Clinical differentiation between ovarian granulosa cell tumor and ovarian cancer: a review

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Abstract

Differentiation of granulosa cell tumor and ovarian cancer doesn't seem to cause much trouble in everyday clinical work. Despite quite easy distinction, within the researches discussed within this review, findings were suggesting less obvious results. There was a huge urge to take into consideration immunohistochemical differentiation. Common symptoms of many gynecological tumors are very similar, studies investigated that GCT and ovarian cancer frequently overlap. Symptoms, method of treatment and prevalence rate (at some point) are often shared between these neoplasms. Fortunately, great distinction was provided by immunohistochemical findings.

Keywords: ovarian cancer, granuloma cell tumour, GCT, oGCT

Basic characteristics

Granulosa cell tumor (GCT) is a rare ovarian carcinoma belonging to the sex cord gonadal-stromal tumors [1]. It constitutes less than 5% of primary ovarian tumors, at the same time being the most common neoplasm among sex cord tumors. It is characterized by slow growth rate, but due to high and late recurrence rate [2], it is classified among potentially malignant neoplasms [3], however, it is placed within low-grade malignancy neoplasms [4]. Basic classification based on occurrence age divides GCT into two types: juvenile (JGTC) and adult granulosa cell tumor (AGTC) [5]. This classification will be necessary for further distinction between different neoplasms, as it has a distinct prevalence rate at different age. Important distinctive feature of GCT is hormonal activity. It was found that a granulosa cell tumor is capable of secreting estradiol [19].

Second investigated within this review ovarian malignancy is ovarian cancer. Ovarian cancer is a malignant, cancerous tumor of an ovary [17]. One of its most misfortunate features is that it is usually asymptomatic until it has progressed to an advanced stage. At the beginning of the disease, the symptoms are nonspecific but very common in the community, including early satiety, bloating, loss of appetite, urinary urgency, weight loss, vaginal or rectal bleeding. In more advanced stages an adnexal mass is frequently discovered during an abdominal or pelvic bimanual examination. Very often it can be an incidental finding [15]. Ovarian cancer belongs to nonfunctional tumors, which means that it has no hormonal activity [18].

Epidemiology

Granulosa cell tumor has various occurrence age based on its classification. Juvenile GCT mostly affects patients before, or at the early stage of puberty, ranging approximately between 22 months to 15 years 7 months age [6]. At the same time, the adult type of GCT is most commonly found in patients aged between 50 and 54 years of age during their perimenopausal or early postmenopausal stages [8].

Ovarian cancer has a less scattered prevalence rate, as in 80% it affects women in their postmenopausal period starting from their 50's, successively increasing in prevalence until their 80's [16].

Treatment

In both JGCT and AGCT cases, the first-choice treatment is surgical removal of tumor-affected ovary [7]. 40 patients in the age range from 7 months to 22 years affected by ovarian GCT were investigated within the study [7]. All of the subjects had undergone surgical treatment. Unilateral ovariectomy in 35 cases, bilateral in 4 and biopsy alone in 1 case were performed. Over 30% patients received combined chemotherapy and 5% were qualified for abdominal radiotherapy. The outcome has shown very favorable results and good prognosis for patients, being disease-free 10 months to 26 years after surgery. At the same time combined chemotherapy does not appear to improve the prognosis in survival rate [7]. These findings seem to show that despite various age and staging of the tumor, surgery should remain first-choice treatment.

Within the case of ovarian cancer, surgery followed by additional chemotherapy is a therapeutic method of choice [20]. Meta-analysis of five-year data from three trials indicated that women who received adjuvant platinum-based chemotherapy had better overall survival than those who did not [21].

Symptoms

There is a huge variety of symptoms that can be presented by patients with ovarian granulosa cell tumor. According to Oliviera et al. (2019) above 40% of patients the very first symptom was abdominal pain, for around 17% it was abdominal distension, stress urinary incontinence, and abnormal uterine bleeding, and at the same time 25% patients were completely asymptomatic. [9]. Different studies support the statement that the most common symptom of GCT is abdominal pain [10].

On the other hand, ovarian cancer in the vast majority of cases is asymptomatic, especially at the early stages. Out of 419 patients evaluated for symptoms, 28% were asymptomatic but had a mass found during physical examination. Among symptomatic patients the most common were abdominal and pelvic pain (31%), and increased girth or fullness (26%) [15].

Survival rate

The estimated 5 and 10 year overall survival rate in patients with GCT was 84.6% and 72.5%, respectively. Event-free survival was 76.5 and 52.9% at 5 and 10 years, respectively. Advanced stage was a significant independent poor prognostic indicator for both OS and EFS [10].

In comparison, the 5 year survival rate of ovarian cancer is much lower. It is estimated around 29%, as it is usually discovered very late at high staging [13].

Diagnostic methods

As the radiological imaging methods together with basic gynecological examination are identical to both GCT and ovarian cancer, they will be described altogether within the following paragraph. There are several methods of basic confirmation of ovarian tumor presence. Diagnostic methods will be listed starting from the simplest, most basic to more complex and more precise ones. Investigation towards confirmation of ovarian neoplasm presence should begin with gynecological transvaginal examination - pelvic palpation. If a specialist within the gynecological examination stumbles upon abnormality during palpation of adnexa, ultrasound imaging should be performed. Transvaginal, sometimes additionally, especially if the tumor is big in size - transabdominal ultrasound [9]. Both of the listed methods are non-specific, simple diagnostic methods that should and could be performed during any gynecological examination. Both methods can only confirm the presence of the lump, without any clarification of its type and origin. As these methods are fast, safe and easy to perform, basic examination should begin from gynecological examination and ultrasound imagination of the ovaries. As there are many limitations to those techniques, further investigation should be performed. Secondary techniques used to image an ovarian tumor are MRI of the lower abdomen. If the tumor is large in size, or ascites is present, the investigated region should be expanded to the upper abdomen as well. MRI technique provides much greater insight than basic ultrasound imaging technique, and according to Zhang et al. (2018) there is a possibility to differentiate GCT from ovarian cancer, based on MRI findings [14]. However, the only possibility to determine with highest percentage of certainty the type of ovarian malignancy is to perform histopathological investigation of ovarian tumor.

Histopathological investigation

When investigated immunohistochemically, there were major differences between granulosa cell tumor and ovarian cancer. 53 ovarian malignancies were investigated, among which 12 were GCT and 11 were ovarian cancers. Different cytokeratins presence was taken into consideration. Researchers proved that CK HMW was not present in GCT, but it was detected in 50% of the carcinomas. AE1/AE3 was expressed by more than 90% of ovarian carcinomas but by one granulosa cell tumor only. Rest of the cytokeratins taken under investigation showed higher expression rates in granulosa cell tumors and/or lower

expression rates in ovarian carcinomas [11]. Despite great insight provided by the research, all the studies found while writing this review were from 1992 or older. This outcome proves that more modern investigation should be conducted, as cytokeratin immunohistochemistry seems to show the greatest value in differentiating between granulosa cell tumors and ovarian carcinomas. One research, performed by Gomez et al. (2020), shows more modern insight to molecular differentiation of granulosa cell tumor and ovarian cancer [12]. Unfortunately, that research takes into consideration only CA125, CA and HE4 levels measured in serum, which does not belong to histopathological investigation.

Disclosures

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