprotein[a]	Yolk sac tumor
	Immature teratoma
	Embryonal carcinoma
	Mixed germ cell tumor
	Sertoli-Leydig cell tumor
β-human chorionic gonadotrophin	Choriocarcinoma
	Embryonal carcinoma
	Dysgerminoma
Inhibin	Juvenile granulosa cell tumor
Lactate dehydrogenase[a]	Dysgerminoma

[a] Sometimes test positive in children with mature cystic teratoma

SURVEILLANCE
MALIGNANT GERM CELL/SEX CORD-STROMAL TUMORS

Malignant Germ Cell Tumors					
	Year 1	Year 2	Year 3	Years 4–5	After 5 Years
Dysgerminoma					
Physical exam and serum tumor markers[a]	Every 2–3 mo	Every 3–4 mo	Every 6 mo	Every 6 mo	Annually
Radiographic imaging	Abdominal/pelvic CT (every 3–4 mo)	Abdominal/pelvic CT (every 6 mo)	Abdominal/pelvic CT (annually)	Abdominal/pelvic CT (annually)	As clinically indicated
Non-dysgerminoma					
Physical exam and serum tumor markers[a]	Every 2 mo	Every 2 mo	Every 4–6 mo	Every 6 mo	Annually
Radiographic imaging	Chest/abdominal/pelvic CT (every 3–4 mo)	Chest/abdominal/pelvic CT (every 4–6 months)	Abdominal/pelvic CT (every 6–12 mo)	Abdominal/pelvic CT (every 6–12 mo)	As clinically indicated

Malignant Sex Cord-Stromal Tumors[c]		
	0–2 Years	After 2 Years
Physical exam	As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Serum tumor markers[a]	• Testing as clinically indicated, if applicable • If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	• Testing as clinically indicated, if applicable • If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Radiographic imaging[b]	Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam	Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam

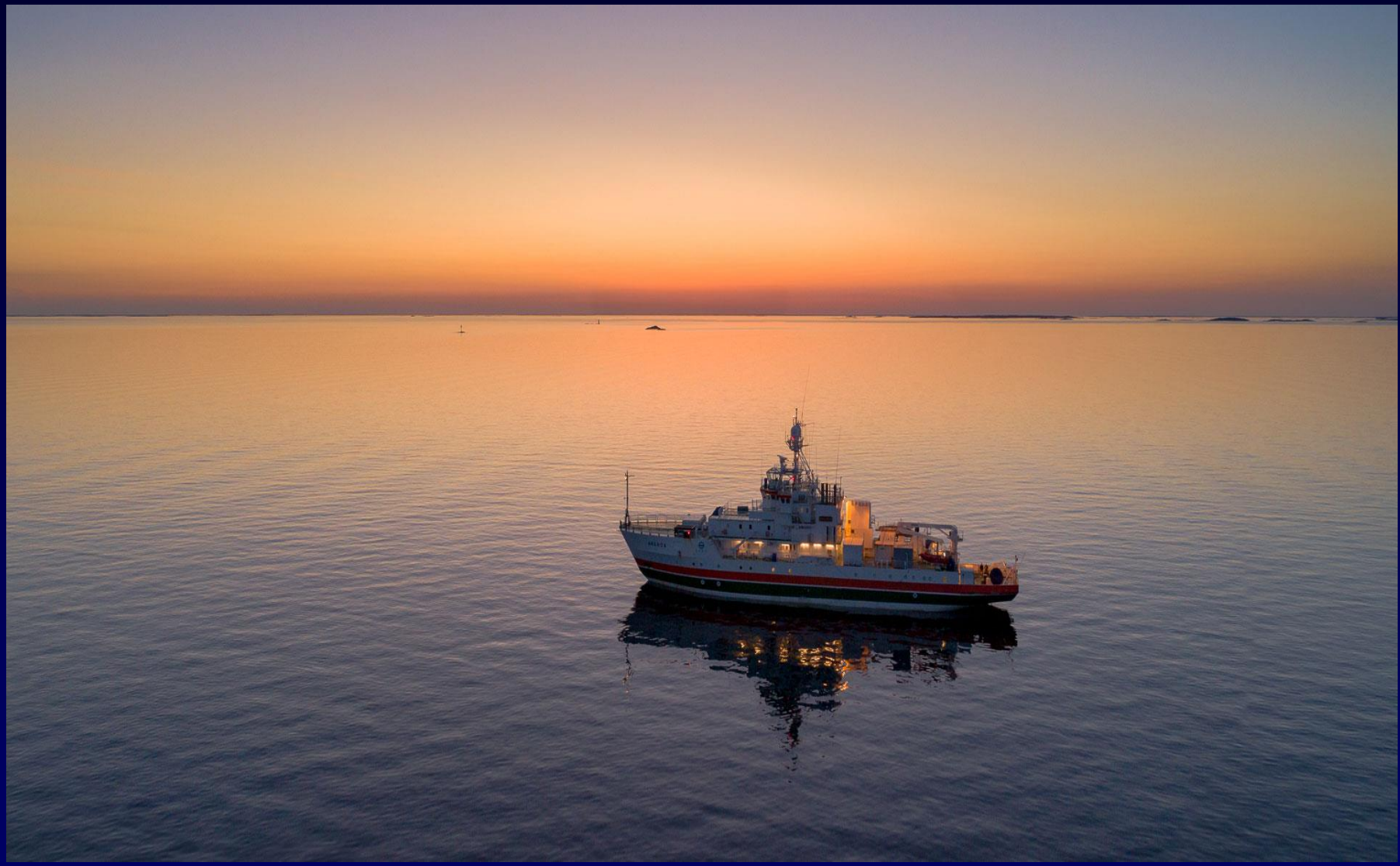
[a] See OV-1 for markers.
[b] Chest x-ray, chest/abdominal/pelvic CT, MRI, PET/CT, or PET; with contrast unless contraindicated.
[c] Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of

Clinical scenario: A child or adolescent who presents with an adnexal mass

- Germ cell tumor :
- human chorionic gonadotropin, lactate dehydrogenase, and alpha-fetoprotein,
- and add total testosterone and dehydroepiandrosterone if the child has virilization
- and estradiol, and luteinizing hormone and follicle-stimulating hormone if the child has precocious puberty.
- Very high concentrations of estradiol, with associated suppression of gonadotropins, are generally indicative of peripheral precocity, such as from an ovarian tumor.
- ●Patients with an adnexal mass who present with symptoms or signs of estrogen excess (abnormal uterine bleeding) or androgen excess (virilization or hirsutism) may have a germ cell or sex cord-stromal tumor.

summary

- Tumor markers may include CA-125, inhibin, beta-hCG, alfa-fetoprotein,LDH and carcinoembryonic antigen (CEA).
- Women younger than 35 years with a pelvic mass should have tumor markers measured to assess for germ cell tumors and to rule out pregnancy.
- An intraoperative frozen section evaluation is recommended for women who would like to maintain their fertility.



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