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Granulosa cell tumor of ovary: Perspective of Taiwan

A 6-month-old girl presented to our institution with intermittent vaginal bleeding for two months. After careful examination, neither trauma nor foreign body was noted. Laboratory examination revealed an elevated serum level of estradiol (669 pg/ml) associated with very low serum levels of follicular stimulating hormone and luteinizing hormone. Both pelvic ultrasound and magnetic resonance image showed a well-encapsulated mass lesion at right adnexa, measured 4.0 × 5.4 cm in size, containing mainly soft tissue with cystic component. Right salpingo-oophorectomy was done uneventfully. The pathology revealed juvenile granulosa cell tumor (JGCT) with a predominantly solid and partially cystic cut surface (varied gated yellow to brown with focal areas of hemorrhage), confirming the final surgical–pathological stage of IA, based on FIGO (International Federation of Gynecology and Obstetrics) stage system [1].

To provide the current perspective of Taiwan's experience in the management of ovarian granulosa cell tumors (GCTs), we used the following strategy to target this topic. Based on our search of PubMed (1970–June 2017; search terms: "granulosa cell tumor ovary," "Taiwan" and "sex-cord tumor ovary," "Taiwan"; https://www.ncbi.nlm.nih.gov/pubmed/?term=granulosa+cell+tumor+ovary%2C+taiwan; and https://www.ncbi.nlm.nih.gov/pubmed/?term=sex-cord+tumor+ovary%2C+taiwan), there are only a limited number of publications available in Taiwan [2–9]. GCTs account for less than 5% of all ovarian tumors and more than 70% of the sex cord-stromal tumors [2,3]. Two types are distinguished histologically—adult-type GCTs (AGCTs) and JGCTs [10]. AGCTs occur predominantly in perimenopausal and postmenopausal women, with a peak at 50–55 years of age [2,3]. JGCTs represent only 5% of all GCTs, and often occur in premenarchal girls and young women, with more than 50% cases diagnosed before 20 years and 45.5% in the premenarche [10]. Increasing abdominal girth with a palpable mass are most common clinical features of JGCT, and sex hormone-related symptoms or signs are also common in both AGCTs and JGCTs, including vaginal bleeding (postmenopausal bleeding for AGCTs) and the development of the 2nd sex characteristics (JGCTs), contributing to the possibility of an early diagnosis (stage I) [11].

Pathologically, GCTs appear as a large unilateral mass having a tan yellow color due to steroid production. Granulosa cells are small round to oval pale cells with characteristic coffee-bean nuclei (longitudinal nuclear grooves). Histology patterns include a well differentiated pattern, such as microfollicular (Call-Exner bodies are common), macrofollicular, trabecular, insular, solid-tubular and hollow tubular patterns and a poorly differentiated pattern, such as undulating parallel (watered-silk) or zigzag (gyriform) rows of granulosa cells in a single file and diffuse pattern [12]. JGCT is characterized by at least 3 of the 5 following criteria: (1) diffuse or macrofollicular pattern; (2) rare Call-Exner bodies; (3) frequent luteinization of either or both the granulosa and theca cell elements; (4) hyperchromatic nuclei and nuclear atypia (round and ungrooved with moderate to abundant eosinophilic or vacuolated cytoplasm); and (5) frequent mitotic figures [11,12]. Inhibin-A and calretinin have been proved as 2 optimal markers for JGCT with high sensitivity, and whereas inhibin-A seemed to be more specific [13].

FOXL2 gene encodes the transcription factor required for the normal development of the granulosa cell [14]. However, the mutant form of FOXL2 occurs frequently in AGCTs but rare in JGCTs (10%), supporting the evidence that AGCTs and JGCTs are two distinguished diseases [14]. In Taiwan, comparative genomic hybridization was used to identify chromosomal imbalances in 37 adult-type GCTs from 36 women [5]. The nonrandom chromosomal imbalances were found, including losses of 22q (31%), 1p33–p36 (6%), 16p13.1 (6%), and 16q (6%) and gains of 14 (25%), 12 (14%), and 7p15–p21 (6%) [5].

The typical findings of ultrasound and computed tomography in the study of 13 AGCTs are categorized into 5 morphologic patterns, including multilocular cystic (n = 6), thick-walled unilocular cystic (n = 2), thin-walled unilocular cystic (n = 1), homogeneously solid (n = 2), and heterogeneously solid (n = 2) masses [6]. In fact, features of images were not specific, and its purpose is only for identification of presence of ovarian mass.

The treatment of choice for either JGCTs or AGCTs is surgery. Since the majority of cases are unilateral and FIGO stage I tumors, ipsilateral oophorectomy or salpingo-oophorectomy can be done with a satisfactory prognosis [2,3]. Patients with advanced-stage GCT (stages II–IV) should undergo cytoreductive surgery to remove as much of the tumor and its metastases as possible, which may include total hysterectomy and bilateral salpingo-oophorectomy, total omentectomy, resection of any metastatic lesions from the peritoneal surfaces or from the intestines, pelvic and paraaortic lymphadenectomy if necessary [2,3]. The Taiwanese Gynecologic Oncology Group Study Group (TGOG Study Group) evaluated 176 women with pathologically-confirmed GCTs diagnosed between 1984 and 2010, and the results showed the majority of patients had stage I diseases (77.8%), and the recurrent rate was 21% in all cases, regardless of stages [2]. The overall 5- and 10-year survival rates were 96.5% and 94.1%, respectively [2], supporting the indolent clinical behaviors of GCTs. The prognosis was related to initial stage, presence of residual tumor after initial surgery, and tumor size (>13.5 cm) [2]. However, different surgical approaches and/or adjuvant therapy appear not to affect the outcome [2]. Even for the outcome of patients with recurrent GCTs, the overall survival after treatment is dependent on the interval between the initial treatment and recurrence, which further supported that the characteristic of the GCTs was indolent and the natural behavior of the GCTs is a critical factor for patients' overall

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survival, regardless of application of postoperative adjuvant therapy [15].

Although the 5-day bleomycin, etoposide and cisplatin (BEP) regimen is the most widely used first-line adjuvant therapy, this 5-day regimen cannot be copied for Taiwanese women with GCTS. According to the recent publication of the TGOG Study Group's study, the side effects or adverse events were significantly decreased when patients with ovarian sex-cord tumors, including GCTs were treated with a 3-day BEP regimen, and of most importance, a 3-day BEP regimen was effective and safe for these patients [16], although it is still unclear how many cycles of postoperative adjuvant chemotherapy should be given for these patients, regardless of disease statues, such as completely or incompletely resected diseases [15]. Now, the combination of carboplatin and paclitaxel is reported as an active treatment for various kinds of gynecology-related cancers, such as epithelial ovarian cancers, endometrial cancers, and cervical cancers [17–19], this combination is also effective in patients with GCTs [2,3,15]. As shown above, the complete excision is a determinant factor for overall survival of patients with GCTs, and the role of postoperative adjuvant chemotherapy for patients with GCTs is not clear. For infants with GCTs, it is much more unknown whether adjuvant therapy is needed or not.

In conclusion, it is extremely critical to detect and diagnose patients with GCTs as early as possible, since FIGO stage I disease can be safely treated by surgery along with an excellent outcome. Complete surgical excision is the key step in the management of patients with GCTs. A 3-day BEP regimen can be used with fewer side effects and of most importance, this 3-day regimen provides the similar therapeutic effects for Taiwanese women with GCTs.

Conflicts of interest

All authors declare no conflict of interest.

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