Pathogenic and therapeutic particularities in recurrent ovarian granulosa cell tumors

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ABSTRACT

Ovarian granulosa cell tumors represent a rare histopathological subtype of ovarian malignancies which are usually diagnosed in early stages of the disease and have a favorable prognosis. However, in certain cases recurrence might occur even if long disease free survival periods are encountered. The aim of the current paper is to discuss the patterns of spread in this histopathological subtype as well as the most important therapeutic strategies in cases diagnosed with ovarian granulosa cell tumors recurrence.

Keywords: ovarian granulosa cell tumors, pathogenesis, spread, recurrence

INTRODUCTION

Ovarian granulosa cell tumors represent a rare histopathological subtype of malignancies representing less than 5% of all ovarian cancers diagnosed worldwide each year [1]. Among these cases, the adult subtype is present in up to 90% of patients and are most often diagnosed in early stages of the disease [2]. Even though, up to 20% of cases will develop after a certain interval recurrent disease, multiple patterns of spread being suspected. However, in such cases, due to the relatively low number of patients, a standard therapeutic strategy is not well standardized. In such cases different therapeutic strategies such as systemic chemotherapy, monoclonal antibodies, hormonal therapy or reoperation have been proposed, their management being usually extrapolated from epithelial ovarian cancer [3-5].

PATTERNS OF SPREAD

Although recurrence after ovarian granulosa cell tumors represent a rare event, relapse has been reported so far after decades from the initial diagnostic; this phenomenon is explained through the fact that these tumors usually exhibit a low proliferation index and an indolent course, leading to the apparition of late recurrences [6].

When it comes to the most commonly incriminated patterns of spread in cases diagnosed with ovarian granulosa cell tumors, they are represented by the lymphatic spread and peritoneal spread. In order to determine the presence of recurrent disease and to provide an efficient follow up of patients with previous history of surgically treated ovarian granulosa cell tumors, different serum markers have been proposed, with various results. Therefore, although traditionally ovarian tumors have been monitored by detecting the serum levels of CA 125, it seems that in this tumoral subtype does not secrete such mole-

cules and therefore, CA125 determination will fail to demonstrate the presence of recurrent disease. Another proposed biomarker was represented by the anti- Mullerian hormone, which is also useful in order to monitor the ovarian function and fertility; the anti- Mullerian hormone is produced by granulosa cells and might present increased serum values in both newly diagnosed and relapsed ovarian tumors. However, the most sensitive biomarker in order to detect the risk of developing recurrent disease is represented by Inhibin B [6,7]. Increased serum levels of inhibin B and anti-Mullerian hormone are usually encountered before the apparition of symptoms or before the apparition of any imagistic suspicion of recurrent disease [7].

THERAPEUTIC STRATEGIES IN RECURRENT OVARIAN GRANULOSA CELL TUMORS

As mentioned before, the highest number of granulosa cell tumors are diagnosed in early stages of the disease and therefore, they are perfectly curable by performing a radical surgical procedure. In such cases the role of adjuvant chemotherapy is strongly debatable; meanwhile, cases diagnosed in more advanced stages of the disease are at a higher risk of developing recurrent lesions. In such cases combined therapeutic options such as chemotherapy, radiotherapy and surgery might be the option of choice. Radiotherapy has been proposed in order to improve the long-term outcomes, however, the benefits are not clearly defined. Therefore, although an improved disease free survival is achievable, the long term survival is not significantly modified [8]. Another therapeutic option which should be taken in consideration in cases presenting recurrent disease is represented by the endocrine therapy consisting of estrogen receptor antagonists, progesterone, aromatase inhibitors or gonadotropin releasing hormone agonists [9]. However the efficacy of the method ranges between 20% and 70%, being significantly influenced by the amount of hormonal receptors at the level of the tumoral masses [10].

As expected, cases which are suitable for surgery with curative intent will be submitted to peer primam resection, while cases presenting locally advanced or disseminated lesions are considered to be rather candidates for neoadjuvant chemotherapy or hormonal therapy; once tumoral regression is achieved, surgery will be proposed with better chances to control the disease. Most often recurrent disease is found at the level of the peritoneal cavity suggesting the idea that peritoneal tumoral implants already existed at the time of the initial diagnostic and were probably missed at that moment. As expected, while at the time of the initial diagnostic up to 100% of cases will benefit from radical surgery, at the time of relapse this percent will decrease at 75-85%. When it comes to the time of relapse, most often these cases recur within the first 10 years from the initial diagnosis while the most commonly encountered sites of relapse are represented by the pelvic area followed by peritoneum and omentum; in isolated cases hematogenous, distant metastases at the level of the lungs and liver might be encountered [11]. In such cases, depending on the number, location and dimensions of the recurrences, surgery should be the option of choice; in cases in which is not feasible, neoadjuvant therapy for conversion or palliative systemic therapy might be performed.

The presence of high amounts of vessels at the level of these recurrent tumors make them susceptible to angiogenesis inhibitors such as vascular endothelial growth factor (VEGF) inhibitors. Interesting results have been reported in this direction after administration of Bevacizumab, a VEGF inhibitor, repsonse rates of up to 40% of cases being reported; meanwhile, cases in which bevacizumab was administrated reported similar progression free survival intervals when compared to cases submitted to systemic chemotherapy [12].

Another promising therapy is represented by the administration of monoclonal antibodies such as imatinib, their efficacy being influenced by the overexpression of stem cell growth factors [13].

Meanwhile, tumor necrosis factor related apopptosis inducing ligands are now under investigation. However more studies are needed before introducing these molecules as standard therapeutic options in recurrent granulosa cell tumors [14].

CONCLUSIONS

Patients with ovarian cell granulosa tumors might develop recurrent disease, the incidence of relapse being related to the initial stage at diagnostic; although most often recurrent disease develop in cases presenting advanced stages at the time of diagnostic, relapsed disease can be also encountered in cases diagnosed in early stages of the disease. The most frequently incriminated patterns of spread are represented by the peritoneal, hematogenous and lymphatic route. When it comes to the therapeutic approaches in such cases, it can range between surgery, systemic chemotherapy or hormonal therapy, the first intent option being chosen accordingly to the extent and location of recurrent disease.

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