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ADULT GRANULOSA CELL TUMOR OF OVARY: AN OVERVIEW

Pathology

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ABSTRACT

Ovarian adult granulosa cell tumors (GCTs) are uncommon neoplasms that arise from the sex-cord stromal cells of the ovary. GCTs are characterized by long natural history and their tendency to recur years after the initial diagnosis. They present with symptoms and signs due to estradiol secretion, including vaginal bleeding and precocious puberty. Occasionally, tumor rupture causes abdominal pain and hemoperitoneum. GCT is usually associated with a mass on pelvic examination which is subsequently confirmed with imagine techniques. Surgery is the mainstay of initial management for histological diagnosis. The most important prognostic factor associated with a higher risk of relapse is the stage of disease.

KEYWORDS

Ganulosa cell tumor, Pathology, Prognosis

INTRODUCTION

Ovarian sex cord-stromal tumors are uncommon neoplasms that typically present in the first two to three decades of life, with the exception of adult granulosa cell tumors, which typically present later, with risk for development peaking at age 50 to 55 years. In aggregate, these tumors account for approximately 5% of ovarian malignancies in women age 15 to 24 years.[1]

CLINICAL FEATURES

As with other ovarian tumors, sex cord-stromal tumors usually present with the typical symptoms of an adnexal mass, including abdominal pain, distention, and, rarely, torsion. In contrast to epithelial and germ cell tumors, however, sex cord-stromal tumors frequently present with signs of hormonal production, such as hirsutism and virilization, menstrual changes, or precocious puberty.[2] Initial evaluation should include a thorough history with careful attention to any individual or family history of possible tumor predisposition as well as physical examination with attention to presence of precocious puberty or delayed menarche, hyper pigmented macules that are suggestive of Peutz-Jegher, or thyroid nodules that are suggestive of *DICER1* syndrome. Tumors are often large at diagnosis and may rupture, which can result in an acute presentation with hemoperitoneum.

PATHOLOGY

These tumors are typically unilateral, 10 to 15 cm in greatest dimension, and may vary from solid, firm, and lobulated to soft and friable, often with hemorrhage and/or necrosis. The following histologic subtypes are seen: adult granulosa cell tumor, juvenile granulosa cell tumor, Sertoli-Leydig cell tumor, sex cord tumor with annular tubules, and mixed forms, including gynandroblastoma.

In one review of 72 pediatric patients with sex cord-stromal tumors, juvenile granulosa cell tumors and Sertoli-Leydig cell tumors together accounted for 85% of such neoplasms in children and adolescents.2Almost two thirds of cases were juvenile granulosa cell tumors. Juvenile granulosa cell tumors are characterized by polygonal cells with usually abundant cytoplasm growing in nodules or diffusely. Follicles of varying size and shape typically punctuate the tumor. Tumor cells are typically immature, sometimes strikingly pleomorphic, and are usually briskly mitotic.[2] The capsule of the ovary is intact in most cases, which accounts, in part, for the excellent outcome; however, in tumors with rupture or invasion beyond the capsule, juvenile granulosa cell tumors can pursue an aggressive clinical course. Adult granulosa cell tumor is uncommon in children just as juvenile granulosa cell tumor is uncommon in adults.

Approximately 20% of ovarian sex cord-stromal tumors in children are Sertoli-Leydig cell tumors. Sertoli-Leydig cell tumors may be well differentiated with Sertoli cell tubules separated by delicate stroma that contain clusters of Leydig cells, intermediately differentiated with lobules of hyperchromatic Sertoli cells that often grow focally as cords and tubules with stromal Leydig cells, or poorly differentiated. Poorly differentiated tumors are usually dominantly sarcomatoid, with only rudimentary differentiation of the types already listed. Heterologous elements include mucinous epithelial glands or rhabdomyosarcomatous and/or chondrosarcomatous elements, the latter being of adverse prognostic significance. Elevation of alpha-fetoprotein (AFP) may be observed but rarely to the degree seen in yolk sac tumor.[3-5]

Sex cord tumors with annular tubules are a distinctive histologic category and show tubules with Sertoli cells arranged around one or more hyaline bodies. In patients with Peutz-Jegher syndrome, these tubules may be scattered and admixed with normal ovarian tissue rather than forming a distinct mass

MOLECULAR PATHOLOGY

Recent analyses have reshaped our understanding of the pathophysiology of some of these tumor subtypes. Mutations in *DICER1, STK11*, and *FOXL2* influence the development of some of these neoplasms.

DICER1

Sertoli-Leydig cell tumors and gynandroblastomas are associated with *DICER1* mutations.[6-9]

STK11

Sex cord-stromal tumors with annular tubules may be associated with Peutz-Jegher syndrome and specifically with mutations in the *STK11* gene. Individuals with clinical findings of Peutz-Jegher syndrome should undergo genetic testing that includes screening for deletion and/or duplication of *STK11* and relevant organ-specific screening.[10]

Ollier Disease and Mafucci Syndrome

Ollier disease includes enchondromatosis, whereas Mafucci syndrome includes enchondromatosis and hemangiomas. Both Ollier disease and Maffucci syndrome are associated with an increased risk of juvenile granulosa cell tumors.[11]

FOXL2

Nearly all adult granulosa cell tumors are characterized by missense somatic point mutations (402 C→G) in FOXL2, which may be useful diagnostically. This mutation may alter antiproliferative pathways and limit apoptosis, which contributes to the pathogenesis of adult granulosa cell tumors.[12]

TREATMENT

Our understanding of the pathophysiology of these tumors continues to advance, yet, at this point, this knowledge has not yet been translated into novel therapeutic approaches. Currently, individuals with adult granulosa cell tumors receive treatment that is similar to that in individuals with germ cell or epithelial tumors. As translational efforts advance, it is likely that treatment will evolve and that therapies

directed at the underlying genetic aberrations may replace more generic treatment.

CONCLUSION

Due to high chance of recurrence even years after apparent clinical cure of the primary tumor, lifelong follow up with clinical examination and tumor markers like inhibin B is recommended. Other than stage of the disease, the other prognostic factors like age, tumor size, rupture of tumor, mitotic activity are not able to predict recurrences accurately. Thus the identification of prognostic and predictive factors for tumor recurrence is of paramount importance. Although it has been determined that *FOXL2 (402C->G)* mutation is characteristic of Adult Granulosa Cell Tumor, the implications of this finding is yet to be elucidated. Further research in the molecular pathogenesis of GCT can shed light on various prognostic factors and therapeutic agents which can be effective in the adjuvant and palliative setting. Due to the rarity of this disease, multicentric RCT's would be needed to determine the role of newer therapeutic agents in Granulosa cell tumor.

Conflict of interest- NONE

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