Ovarian germ-cell malignant tumors

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Abstract
Ovarian germ-cell tumors represent 15–20% of all ovarian tumors. They are rapidly growing neoplasms that arise from primordial germ cells derived from the embryonal gonad. Malignant germ-cell tumors represent 5% of ovarian tumors. Their annual incidence in France is 0.5/100,000 females. The diagnosis, suspected on physical examination, relies on pelvic or transvaginal ultrasonography detection of a voluminous ovarian mass responsible for abdominal discomfort and/or swelling, but is only confirmed during the initial surgical intervention (laparotomy). Dosage of tumor markers -human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH) and alpha-fetoprotein (αFP)- also contribute to the diagnosis, the prognosis and follow-up of the disease. Surgery is the main therapeutic modality; it consists of excision of the tumor masses and preservation of reproductive function should be attempted. Among non-hematological cancers, malignant germ-cell tumors can be curable with cytotoxic chemotherapy and the introduction of cisplatin into therapeutic regimens constituted a decisive advancement. Malignant ovarian germ-cell tumors share a common cytogenetic characteristic with all ovarian, testicular or extragonadal germ-cell tumors of children and adults: the presence of an isochromosome of the short arm of chromosome 12 [(12p)], which is not found in any other type of cancer.

Keywords
Ovarian germ-cell tumors, embryonal gonad, chorionic gonadotropin (hCG), lactate dehydrogenase (LDH), alpha-fetoprotein (αFP), isochromosome 12 [(12p)]

Definition
Germ-cell tumors of the ovary represent 15–20% of all ovarian tumors. These rapidly growing neoplasms arise from primordial germ cells derived from the embryonal gonad and can reach impressive dimensions in a short period of time. Approximately 95% of germ-cell tumors are represented by benign cystic teratomas and are relatively easy to diagnose. The remaining 5% are malignant germ-cell tumors and are responsible for most of the diagnostic difficulties encountered, particularly for tumors associating several histological types. Two histological groups are distinguished: dysgerminomas (45%), equivalent to testicular seminomas, and non-dysgerminomatous (non-seminomatous) tumors. The latter include: 1. yolk-sac tumors or endodermal sinus tumors (20%); 2. teratomas (20%) classified into three grades according to the extension of the immature...
neuroectodermal component (the present tendency is to combine grades II and III);
3. rare pure embryonal carcinomas (< 5%);
4. pure choriocarcinomas (< 1%);
5. composite tumors (10%), including mature and immature teratomas and/or yolk-sac tumors, and embryonal carcinoma associated with a predominantly dyserminomatous component (Scully, 1979).

Frequency
Malignant germ-cell tumors represent 5% of ovarian tumors. The annual incidence in France is 0.5/100,000 females and the number of new cases/year is estimated to be around 100 (Williams and Gershenson, 1993).

Diagnostic methods
The diagnosis, suspected based on physical examination, relies on pelvic or transvaginal ultrasonographic demonstration of a voluminous ovarian mass responsible for abdominal discomfort and/or swelling. For certain histological subtypes, notably embryonal carcinoma, signs of precocious puberty are sometimes the factors motivating consultation. But it is the first surgical intervention (laparotomy) that establishes the diagnosis. The latter can also be made based on dosage of the following tumor markers (see Table 1):

**Human chorionic gonadotrophin (hCG)**
hCG, a glycoprotein with molecular mass of 33 kDa and a half-life of 3 days, can be measured by radioimmunoassay. It is secreted by pure dysgerminomas. hCG is comprised of two subunits: an alpha-subunit, common with hypophyseal hormones, and a beta-subunit specific to hCG.

**Alpha-fetoprotein (αFP)**
αFP, a glycoprotein with molecular mass of 130 kDa and a half-life of 7 days, can be measured by radioimmunoassay. It is secreted by yolk-sac tumors and some embryonal carcinomas. Its level is often elevated in patients with mixed tumors and is never above normal in those with pure dysgerminomas.

**Lactate dehydrogenase (LDH)**
Measurement of LDH concentrations is particularly informative for patients with dysgerminomas for whom they are often elevated (Sheiko and Hart, 1982).

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>αFP</th>
<th>hCG</th>
<th>LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Mixed tumor</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Table 1. Serum markers of malignant ovarian germ-cell tumors

When an ovarian germ-cell tumor is suspected, these markers should systematically be tested before surgical intervention, and even before any surgery for a pelvic mass in a young woman.

**Disease progression**
Dosage of tumor markers — hCG, LDH and αFP — is also informative in terms of prognosis and follow-up of disease progression. Even though their prognostic values have not been clearly established, an increased concentration signals a tumor relapse. Although the specificities of these markers are very high, their sensitivities are not definitive, as clinical progression can occur in the absence of increased concentrations of tumor markers (Bidart et al., 1992; Droz et al., 1992). Patient's age (above 22 years) has also been described a negative prognostic factor to be taken into consideration (Mayordomo et al., 1994).

Other tumor markers have been evaluated (CA125, CA19.9, neuron-specific enolase (NSE), angiotensin, macrophage–colony-stimulating factor (MCSF)) (Kawai et al., 1991). However, their concentrations have only been measured in a small number of patients, so their contribution outside a therapeutic trial has not yet been determined (Suzuki et al., 1998).

Several studies have attempted to identify prognostic factors able to establish metastatic risk. Frequently described factors include: tumor size (> 10 cm), histological type (endodermal sinus, choriocarcinoma) and a high histological grade (for immature teratomas) (Kurman and Norris, 1976a; Norris et al., 1976). Residual tumor after surgery appears to be a determinant negative prognostic factor (Slawton, 1984; Williams et al., 1989).

**Management**
Treatment of rare ovarian tumors is currently as follows.
Surgery is the same as that for ovarian adenocarcinomas, with one major difference: conservation of reproductive function in women of reproductive age is usual case for this type of tumor.

Chemotherapy, based on data reported in the literature, is the same as that prescribed for testicular germ-cell tumors.
Surgery, chemotherapy and possible surgical intervention for residual lesions is highly complex.

**Surgical management**
The initial surgery is primordial for these rare ovarian tumors because it provides the diagnosis, determines the extent of disease dissemination and is also the first therapeutic modality.

Although many patients underwent initial surgery to excise ‘all’ tumor masses (total hysterectomy with bilateral adnexectomy, omentectomy, complete abdominal exploration and lymph-node dissection), some were able to have conservative surgery (preserving the contralateral ovary and the uterus) associated with a complete abdominal exploration (Culine et al., 1997a).

Exploratory surgery after chemotherapy is not indicated for pure dysgerminomas, even if retroperitoneal masses persist, because they often do not contain viable tumor cells and can continue to regress; endodermal sinus tumors and choriocarcinomas secrete sufficiently reliable tumor markers (aFP and bhCG, respectively); patients with early stage disease and for whom the initial surgery was complete. Surgical reintervention is necessary in the following situations. When only biopsies were taken during the first surgery, reintervention consists of excising the ovary where the primary tumor was located. For embryonal carcinomas or mixed non-secretory germ-cell tumors, it is essential to remove residual lesions after chemotherapy because neither imaging nor tumor markers are sufficiently reliable to determine their histological nature (Gershenson, 1993, 1994). Certain components of teratomas, especially neuroectodermal, can, by losing all their malignant potential, evolve towards maturation. This mature tissue can become voluminous (growing teratoma) and be responsible for functional complications (Gershenson et al., 1985, 1986; Williams and Gershenson, 1993; Geisler et al., 1994).

Simple monitoring after surgery is classically recommended only for stage I dysgerminomas or immature stage I and grade I teratomas which carry an extremely low risk of relapse (Norris et al., 1976; Thomas et al., 1987; Dark et al., 1997). As far as the other tumors are concerned, notably embryonal carcinomas or yolk-sac tumors and those discovered at stage II, III or IV, adjuvant chemotherapy after surgery is prescribed because of the high risk of relapse.

**Chemotherapy**
Among non-hematological cancers, malignant germ-cell tumors can be curable by cytotoxic chemotherapy. Too rare to be included in randomized studies, treatment of these tumors has benefited from the therapeutic advancements made against testicular germ-cell tumors. The inclusion of cisplatin in therapeutic regimens constituted a decisive step forward that radically prolonged patient survival (Einhorn, 1981). Studies that have been published mainly considered the association of PVB (cisplatin, vinblastine and bleomycin). Since 1987, vinblastine has been replaced by etoposide, because the BEP (bleomycin, etoposide and cisplatin) regimen was shown to be as effective as PVB against testicular tumors and less toxic (Williams et al., 1987). Chemotherapy should be adapted to the histological type and the tumor stage (Culine et al., 1997b). Because of the rapid tumor growth, it should be started shortly after surgery (1 week to 10 days) (Herrin and Thigpen, 1999).

The acute toxicities observed, especially hematological, are the same as those reported during chemotherapy for testicular germ tumors (Einhorn, 1990).

**Treatment of relapses**
Among patients who had been in relapse after first-line surgery and/or radiotherapy, 69% treated with a cisplatin-containing regimen achieved long-term complete remissions (Williams et al., 1989). Concerning salvage therapy after the failure of chemotherapy, the indications for surgery at relapse are still being discussed and the results of second-line chemotherapy have been difficult to analyze. As regards relapse treatment, sensitivity to platinum has appeared, only recently, to be an important element. Indeed, patients relapsing more than 6 weeks after the end of cisplatin therapy are defined as being platinum-sensitive, whereas those whose disease progressed in less that 6 weeks after the end of the chemotherapy regimens are considered to be platinum-resistant (Loehrre et al., 1988; Motzer et al., 1991; Gershenson, 1993).

**Etiology**
Malignant ovarian germ-cell tumors share a common cytogenetic characteristic with all ovarian, testicular, extragonadal germ-cell tumors of adults or children: the presence of an isochromosome of the short arm of chromosome 12 [(12p)], which is not found in any other type of cancer (Kurman and Norris, 1976b).

**References**


