Ovarian tumors of sex cord-stromal origin

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Abstract

Tumors of the stroma (Leydig cells) and/or sex cords (Sertoli cells) represent approximately 8% of ovarian tumors and develop from the connective tissue (respectively, interstitial and nurse cells) of the ovaries. Because these cells participate in ovarian hormonal function, most of the sex-cord or stromal tumors are able to secrete hormones (estrogens, androgens, corticoids), which explains the hormonal dysfunctions associated with these cancers. Their prognoses are difficult to establish; some of the tumors are almost always benign (Sertoli cell tumors, Leydig cell tumors, ...), whereas others are malignant but with more-or-less delayed local-regional or metastatic relapses. The histological criteria of aggressivity are so poorly known that it is difficult to even propose a dichotomous, benign-malignant histopathological classification. If they do not present clinical criteria of "malignancy", these tumors are considered to be of uncertain prognosis. In this group of tumors, the following might have "malignant" behavior: granulosa cell tumors, androblastomas (or Sertoli-Leydig cell tumors), tumors of the sex cords with annealed tubules, tumors of the steroid-producing (theca) cells without any other specification, and fibrosarcomas. Surgery is the most important therapeutic modality and must be as conservative as possible to preserve reproductive function; it can be effectively combined with chemotherapy.

Keywords

Ovarian tumors, granulosa cell tumors, Sertoli-Leydig cell tumors, gynandroblastomas

Introduction

Granulosa cell tumors, Sertoli-Leydig cell tumors, gynandroblastomas and thecal cell tumors, not further specified belong to the group of sex cord-stromal tumors, which represent approximately 8% of ovarian tumors. As these tumors develop from the connective tissue of the ovaries, which participate in ovarian hormonal function, most of the sex-cord or stromal tumors secrete hormones (estrogens, androgens, corticoids), and thus lead to hormonal dysfunctions.

Granulosa cell tumors

Introduction

Granulosa cell tumors are malignant tumors of sex cord and stromal origin. Two histological forms are known: juvenile and adult. Two histological forms are known: juvenile and adult. This is the most common (95% of granulosa cell tumors).

Frequency/incidence

Granulosa cell tumors represent 2-3% of ovarian tumors and are the most common malignant tumors in the group of sex cord and stroma tumors.
Clinical description
Granulosa cell tumors almost always contain granulosa and thecal cells; the endocrine manifestations associated with them are often estrogenic.

Disease progression
Granulosa tumors are often slowly progressive and can relapse late (at a mean of 6 years). Relapses occurring 20 or 30 years after the first treatment have been reported for 5% of the patients in relapse. However, certain aggressive forms relapse and progress more rapidly (Segal et al., 1995). The International Federation of Gynecology and Obstetrics (FIGO) stage, intraperitoneal tumor rupture and bilateral tumors are the most often reported factors of prognosis. The patient's age and the size of the tumor (> 5 cm) have a less certain prognostic value (Garcia and Morrow, 1999). Among the cytological factors, the number of mitoses has the highest prognostic value, with prognosis being pejorative beyond 5 or 10 mitoses per 10 high power fields (HPF). Cellular atypia and poor differentiation (rarity of Call-Exner bodies) have a lower prognostic value (Miller et al., 1997). Markers of cell proliferation (ploidy, DNA content) and expression of P53, C-MYC or C-ERB-B2 have no proven prognostic value (Hitchcock et al., 1989; Suh et al., 1990; King et al., 1996).

Management and Treatments
Surgery
Because 70% of the patients present with stage I tumors, surgery represents the most important therapeutic arm (Garcia and Morrow, 1999). Its role is essential but no precise recommendation can be given concerning its modalities: exeresis of all the lesions remains the foundation of therapy. For early-stage tumors, conservative surgery, preserving the possibility of a future pregnancy, can often be performed. Otherwise, it is reasonable to perform a total hysterectomy with bilateral adnexectomy (Pankratz et al., 1978). For young women who can be offered conservative therapy, uterine curettage should be performed before surgery, because of the frequent association of tumors of granulosal origin with endometrial hyperplasia (55%) or endometrial adenocarcinoma (4-20%) (Evans et al., 1980; Ohel et al., 1983). Finally, the long natural history of the disease pleads for repeated surgery should a relapse occur (Jacobs et al., 1982).

Radiotherapy
Granulosa cell tumors are radiosensitive but the role of radiotherapy has not yet been defined: the volume to be irradiated has not been determined, the radiation doses are not specified and no data are available on survival after radiotherapy.

Chemotherapy
The chemosensitivity of these tumors has been demonstrated by the numerous responses observed in the contest of palliative therapy: responses of short duration to alkylating agents, frequent responses to Adriamycin-bleomycin, Actinomycin-fluorouracil-cyclophosphamide combinations added to cisplatin. The highest response rate (80%) was obtained with PVB (cisplatin, vinblastine and bleomycin).

Monitoring
Two serum markers seem to be useful as indicators of relapse: estradiol for secretory tumors (Kaye and Davies, 1986) and inhibin, a peptide hormone secreted by granulosa cells (Lappohn et al., 1989). Because the risk of breast cancer in these patients is non-negligible, especially those with the juvenile form, clinical monitoring and regular mammograms should be performed (Evans et al., 1980).

Sertoli-Leydig cell tumors
Definition
Sertoli-Leydig cell tumors belong to the group of sex cord-stroma tumors. These tumors are derived from mesenchyme and sex cords, which regroup histologically all the embryonic phases of testicular development: from a diffuse stromal and undifferentiated cord appearance to well-differentiated Sertoli tubes.

The majority of these tumors are benign, but around 20% relapse or give rise to metastases that can be fatal. Familial forms have been described frequently and should be sought (Zaloudek and Norris, 1984). These tumors contain variable proportions of Sertolian and Leydigian elements. Tumors with only a Sertolian component (Sertoli tumors) belong to the benign group. Tumors containing both types of components are classified into three groups as a function of the more-or-less differentiated character of the two constituents:
1. benign differentiated forms (androgenic, secretory in 60% of the cases);
2. intermediate differentiation (immature Sertoli cells);
3. poorly differentiated forms (sarcomatoid or retiform). It is possible to see heterologous elements in the forms with poor or intermediate differentiation (primarily epithelial or mesenchymatous).

Frequency/Incidence
These tumors represent 0.2% of ovarian tumors.
Clinical description

These tumors occur most frequently in 25-year-old women. The majority of patients present with non-specific symptoms, such as an abdominal mass, pain, menstrual disorders, and 50% have signs of virilization (Garcia and Morrow, 1999). Three clinical signs are highly evocative of the disease: amenorrhea, masculine voice and hirsutism associated with hypertrrophy of the clitoris. Very rarely, these tumors can secrete estrogens, which sometimes lead to precocious puberty.

Disease progression

Malignant Sertoli-Leydig tumors tend to relapse early (2-3 years). The prognostic factors include stage, histological grade (differentiation), tumor rupture and the presence of heterologous mesenchymatous constituents. The number of mitoses is a potential prognostic factor but seems to be associated with the histological grade of the tumor (Young and Scully, 1985; Zaloudeek and Norris, 1984).

Management and Treatments

Surgery

The comment made concerning granulosa cell tumors applies here as well. Surgery is essential but no precise recommendations can be given concerning its modalities: excision of all the lesions present remains the basic treatment. Conservative surgery to allow a future pregnancy is often possible for early stage tumors. Otherwise, it is reasonable to perform a total hysterectomy with bilateral adnexitomy (Pankratz et al., 1978). For young women who can be offered conservative surgery, uterine curettage must be performed before surgery (Evans et al., 1980; Ohel et al., 1983). Reintervention is recommended for relapses (Jacobs et al., 1982).

Radiotherapy

No data are available on the effect of radiation therapy on Sertoli-Leydig cell tumors. Although several reports indicated a certain radiosensitivity of these tumors, the associated toxicity was more severe than that of chemotherapy (Kietlinska et al., 1993; Zaloudeek and Norris, 1984).

Chemotherapy

Several chemotherapy regimens have been used to treat Sertoli-Leydig cell tumors: alkylating agents, adriamycin, CAP (cisplatin, adriamycin and cyclophosphamide), PVB (cisplatin, vinblastine and bleomycin). In the majority of cases, the effect could not be evaluated. Partial responses of short duration have been observed and survival appeared not to be or only slightly modified (Reddick and Walton, 1982; Zaloudeek and Norris, 1984; Ulbright et al., 1987; Roth et al., 1988). Complete responses have been described for the combination of VAC and BV-CAP (Schwart and Smith, 1976; Gershenson et al., 1987).

Monitoring

Patients presenting with signs of virilization, i.e., those who had developed a secretory tumor, can benefit from dosaging of hormone (dehydroepiandrosterone (DHEA)-sulfate, estrogen, 17-hydroxyprogesterone, cortisol) levels at the time of diagnosis. This testing can exclude adrenal abnormalities, and monitor the efficacy of treatment and post-surgical follow-up.

Gynandroblastomas

Gynandroblastomas are extremely rare tumors that represent less than 1% of sex-cord tumors and are probably derived from undifferentiated mesenchyme. This origin would explain their "bisexual" potential. These tumors contain variable but high proportions of granulosa cells and Sertoli (sex-cord, nurse)-Leydig (interstitial stroma) cells. Because of the androgenic stimulation, signs of virilization generally predominate over estrogenic effects. In the majority of cases, these tumors are benign and only adapted surgery is recommended. However, certain malignant tumors have been described in the literature and they are usually large tumors, 7-10 cm in diameter, developing in women 30-50 years old. Endometrial hyperplasia is often associated and should be sought.

Therapy is the same at that for granulosa cell tumors, particularly those concerning surgery. Chemotherapy can be prescribed for tumors with a pejorative prognosis or relapses.

Steroid-producing (thecal) cell tumors, not further specified

Thecal cell tumors, not further specified, belong to the group of sex-cord (Sertoli (nurse) cell)-stroma (Leydig (interstitial) cell) tumors and have malignant and thus metastatic potential. Clinically, they can be accompanied by signs of virilization or hyperestrogenic manifestations. The stage, patient's age, size of the tumor, presence of necrosis, nuclear atypia and the number of mitoses have been reported to have an impact on the prognosis of the disease.

Therapy is the same as that recommended for granulosa cell tumors, especially concerning surgery. Chemotherapy can be prescribed for patients with pejorative prognoses and those with relapses.
References


