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卵巢成人型颗粒细胞瘤腹水的细胞病理观察

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[摘要] 目的: 探讨卵巢成人型颗粒细胞瘤(adult granulosa cell tumor, AGCT)腹水的细胞病理特点及诊断要点。方法: 分析18例卵巢AGCT腹水液基细胞学诊断、DNA定量及细胞蜡块免疫细胞化学结果, 并复习相关文献。结果: AGCT腹水液基细胞学诊断轻度核异质细胞13例, 小圆细胞肿瘤5例。液基细胞片中见散在圆形、多角形小细胞, 部分成团, 核膜有皱褶, 核内见明显核沟, 染色质疏松泡状或致密, 细胞质较少, 细胞可裸核状或瓜子状, 偶见Call-Exner小体。DNA定量分析均为阴性。免疫细胞化学 α -inhibin, S-100, Calretinin, CD99阳性, Ki-67增殖指数为2%~10%。结论: 卵巢AGCT腹水联合液基细胞学、DNA定量分析和免疫细胞化学可以得出准确结论, 有利于临床诊断和治疗。

[关键词] 成人型颗粒细胞瘤; 腹水; 细胞学; DNA定量分析; 免疫细胞化学

Cytopathological observation of ascites in adult granulosa cell tumor

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Abstract **Objective:** To explore the adult granulosa cell tumor ascites cells of the pathological characteristics and diagnostic criteria. **Methods:** We analyzed 18 cases of ovarian granulosa cell tumor ascites liquid-based cytology in the diagnosis of adult type wax, quantitative analysis of DNA and cell block immunocytochemistry results, and reviewed the relevant literature. **Results:** AGCT ascites liquid-based cytology in the diagnosis of 13 cases of mild nuclear heterogeneous cells, small round cell tumor in 5 cases. Liquid based cells which are scattered in the round, small polygonal cells, part of the dough, nuclear membrane folds, nucleus in obviously ditch, chromatin loose bubble or density, less cytoplasm, the cell can be naked nucleus shape or melon seeds, occasional Call-Exner corpuscle. DNA quantitative analysis are all negative. Immunocytochemistry, revealed positivity for α -inhibin, S-100, Calretinin and CD99, and Ki-67 index ranges from 2% to 10%. **Conclusion:** Adult ovary granulosa cell tumor ascites combined liquid-based cytology and DNA double body chemical analysis and immune cell can accurate conclusion, is helpful to clinical diagnosis and treatment.

Keywords adult granulosa cell tumor; ascites; cytology; DNA quantitative analysis; immunocytochemistry

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卵巢颗粒细胞瘤(ovarian granulosa cell tumor, OGCT)是指至少有10%的细胞在形态学上与发育中的卵泡颗粒细胞非常相似的肿瘤。这些肿瘤占全部卵巢恶性肿瘤的2%~5%^[1]。成人型颗粒细胞瘤(adult granulosa cell tumor, AGCT)约占OGCT的95%,可发生于任何年龄,发病高峰年龄为50~55岁,且常见于围绝经期和绝经早期女性^[2]。本文报告18例卵巢AGCT腹水阳性病例,结合液基细胞学诊断、DNA定量分析及细胞蜡块免疫细胞化学结果,讨论其细胞学诊断要点,并复习相关文献。

1 对象与方法

1.1 对象

选取扬州大学附属医院病理科2015年1月至2018年8月组织病理学诊断为卵巢AGCT患者阳性腹水18例,年龄25~80(中位数49.4)岁。

1.2 方法

1.2.1 液基细胞学制片及诊断

采用美国BD公司沉降式液基薄层全自动制片系统,同时制作2张细胞片,1张做HE染色镜检,另1张采用Feul-gen染色,干片后做细胞DNA定量分析。液基细胞学诊断结果分为阴性、核异质细胞、疑癌细胞、恶性肿瘤细胞。

1.2.2 细胞DNA定量分析

采用细胞DNA定量分析系统(武汉兰丁医学高科技有限公司),阳性诊断 $>5c$ 的为见异倍体细胞, $<5c$ 的为未见异倍体细胞。

1.2.3 细胞蜡块免疫细胞化学检测

用剩余胸水制成细胞蜡块做免疫细胞化学检测。免疫细胞化学采用EnVision二步法,一抗选用 α -inhibin, S-100, Calretinin, CD99, imentin, LCA, EMA, CKpan, CK8, CK18, Syn, HMB-45, WT-1, Ki-67等。

2 结果

在18例卵巢AGCT患者中,腹水液基细胞学诊断核异质细胞13例,小圆细胞肿瘤5例。腹水液基细胞学观察见瘤细胞为散在圆形、卵圆形、多边形的小细胞,核膜有皱褶,核染色质

疏松,有明显的核沟,呈“咖啡豆”样外观,细胞质很少(图1, 2),偶有簇状排列的细胞团(图3, 4);类似呈放射状排列的Call-Exner小体细胞团(图4)。低分化AGCT腹水瘤细胞与高分化型AGCT瘤细胞相比,细胞更小,排列较紧密,核染色质较致密,核染色略加深(图5),与低分化颗粒细胞瘤组织学切片形态一致(图6)。AGCT腹水细胞蜡块(图7)免疫细胞化学结果,瘤细胞 α -inhibin(图8), CD99(图9), S-100(图10), Calretinin, vimentin阳性, Ki-67增殖指数为2%~5%。腹水DNA定量分析18例均为阴性(图11, 12, 表1)。

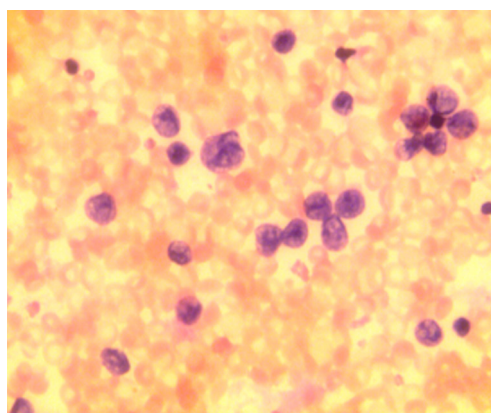


图1 AGCT腹水细胞(核沟)(HE, $\times 40$)

Figure 1 AGCT ascites cell (nuclear sulcus) (HE, $\times 40$)

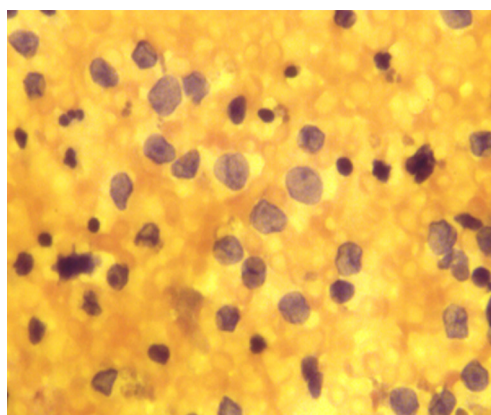


图2 AGCT腹水细胞(“咖啡豆”样外观)(HE, $\times 40$)

Figure 2 AGCT ascites cells (“coffee bean”-like appearance) (HE, $\times 40$)

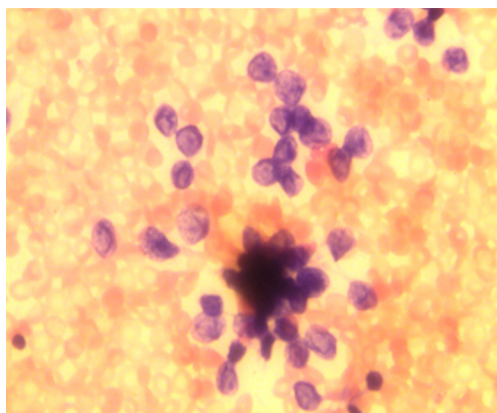


图3 AGCT腹水细胞(簇状细胞团)(HE, × 40)
Figure 3 AGCT ascites cells (cluster cells) (HE, × 40)

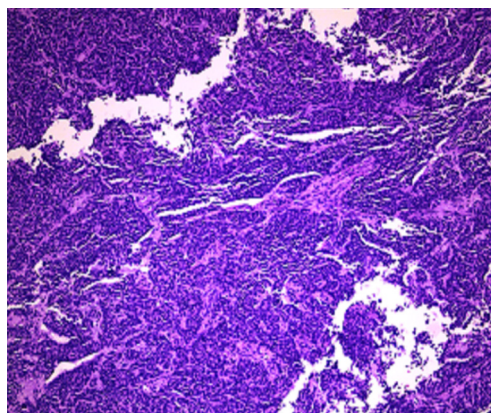


图6 低分化AGCT组织切片(HE, × 40)
Figure 6 Low-differentiated AGCT tissue section (HE, × 40)

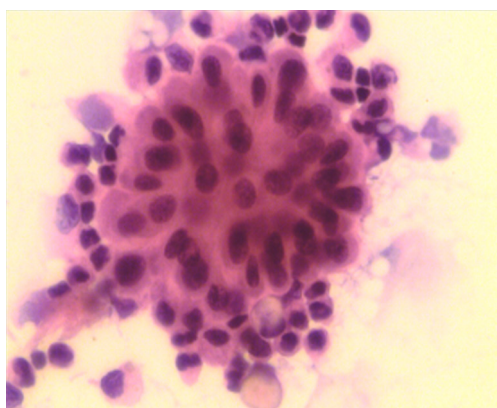


图4 AGCT腹水细胞(类似放射状排列细胞团)(HE, × 40)
Figure 4 AGCT ascites cells (similar to radial arrangement of cells) (HE, × 40)

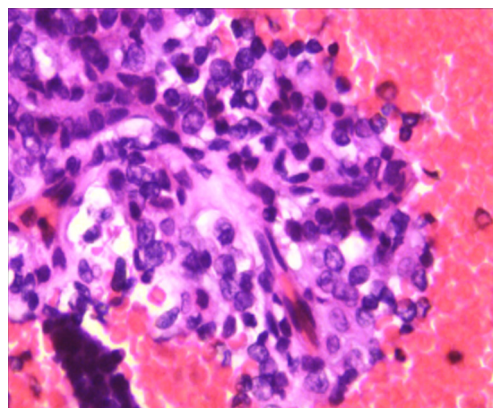


图7 AGCT腹水细胞蜡块切片(HE, × 40)
Figure 7 AGCT ascites cell wax section (HE, × 40)

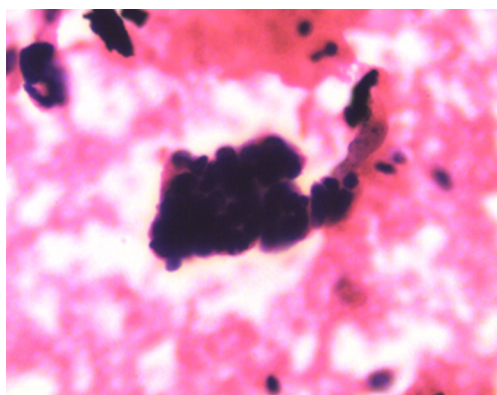


图5 低分化AGCT腹水液基细胞片(HE, × 40)
Figure 5 Low-differentiated AGCT ascites-based cell sheet (HE, × 40)

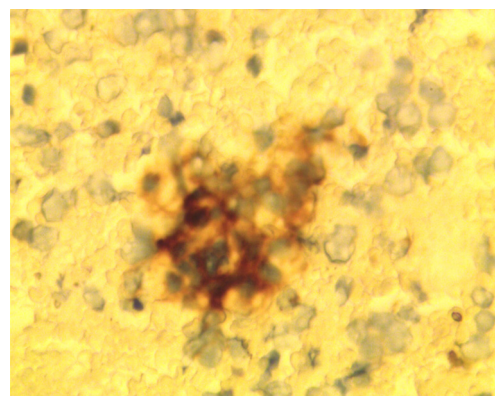


图8 AGCT腹水细胞蜡块 α -inhibin(+), 细胞质阳性 (EnVision, × 40)
Figure 8 AGCT ascites cell wax block α -inhibin (+), cytoplasmic positive (EnVision, × 40)

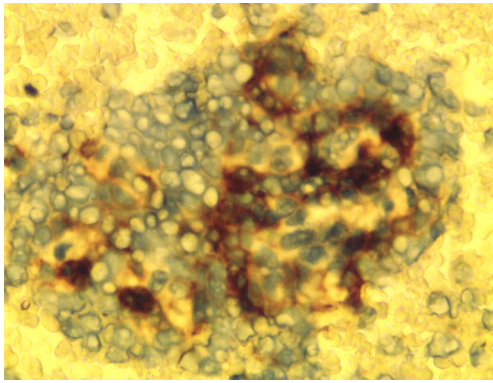


图9 AGCT腹水细胞蜡块CD99(+), 细胞膜阳性 (EnVision, ×40)
Figure 9 AGCT ascites cell wax CD99 (+), membrane positive (EnVision, ×40)

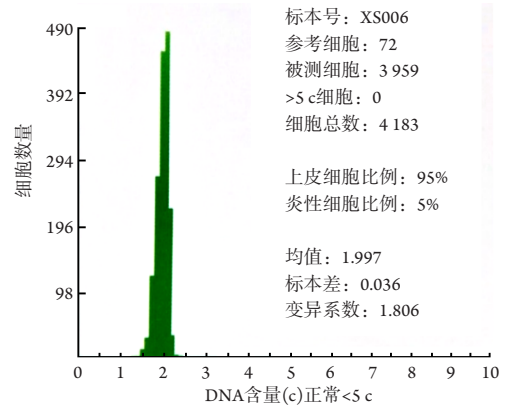


图11 AGCT腹水细胞DNA定量分析(阴性)
Figure 11 Quantitative DNA analysis of ascites cells by AGCT (negative)

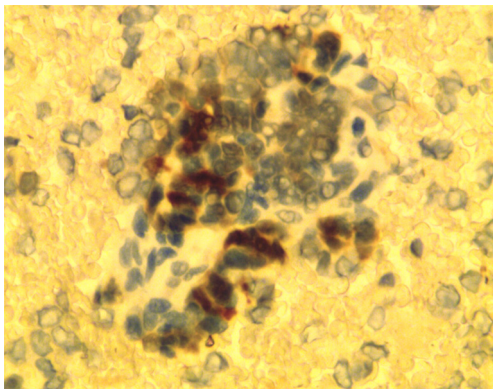


图10 AGCT腹水细胞蜡块S100(+), 细胞核阳性(EnVision, ×40)
Figure 10 AGCT ascites cell wax mass S100 (+), nuclear positive (EnVision, ×40)

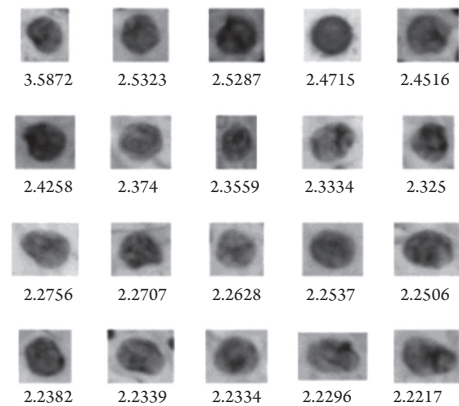


图12 AGCT腹水细胞DNA定量分析(阴性)
Figure 12 Quantitative DNA analysis of ascites cells by AGCT (negative)

表1 18例AGCT腹水液基细胞学及DNA定量分析结果

Table 1 Ascites fluid-based cytology and DNA quantitative analysis of 18 adult granulosa cell tumors

| 诊断方法 | 肿瘤 | 核异质 | 阴性 | 合计 |
|---------|----|-----|----|----|
| 液基细胞学 | 5 | 13 | 0 | 18 |
| DNA定量分析 | 0 | 0 | 18 | 18 |

3 讨论

卵巢AGCT为低度恶性肿瘤^[3], 约有10%患者伴有腹水形成^[4]。幼年型颗粒细胞瘤(juvenile granulosa cell tumor, JGCT)约占5%, 20岁以下占87%。本组18例AGCT患者中位数年龄为49.4岁, 与报道^[2]相似。AGCT是伴有雌激素分泌增多症状

最常见的卵巢肿瘤, 3/4的病例伴有雌激素水平过高。患者有月经过多、绝经后阴道流血、腹部肿块等症状。拟诊为AGCT者应尽早行全面诊刮术, 以明确子宫内膜是否存在病变。实验室检查有雌二醇、CA125升高^[5]。多层螺旋CT表现为盆腔单发或多发囊实性混杂密度肿块, 实性部分强化不明显^[6]。病理巨检为单侧肿块, 平均直径12 cm。

有报道^[7]显示: AGCT囊实性肿瘤占65%, 认为多发小囊腔散在分布于实性成分中为OGCT的典型征象。

卵巢AGCT腹水中瘤细胞形态为散在细胞质很少的圆形、卵圆形或多边形的小细胞, 核染色质疏松细致, 不仔细观察容易漏诊, 而低分化AGCT瘤细胞核染色质则有所加深, 容易导致过诊。本研究有13例液基细胞学诊断为核异质细胞, 复阅片时用40倍目镜观察到特征性的核沟及核膜皱褶, 如“咖啡豆”样外观可以帮助瘤细胞分类。抑制素是AGCT免疫组织化学最有用标志物之一, 结合细胞蜡块免疫细胞化学结果瘤细胞 α -inhibin, CD99, S-100, Calretinin, vimentin阳性, Ki-67增殖指数为2%~10%, 可助确诊。

在超微结构中, 肿瘤性颗粒细胞内含有丰富的中间丝和特殊的细胞连接, 某些细胞连接具有典型的桥粒结构。细胞遗传学研究常出现12号染色体三体。其他确定的核型常是14号染色体三体和22号染色体单体。研究^[3,8]表明FOXL2^{C134W}突变具有诊断AGCT的潜力。正常人多为二倍体细胞, 有丝分裂时为四倍体, 当癌变、基因扩增、重组等情况发生时, 细胞的DNA倍体即出现异常, 可以借此检测早期肿瘤, 肿瘤细胞DNA定量分析具有准确性高、敏感性好的特点^[9], 已用于诊断和预测宫颈上皮病变和侵袭性癌的诊断和预后^[10]。与异常增生相比, DNA定量分析不仅具有同样的预测价值, 还能检测无异常增生的风险病损, 且客观、快速, 易于操作^[11]。研究^[12]显示绝大多数AGCT是二倍体或近二倍体。本研究中18例AGCT腹水DNA定量分析结果均为阴性, 与文献^[13]相符。

AGCT治疗以手术为主^[14]。目前, 激素治疗还没有引起足够的重视, 可供讨论研究的参考病例和可以获得的治疗经验均有限^[15]。影响AGCT预后的主要因素包括肿瘤分期、肿瘤大小、肿瘤破裂程度、诊断年龄、核异形性、有丝分裂指数及初次手术后是否残存肿瘤, 其中肿瘤分期最为重要^[16-17]。OGCT的另一个特点是远期复发, 复发时间1~27年不等^[18-19], 常复发或转移常出现在原发性肿瘤切除5~10年后^[20], 因此OGCT患者需长期随访。

综上所述, 仔细观察AGCT腹水液基细胞学特点, 联合DNA定量分析及免疫细胞化学检查, 可以提高AGCT腹水诊断准确性, 有助于临床进行诊疗。

参考文献

1. Khosla D, Dimri K, Pandey AK, et al. Ovarian granulosa cell tumor: clinical features, treatment, outcome, and prognostic factors[J]. *N Am J Med Sci*, 2014, 6(3): 133-138.
2. Lim D, Oliva E. Ovarian sex cord-stromal tumors: an update in recent molecular advances[J]. *Pathology*, 2018, 50(2): 178-189.
3. Nolan A, Joseph NM, Sangoi AR, et al. FOXL2 mutation status in granulosa theca cell tumors of the ovary[J]. *Int J Gynecol Pathol*, 2017, 36(6): 568-574.
4. 回允中. 女性生殖道病理学[M]. 北京: 北京大学医学出版社, 2005: 608.
HUI Yunzhong. *Female genital tract pathology*[M]. Beijing: Peking University Medical Press, 2005: 608.
5. 李铭, 段成洲, 张耀文, 等. 成人型卵巢颗粒细胞瘤的MRI特征表现与病理相关性分析[J]. *中国CT和MRI杂志*, 2018, 16(6): 89-92.
LI Ming, DUAN Chengzhou, ZHANG Yaowen, et al. Ovarian granulosa cell tumor of the MRI characteristics of adult type with pathologic correlation analysis[J]. *Chinese Journal of CT and MRI*, 2018, 16(6): 89-92.
6. 王茂林, 何慧. 卵巢颗粒细胞瘤的MSCT表现与病理对照分析[J]. *中华肿瘤防治杂志*, 2016, 12(23): 250-251.
WANG Maolin, HE Hui. Ovarian granulosa cell tumor of MSCT manifestations and pathologic contrast analysis[J]. *Chinese Journal of Cancer Prevention and Treatment*, 2016, 12(23): 250-251.
7. 覃伶俐, 洪燕, 符小艳, 等. 卵巢颗粒细胞瘤的超声表现及误诊分析[J]. *医学影像学杂志*, 2016, 26(4): 702-704.
QIN Lingling, HONG Yan, FU Xiaoyan, et al. The sonographic findings of ovarian granulosa cell tumor and misdiagnosis analysis[J]. *Journal of Medical Imaging*, 2016, 26(4): 702-704.
8. Leung DTH, Fuller PJ, Chu S. Impact of FOXL2 mutations on signaling in ovarian granulosa cell tumors[J]. *Int J Biochem Cell Biol*, 2016, 72: 51-54.
9. 杨新, 方三高, 马强, 等. 细胞DNA定量分析检测在甲状腺癌冷冻组织中的应用研究[J]. *诊断病理学杂志*, 2018, 25(10): 692-696.
YANG Xin, FANG Sangao, MA Qiang, et al. Testing in thyroid cancer cell DNA quantitative analysis for the application of frozen tissue[J]. *Chinese Journal of Diagnostic Pathology*, 2018, 29(10): 692-696.
10. Yamal JM, Guillaud M, Atkinson EN, et al. Prediction using hierarchical data: Applications for automated detection of cervical cancer[J]. *Stat Anal Data Min*, 2015, 8(2): 65-74.
11. Wang M, Hao C, Ma Q, et al. DNA image cytometry test for primary screening of esophageal cancer: a population-based multi-center study in high-risk areas in China[J]. *Chin J Cancer Res*, 2016, 28(4):

- 404-412.
12. Vilella J, Herrmann FR, Kaul S, et al. Clinical and pathological predictive factors in women with adult-type granulosa cell tumor of the ovary[J]. *Int J Gynecol Pathol*, 2007, 26: 154-159.
 13. 郑杰. 罗塞-阿克曼外科病理学(第10版): 乳腺与女性生殖系统分册[M]. 北京: 北京大学医学出版社, 2017: 197.
ZHENG Jie. Rosai and Ackerman's surgical pathology (10th ed): the archies of mammary gland and the female reproductive system[M]. Beijing: Peking University Medical Press, 2017: 197.
 14. 刘华梅. 临床I期成人型卵巢颗粒细胞瘤31例临床分析[J]. *临床医学研究与实践*, 2018, 3(7): 79-80.
LIU Huamei. Clinical I adult ovarian granulosa cell tumor of 31 cases of clinical analysis[J]. *Clinical Research and Practice*, 2018, 3(7): 79-80.
 15. 孙慧, 白萍. 激素治疗在复发或难治型卵巢颗粒细胞瘤中的应用[J]. *中华肿瘤杂志*, 2016, 38(7): 481-484.
SUN Hui, BAI Ping. Hormone therapy in recurrent or refractory ovarian granulosa cell tumor[J]. *Chinese Journal of Oncology*, 2016, 38(7): 481-484.
 16. Dridi M, Chraiet N, Batti R, et al. Granulosa cell tumor of the ovary: a retrospective study of 31 cases and a review of the literature[J]. *Int J Surg Oncol*, 2018, 2018: 4547892.
 17. Thomakos N, Biliatis I, Koutroumpa I, et al. Prognostic factors for recurrence in early stage adult granulosa cell tumor of the ovary[J]. *Arch Gynecol Obstet*, 2016, 294(5): 1031-1036.
 18. 万虹利, 伍治强, 刘志杰. 卵巢颗粒细胞瘤21例诊治分析[J]. *现代肿瘤医学*, 2015, 23(4): 544-547.
WAN Hongli, WU Zhiqiang, LIU Zhijie. Ovarian granulosa cell tumor diagnosis and treatment of 21 cases analysis[J]. *Journal of Modern Oncology*, 2015, 23(4): 544-547.
 19. 田亮, 邢荣格, 张欣, 等. 卵巢颗粒细胞瘤术后27年膈肌转移1例[J]. *临床与实验病理学杂志*, 2018, 34(5): 586-587.
TIAN Liang, XING Rongge, ZHANG Xin, et al. Ovarian granulosa cell tumor after 27 years diaphragm transfer 1 case[J]. *Chinese Journal of Clinical and Experimental Pathology*, 2018, (5): 586-587.
 20. 汪颖南, 顾依群, 王爱春, 等. 卵巢囊性颗粒细胞瘤临床病理观察[J]. *诊断病理学杂志*, 2015, 20(8): 466-468.
WANG Yingnan, GU Yiqun, WANG Aichun, et al. Ovarian granulosa cell tumor pathological observation[J]. *Chinese Journal of Diagnostic Pathology*, 2015, 20(8): 466-468.

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