

Case Report

## Juvenile Granulosa Cell Tumor with an Unusual Clinical Course: A Late-onset and Late Recurrent Case

Thar Htet San<sup>a</sup>, Yoko Ota<sup>a\*</sup>, Soichiro Fushimi<sup>b</sup>, Masayoshi Fujisawa<sup>a</sup>,  
Hiroyuki Yanai<sup>c</sup>, Hiroko Toda<sup>d</sup>, Tadayoshi Kunitomo<sup>e</sup>, Keisuke Kodama<sup>f</sup>, and Akihiro Matsukawa<sup>a</sup>

<sup>a</sup>Department of Pathology and Experimental Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, <sup>c</sup>Department of Pathology, Okayama University Hospital, Okayama 700-8558, Japan,

<sup>b</sup>Department of Pathology, Himeji Red Cross Hospital, Himeji, Hyogo 670-8540, Japan,

<sup>d</sup>Section of Diagnostic Pathology, Fukuyama Medical Association, Fukuyama, Hiroshima 720-0032, Japan,

Departments of <sup>e</sup>Pathology and <sup>f</sup>Gynecology, Kurashiki Medical Center, Kurashiki, Okayama 710-8522, Japan

Juvenile granulosa cell tumors (JGCTs) are rare ovarian tumors with overall good prognoses. They differ from adult granulosa cell tumors (AGCTs), which are well known for late recurrence. Most JGCTs (~97%) occur in individuals <30 years old. We report a recurrent JGCT in a 40-year-old woman 5 years after initial presentation. The histological appearance and lack of 402C>G missense point mutation of *FOXL2* gene (characteristic of AGCT but absent in JGCT) allowed differentiation from AGCT. This is the first comprehensive report of JGCT with late recurrence. Although rare, late recurrence of JGCT can occur; long-term surveillance is suggested.

**Key words:** juvenile granulosa cell tumor, late recurrence, adult granulosa cell tumor

Juvenile granulosa cell tumors (JGCTs) are rare ovarian tumors with an overall good prognosis. They differ from adult granulosa cell tumors (AGCTs) by distinctive histologic features as well as these tumors' usual age of onset. While over 80% of AGCTs were encountered in women >40 years of age [1, 2], JGCTs have been observed mostly in children and young adults. In the largest case series of JGCTs (125 cases), 97% occurred in the first 3 decades of life [3].

AGCTs are well known to develop late recurrence. Late recurrences (*i.e.*, recurrences >5 years postoperatively) were recorded in 51% of AGCT cases in a long-term follow-up study of 118 AGCT patients [4]. In 3 other studies of 34 cases, 14 cases, and 9 cases of JGCT followed for >5 years, no late recurrence was observed [3, 5, 6].

### Case Presentation

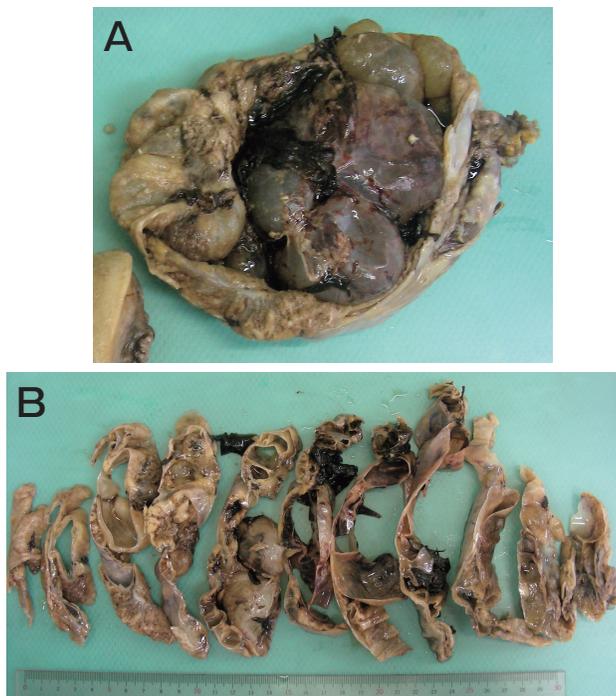
A 40-year-old Japanese woman, gravida 4, para 3, with a history of an operated right ovarian tumor 5 years earlier complained of secondary amenorrhea and loss of appetite with some weight loss at her follow-up visit. The patient's tumor marker values and serum estradiol results are shown in Table 1. At ultrasound examination, a 10.3×10.4×9.3 cm multi-cystic mass with free fluid around the uterus was revealed. We performed a total abdominal hysterectomy with left salpingo-oophorectomy and omentectomy. At the operation, the left ovarian mass was resected together with an 8.0-cm mass at the pouch of Douglas (POD) and 2 small nodules in the omentum.

The resected left ovarian tumor was multicystic with some solid parts (Fig. 1A, B). Microscopic sections

**Table 1** The tumor markers and serum hormone assay results of the patient, a 40-year-old woman

	Pre-op (5 years ago)	5 months post-op (5 years ago)	Follow-up (4 years ago)	Follow-up (1 year ago)	Pre-op (this time)	2 months post-op (this time)
CA125, U/ml	27.0	11.4	15.3	13.0	283.0	9.0
CA19-9, U/ml	8.6	4.4	5.2	NA	NA	1.1
CA72-4, U/ml	4.3	16.0	19.0	3.6	11.3	7.0
Estradiol, pg/ml	NA	NA	NA	NA	360.0	< 10.0

mos, months; yrs, years.



**Fig. 1** Macroscopic findings. **A**, Left ovarian solid-cystic swelling; **B**, Cut sections showing multiple cysts with some solid components and some hemorrhagic areas.

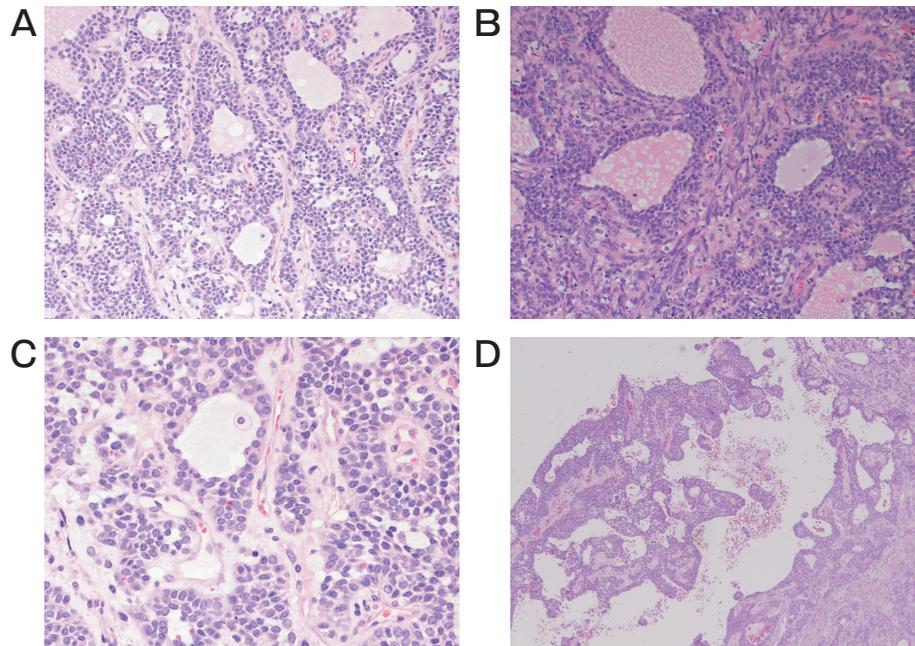
revealed multiple cystic lesions, the wall of which revealed solid and follicular proliferations of tumor cells (Fig. 2A). The follicles varied in size and shape: most were of irregular shape rather than regular or round shapes. Some of the follicles contained eosinophilic material. The tumor cells had relatively monomorphic hyperchromatic nuclei lacking nuclear grooves (Fig. 2C). Most of the cells had scant cytoplasm and indistinct cell borders. The stroma was composed of spindle-shaped cells with myxoid background. In some areas, a pseudopapillary pattern was created by a proliferation of tumor cells into the cyst lumen (Fig. 2D). Mitoses were frequent (24/10 HPF). Steroid cells were

noted focally.

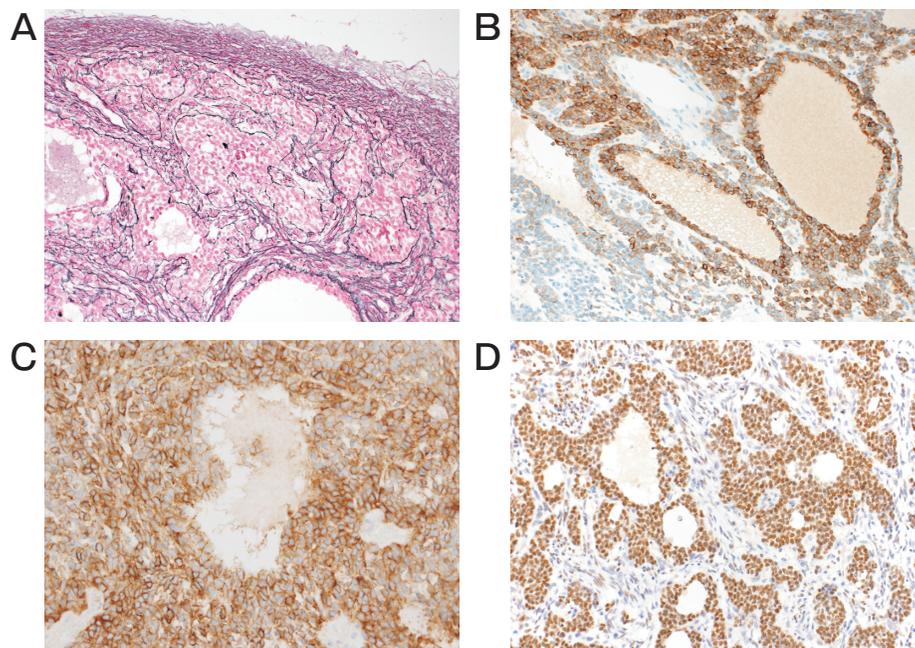
Though the histological features of the patient's tumor were compatible with those of JGCT, we performed a number of ancillary studies for confirmation. Reticulin staining revealed reticulin fibers surrounding nests of tumor cells rather than individual cells (Fig. 3A). The sex cord nature of the tumor cells was confirmed by the results of immunohistochemistry for inhibin A (Fig. 3B), calretinin, CD56 (Fig. 3C), and FOXL2 (Fig. 3D). Histologic mimics such as surface epithelial tumors, neuroendocrine tumors, struma ovarii, gonadoblastoma and germ cell tumors were excluded by the observed negativity for WT1, p53, chromogranin A, synaptophysin, TTF-1, and OCT3/4.

The histological findings of the nodules in the omentum and the mass at the POD were identical to those of ovarian tumor. Our histologic review of the contralateral ovarian tumor operated 5 years earlier revealed a greater predominance of the cystic structure and focal evidence of follicular structures. Pseudopapillary structures at cyst walls were also noted (Fig. 4A,B). Mitoses were less evident (12/10 HPF). Although the histologic features from 5 years earlier were similar to the present tumor's features, the tumor was misdiagnosed at that time as a serous cystadenoma; it was difficult to diagnose the tumor due to an artifact by torsion.

Although the histologic features of the tumor at the patient's presentation to us (such as the lack of nuclear grooves and Call-Exner bodies specific to AGCTs) suggested that the likelihood of the tumor being an AGCT was extremely low, we investigated whether a characteristic mutation of AGCT was present. The 402C>G missense point mutation of *FOXL2* gene was present in 86 of 89 AGCTs (97%) [7]. The method of mutation detection that we used herein was as described [8]. A typical case of AGCT was used as the control. As shown in Fig. 5B, the 402C>G mutation was not present in our



**Fig. 2** Histological appearance of left ovarian tumor (Hematoxylin & Eosin staining). **A**, Follicles are irregular in shape with eosinophilic material in lumens. Mitoses are frequent; **B**, Follicles of tumor cells with spindle-shaped cells seen between the follicles. Some steroid cells are noted; **C**, Tumor cell nuclei lack nuclear grooves; **D**, Proliferation of tumor cells creating focal pseudopapillary structures.



**Fig. 3** Ancillary stains. **A**, Reticulin stain revealed reticulin fibres surrounding groups of tumor cells; **B**, Inhibin staining seen in cytoplasm of tumor cells; **C**, CD56 strong and diffuse cytoplasmic staining; **D**, FOXL2 diffuse immunostaining of tumor cell nuclei.

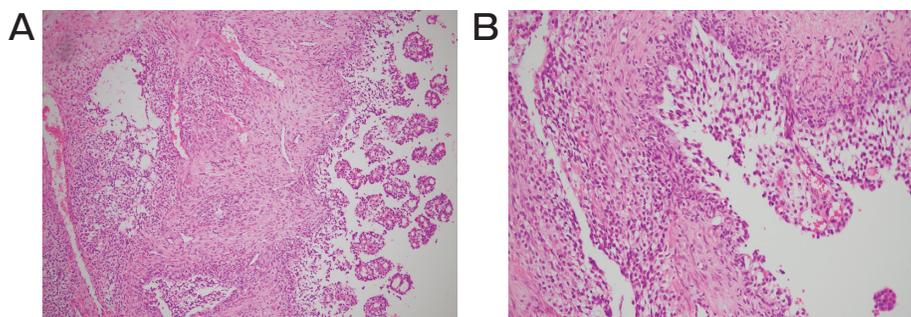


Fig. 4 Histological appearance of primary tumor (Hematoxylin & Eosin staining). A, B, Pseudopapillary pattern at cyst wall were noted.

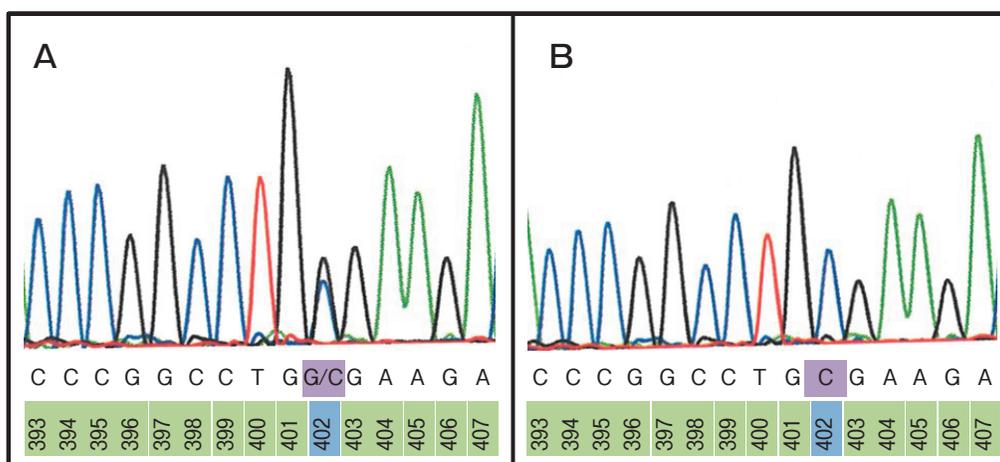


Fig. 5 *FOXL2* mutation analysis. A, 402C>G mutation of *FOXL2* gene is detected in a typical adult granulosa cell tumor; B, 402C>G mutation of *FOXL2* gene is absent in DNA extracted from left ovarian tumor.

patient's tumor.

Based on the above-described findings, we made the diagnosis of a late recurrence of JGCT. The recurrence took an aggressive course. Despite treatment with the aromatase inhibitor anastrozole, other recurrences were revealed by a CT scan 6 months post-operatively. Chemotherapy was planned but the patient declined. She chose to be on palliative therapy and died 20 months after the operation.

To the best of our knowledge, the late recurrence of a JGCT is a rare event, whereas late recurrence is frequent in AGCT. Although the histologic features of our patient's tumor were quite typical of JGCT, the tumor also had some unusual features. The first is that the tumor first presented when the patient was 35, which itself is a quite unusual age of onset for a JGCT. Only 3% of the reported JGCTs presented after age 30 [3]. The second unusual feature of the tumor is its late recurrence. After the first removal of a right ovarian

tumor, the patient was free of tumor as demonstrated by the low and static levels of tumor markers throughout her follow-up visits for 5 years (Table 1). Recurrences of JGCT are uncommon, and almost all reported recurrences occurred within 2 years postoperatively [3,5,6,9-11]. There is only one reported case of a JGCT that recurred nearly 4 years after the initial diagnosis [12]. Another case of JGCT that recurred 126 months after the initial presentation was described in a case series but it was regarded as a metachronous contralateral tumor [13]. Cases of JGCT recurrence at >5 years post-operatively has never been reported, to our knowledge. The unique presentation of our patient's case warrants a check for syndromic associations. However, features of Ollier disease or Maffucci syndrome have not revealed by our review of the patient's clinical history.

Another interesting finding about our patient's tumor is its pseudopapillary pattern. The JGCT of both

ovaries revealed pseudopapillary proliferation, which was more prominent in the primary tumor of the right ovary. A collection of 14 cases of granulosa cell tumors with pseudopapillary pattern was described; interestingly 71% (n = 10) of these cases were JGCTs [14]. The pseudopapillary pattern may be a feature more suggestive of JGCT rather than AGCT. Compared to AGCTs, JGCTs generally display more mitotic activity. The more proliferative characteristic of JGCTs may be responsible for their propensity to have the pseudopapillary pattern. Further study focusing on this interesting feature is needed.

In conclusion, this is the first comprehensive report of a case of JGCT with late recurrence (> 5 years post-operation). The pseudopapillary pattern suggested that our patient's JGCT tumor had a more proliferative character. When an unusual morphological pattern is observed, long-term close surveillance is advisable.

**Acknowledgments.** We thank Mrs. Mariko Ishihara and Mr. Haruyuki Watanabe for their technical assistance.

## References

1. Bjorkholm E and Pettersson F: Granulosa-cell and theca-cell tumors. The clinical picture and long-term outcome for the Radiumhemmet series. *Acta Obstet Gynecol Scand* (1980) 59: 361–365.
2. Bjorkholm E and Silfversward C: Prognostic factors in granulosa-cell tumors. *Gynecol Oncol* (1981) 11: 261–274.
3. Young RH, Dickersin GR and Scully RE: Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. *Am J Surg Pathol* (1984) 8: 575–596.
4. Stenwig JT, Hazekamp JT and Beecham JB: Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. *Gynecol Oncol* (1979) 7: 136–152.
5. Lack EE, Perez-Atayde AR, Murthy AS, Goldstein DP, Crigler JFJ and Vawter GF: Granulosa theca cell tumors in premenarchal girls: a clinical and pathologic study of ten cases. *Cancer* (1981) 48: 1846–1854.
6. Zaloudek C and Norris HJ: Granulosa tumors of the ovary in children: a clinical and pathologic study of 32 cases. *Am J Surg Pathol* (1982) 6: 503–512.
7. Shah SP, Kobel M, Senz J, Morin RD, Clarke BA, Wiegand KC, Leung G, Zayed A, Mehl E, Kalloger SE, Sun M, Giuliany R, Yorida E, Jones S, Varhol R, Swenerton KD, Miller D, Clement PB, Crane C, Madore J, Provencher D, Leung P, DeFazio A, Khattria J, Turashvili G, Zhao Y, Zeng T, Glover JN, Vanderhyden B, Zhao C, Parkinson CA, Jimenez-Linan M, Bowtell DD, Mes-Masson AM, Brenton JD, Aparicio SA, Boyd N, Hirst M, Gilks CB, Marra M and Huntsman DG: Mutation of FOXL2 in granulosa-cell tumors of the ovary. *New Engl J Med* (2009) 360: 2719–2729.
8. D'ngelo E, Mozos A, Nakayama D, Espinosa I, Catusus L, Munoz J and Prat J: Prognostic significance of FOXL2 mutation and mRNA expression in adult and juvenile granulosa cell tumors of the ovary. *Mod Pathol* (2011) 24: 1360–1367.
9. Lee IH, Choi CH, Hong DG, Song JY, Kim YJ, Kim KT, Lee KW, Park IS, Bae DS and Kim TJ: Clinicopathologic characteristics of granulosa cell tumors of the ovary: a multicenter retrospective study. *J Gynecol Oncol* (2011) 22: 188–195.
10. Karalok A, Tasci T, Ureyen I, Turkmen O, Ocalan R, Sahin G, Turan T and Tulunay G: Juvenile granulosa cell ovarian tumor: clinicopathological evaluation of ten patients. *J Turk Ger Gynecol Assoc* (2015) 16: 32–34.
11. Wu H, Pangas SA, Eldin KW, Patel KR, Hicks J, Dietrich JE and Venkatramani R: Juvenile granulosa cell tumor of the ovary: a clinicopathologic study. *J Pediatr Adolesc Gynecol* (2017) 30: 138–143.
12. Frausto SD, Geisler JP, Fletcher MS and Sood AK: Late recurrence of juvenile granulosa cell tumor of the ovary. *Am J Obstet Gynecol* (2004) 191: 366–367.
13. Schneider DT, Janig U, Calaminus G, Gobel U and Harms D: Ovarian sex cord-stromal tumors - a clinicopathological study of 72 cases from the Kiel Pediatric Tumor Registry. *Virchows Arch* (2003) 443: 549–560.
14. Irving JA and Young RH: Granulosa cell tumors of the ovary with a pseudopapillary pattern: a study of 14 cases of an unusual morphologic variant emphasizing their distinction from transitional cell neoplasms and other papillary ovarian tumors. *Am J Surg Pathol* (2008) 32: 581–586.