[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

ORIGINAL ARTICLE

A clinicopathological study of granulosa cell tumors of the ovary: Can morphology predict prognosis?

Prerna Guleria, Lalit Kumar[1], Sunesh Kumar[2], Neerja Bhatla[2], Ruma Ray, Seema Singhal[2], Jyoti Meena[2], Sandeep R. Mathur

Departments of Pathology and [2]Obstetrics and Gynaecology, All India Institute of Medical Sciences, [1]Department of Medical Oncology, Dr. BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Sandeep R. Mathur, Department of Pathology, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: mathuraiims@gmail.com

ABSTRACT

Objective: Granulosa cell tumors (GCT) are low-grade malignant sex cord-stromal tumors (SCST) with late metastasis/recurrences and long disease-free periods. We performed a clinicopathological evaluation of GCT to ascertain features having prognostic impact. **Materials and Methods:** All cases of GCT of ovary from January 2006 to December 2018 were assessed for architectural patterns, nuclear grooves, and Call-Exner bodies. Each feature was graded on frequency of occurrence: not present (0)–very frequent (3). Anisonucleosis, necrosis, and inflammation were noted. Cases were grouped on mitotic count; <10 mitosis/10 High power field (HPF) or >=11 mitoses/10 HPF and Ki-67 index; <10% Ki-67 and >=11% Ki-67. **Results:** GCT formed 60.1% of SCST. Sixty cases' ages were in the range of 15–78 years (median 45). Clinical details were available in 37. Commonest presentation was abnormal uterine bleeding. Serum CA125 was raised in 16.1% and Inhibin in 58.8%. Seventy percent were in stage I. Disease recurrence was associated with higher stage (P = 0.007). The most frequent pattern was diffuse sheets (47%). Call-Exner bodies were absent in 22.2%. Grooves with score 1, 2, and 3 were seen in 35.8%, 23.5%, and 13.6%, respectively. Anisonucleosis was present in 26.7%, necrosis in 11.1%, and lympho-plasmacytic infiltrate in 43%. Out of total, 93.3% had <10 mitosis/10 HPF and 43.2% had recurrence, most with high Ki-67 (P = 0.064). **Conclusion:** Our study outlines histomorphological spectrum of GCT and emphasizes its frequent occurrence in lower stages with late recurrences. The presence of grooves may indicate granulosa-cell origin. Call-Exner bodies are not a necessity. Histomorphological features are not prognostically important. However, prognostic value of Ki-67 cannot be excluded. Limitation of the study was a small number of cases with follow-up.

KEY WORDS: Clinicopathological correlation, granulosa cell tumor ovary, histopathological features, Ki-67 proliferation index, prognostic factors

Access this article online
Website: www.ijpmonline.org
DOI: 10.4103/IJPM.IJPM_403_19
Quick Response Code:

INTRODUCTION

Granulosa cell tumors (GCTs) are low-grade malignant sex cord-stromal tumors with 10–15% recurrence rate in lower stages. Metastasis/recurrences are late and may sometimes occur even after 20-year intervals. Studies focussing separately on the prognostic role of the clinical and histopathological features have been carried out in the past with variable results. Therefore, with this study, we aimed to perform a comprehensive evaluation of the entire spectrum of the clinical, histopathological, and survival characteristics of GCTs being treated at our center. Our objective was to assess whether any of the above parameters held any prognostic role.

MATERIALS AND METHODS

This is a retrospective study which had the approval of the institutional ethics review committee.

All cases of GCTs of the ovary diagnosed in the department over the last 12 years (Jan 2006 to December 2018) were retrieved from the departmental archives. All other types of sex cord-stromal tumors were excluded from the study. The detailed history of cases wherever available were

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Guleria P, Kumar L, Kumar S, Bhatla N, Ray R, Singhal S, *et al*. A clinicopathological study of granulosa cell tumors of the ovary: Can morphology predict prognosis? Indian J Pathol Microbiol 2020;63:53-9.

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

obtained from the clinical case files. The clinical parameters recorded included the age of the patient, presenting symptoms, the FIGO (International Federation of Gynecology and Obstetrics) stage of the tumor, type of surgery performed, chemotherapy offered, and survival status until the last follow-up.

Pathology analysis

The available histopathology slides of the study population were retrieved and reviewed by two experienced pathologists. The histopathological sections of each case were assessed for the varied architectural patterns and the distinctive morphological features of GCT, namely, nuclear grooves and Call-Exner bodies. Each individual feature was then graded on a scale of 0–3 depending upon the frequency of their occurrence. A case where no grooves were identified was given a score of 0, while those with very frequent grooves was scored 3; similar scoring was performed for Call-Exner bodies also. In addition, the slides were assessed for the presence or absence of anisonucleosis, necrosis, and inflammation. Mitotic count was done for each case in the most mitotically active foci and cases were divided into two groups depending on whether the count was <10 mitosis/10 HPF (low mitosis) or >=11 mitoses/10 HPF (high mitosis). Immunohistochemistry (IHC) for Ki-67 was carried out in 17 cases where tumor blocks were available. Like mitosis, cases with <10% Ki-67 positivity and those with >=11% Ki-67 positivity were grouped together.

Statistical analysis

Data analysis was done using statistical software SPSS version 20. Categorical data were expressed as frequency and percentage and quantitative data was expressed as mean +/- standard deviation and median (minimum and maximum). Chi-square/Fisher-exact test was used to check the statistical significance of the data. Survival curve was prepared to check the time to event (recurrence) relationship. A *P* value <0.05 was considered significant.

RESULTS

Demographic data

The total sex cord-stromal tumors (SCSTs) received over the last 12 years in the department were 138. Of these, GCTs were the most common with 83 (60.1%) cases (4 juvenile type and 79 adult type). The rest of them were thecoma (22/138; 15.9%), fibroma (1/138; 0.7%), fibrothecoma (4/138; 2.9%), Sertoli-Leydig cell tumor (8/138; 5.8%), Leydig cell tumor (14/138; 10.1%), sex cord tumor with annular tubules (2/138; 1.4%) and one case each (0.7%) of steroid cell tumor, sclerosing stromal tumor, fibrosarcoma, and sex cord-stromal tumor, NOS. Only 60 cases of GCTs (56 adult GCTs and 4 juvenile GCTs) could be retrieved from the departmental records which were finally included in the study. Our cases' ages were in the range of 15–78 years among adult type of GCT with a median age of 45 years. Three cases of juvenile subtype were below 12 years of age and one was an adult woman. Clinical details were available in 37 cases. The most common presenting complaints were those of abnormal uterine bleeding, abdomen pain, amenorrhoea, and infertility. Postmenopausal bleeding was present in 10 cases. The most common associated comorbidity was that of hypothyroidism. Preoperative serum levels of CA125 were available in 31 patients of which only 5 had raised levels (>35 IU/mL). Readings of serum Inhibin (A or B) were available in 17 patients of which 10 (2 Inhibin A and 8 Inhibin B) showed elevated levels. Most (42/60; 70%) of our patients were in stage I. Disease recurrence had a statistically significant association with the stage ($P = 0.007$), being more common in higher stages. The type of surgeries performed in these patients were simple ovariotomy in only one patient desirous of preserving fertility, secondary cytoreductive surgery in a case of recurrence, and debulking surgeries for staging of the tumor in the rest of the cases. Chemotherapy was offered to 51% of the patients comprising of different regimens having combinations of bleomycin, etoposide, and cisplatin or carboplatin with paclitaxel. Table 1 shows the demographic data of GCT.

Histopathology

The maximum dimension of the tumor varied from 2.4 cm to up to 24 cm. The different architectural patterns seen in the H and E sections were diffuse sheets, nests, papillae, cords, trabeculae, cysts, and microfollicles in varying combinations and have been illustrated in Figure 1. The two most frequent patterns were those of diffuse sheets (47%) and nests (22.2%). Both solid and cystic areas were found in 34.6% of cases. Call-Exner bodies were frequent (score 3) in only 6.2% cases, whereas 22.2% cases showed their complete absence. In comparison, grooves were absent in only 1.2% of cases. The percentage of cases with grooves having score 1, 2, and 3 were 35.8%, 23.5%, and 13.6%, respectively [Figure 2]. Anisonucleosis was present in only 26.7%, while necrosis was seen in only 11.1% of cases. Assessment of associated inflammation in the sections revealed a predominant lymphoplasmacytic infiltrate in 43% of cases. Most (93.3%) of the patients had a low mitotic

Table 1: Demographic characteristics of GCT

Clinical parameter	*Values*
Age range in years (median)	
Adult type (*n*=56)	15-78 (45)
Juvenile type (*n*=4)	1-42 (7.5)
Presenting complaints (*n*=37)	
Abnormal uterine bleeding	13 (35.1%)
Pain abdomen	13 (35.1%)
Amenorrhoea	4 (10.8%)
Infertility	2 (5.4%)
Postmenopausal bleeding	10 (27.0%)
Associated comorbidities	
Hypothyroidism	9 (24.3%)
Raised tumor markers	
CA-125 (*n*=31)	5 (16.1%)
Serum Inhibin A or B (*n*=17)	10 (58.8%)
Stage (*n*=60)	
I	42 (70.0%)
II	1 (1.7%)
III	5 (8.3%)
IV	12 (20.0%)
Correlation of stage with recurrence	*P*=0.007
Chemotherapy given (*n*=37)	19 (51.3%)

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

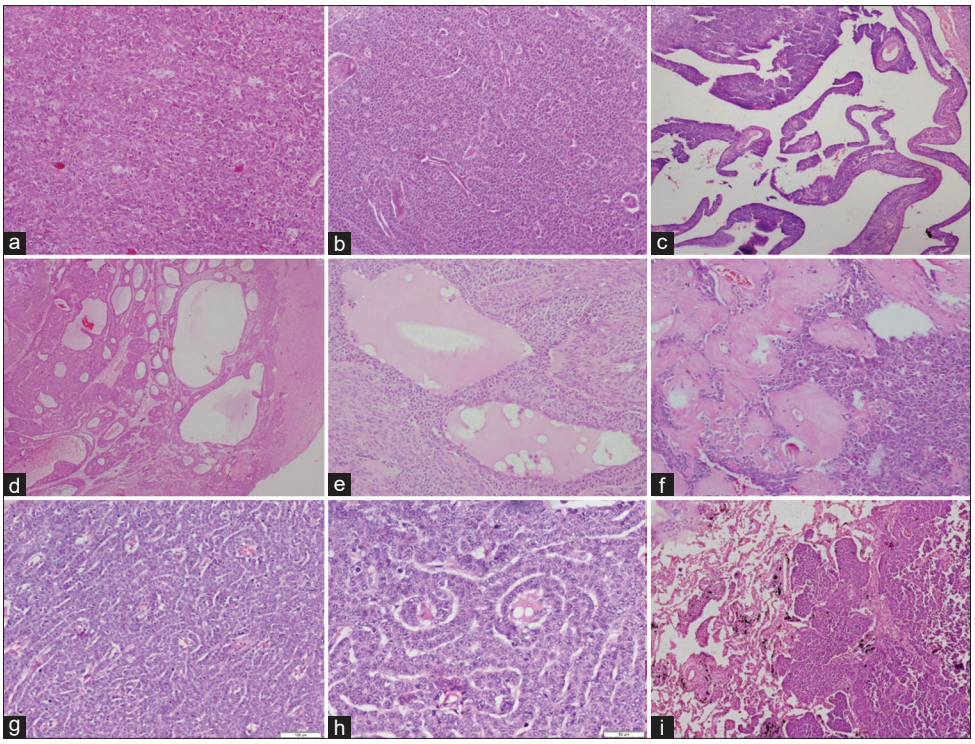

Figure 1: Various histological patterns of GCT. (a) Tumor cells present in diffuse sheets. (b) Areas of tumor with cells arranged in follicular pattern. (c) Areas with cystic change. (d) Microcystic pattern seen in GCT. (e) Macrofollicular pattern with pale eosinophilic material within the follicles. (f) Areas with hyalinisation. (g and h) GCT with tumor cells arrangement in ribbons and cords. (i) Lung metastasis of a case of GCT

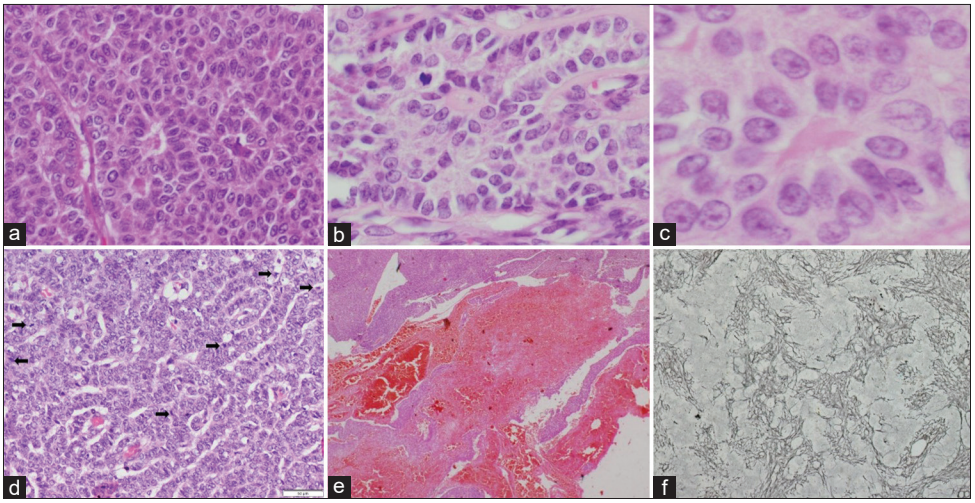

Figure 2: Other histomorphological features of GCT. (a) Tumor cells with longitudinal grooves giving a coffee-bean appearance. (b) Characteristic Call-Exner bodies and the presence of mitosis in the background. (c) Higher power view of Call-Exner body. (d) A case with frequent mitotic figures (arrows). (e) Areas of hemorrhage are common in these tumors. (f) Reticulin staining pattern of granulosa cell tumors

count of <10/10 HPF, whereas only 6.7% of the cases showed mitotic counts of >20/10 HPF [Figure 2]. Immunohistochemical markers for granulosa cell tumors were done in 43 cases to assist in establishing the diagnosis, of which 38 (88.4%) cases were found to be positive for inhibin. The remaining 5 cases even though negative for inhibin displayed positivity for calretinin, MIC-2 or vimentin and were diagnosed as GCTs. None of the cases were negative for calretinin; 20% of cases were negative for MIC-2. IHC for Ki-67 revealed equal distribution of cases in both the low as well as high count groups [Figure 3]. While correlating mitotic count with Ki-67 labeling index, we found 47.4% cases with low mitosis showing high Ki-67 labeling index. However, no case with high mitosis had a low proliferation index. Table 2 shows the histopathological features of GCT.

Survival characteristics

Of the 37 cases with clinical follow-up, the period varied from 1 month to 13 years with median follow-up time of 24 months.

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

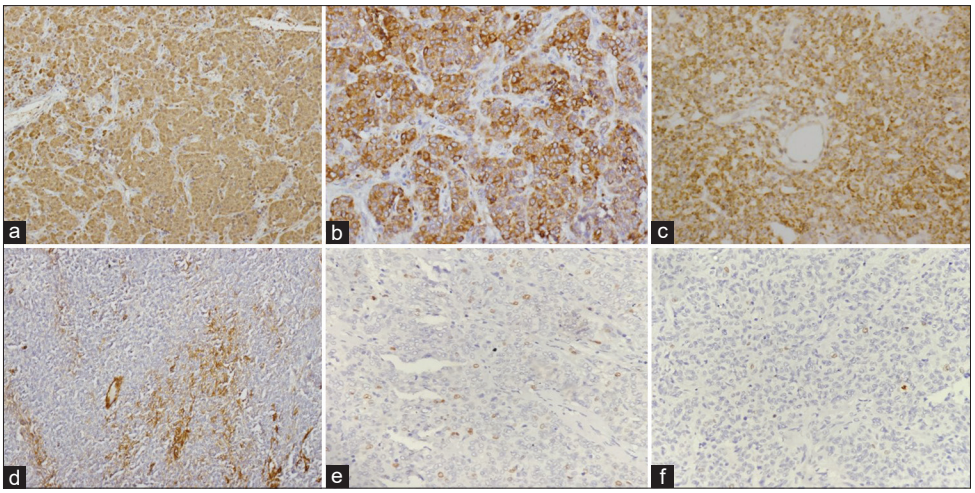

Figure 3: IHC of GCT. (a) Calretinin IHC showing diffuse cytoplasmic positivity. (b) Inhibin IHC showing strong diffuse positivity of tumor cells. (c) Melan-A IHC staining all the tumor cells. (d) Smooth muscle actin showing patchy staining of tumor cells. (e) Ki67 labelling index of 15–20% in one case and (f) another case with low Ki67 index of only 2–3% Ki67

Table 2: Histopathological features of GCT with clinical correlation

Pathologic parameters	*No. of cases*	*Correlation with stage (P)*	*Correlation with recurrence (P)*
Most common histologic patterns			
Nests	18 (30.0%)	0.794	0.322
Solid	38 (63.3%)	0.667	0.471
Cystic	28 (46.7%)	0.291	0.368
Call-Exner bodies		0.610	0.100
Absent	22 (36.7%)		
+	20 (33.3%)		
++	13 (21.7%)		
+++	5 (8.3%)		
Grooves		0.868	0.470
Absent	1 (1.7%)		
+	29 (48.3%)		
++	19 (31.7%)		
+++	11 (18.3%)		
Anisonucleosis		0.737	0.292
Present	16 (26.7%)		
Absent	44 (73.3%)		
Inflammation		0.621	0.260
Present	35 (58.3%)		
Absent	25 (41.7%)		
Necrosis		0.107	0.393
Present	9 (15.0%)		
Absent	51 (85.0%)		
Mitosis (per 10 HPF)		0.934	0.245
<10	56 (93.3%)		
11-20	1 (1.7%)		
>20	3 (5.0%)		
Immunohistochemistry		-	-
Inhibin	32 (%)		
Calretinin	23 (%)		
MIC-2	16 (%)		
Ki-67 (%)		0.971	0.064
</=10	8 (47.1%)		
>10	9 (52.9%)		

Recurrence was seen in 43.2%, of which most exhibited high proliferation index even though there was no statistical significance ($P = 0.064$). We even tried correlating recurrence with histopathological characteristics mentioned above, to establish any correlation if present; however, we found none. The survival function plotted in a curve has been shown in Figure 4.

DISCUSSION

Granulosa cell neoplasms were first described by Rokitansky in 1855.[1] It is a rare neoplasm, forming about 2–3% of all ovarian malignancies of which 95% are of the adult type.[2,3] The median age in our cohort was 45 years which is a decade earlier than its known occurrence in postmenopausal women.[3] In addition, one of the cases of the juvenile type was an adult, the age group in which this subtype is rare. As is already known, the presenting symptoms of patients with GCT vary with age, so was also the situation in our study. Amenorrhoea was the most frequent presentation in the reproductive age group, and menorrhagia associated with postmenopausal bleeding was frequent in the older age group. The most common symptom in patients of juvenile GCT was abdomen pain. None of the patients exhibited virilizing symptoms. Interestingly, hypothyroidism was an associated comorbidity in 16% of the patients, the reason for which we could not ascertain. Huang *et al.* in their study of 30 patients had reported a high number of their patients to be asymptomatic, especially in the postmenopausal age group.[4] In contrast, all the subjects under study in the present paper were symptomatic and we found no incidentally detected cases. Raised tumor markers are useful indicators of ovarian malignancies, of which CA125 marks tumors of epithelial origin and serum inhibin indicates a sex cord origin. Preoperative elevated serum CA125 has been reported in GCTs also.[4-6] It has been considered as a predictive factor[6] and has been associated with tumor recurrence.[4] Five (16%) of our cases had elevated CA125, and one of them had a recurrence. Due to the small percentage of cases with elevated levels, it was difficult for us to consider CA125 as a predictive or prognostic marker for GCTs. On the contrary, raised serum Inhibin, known to be a predictor of GCTs,[7-9] was found in 59% of our cases with 70% (7/10) of them having

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

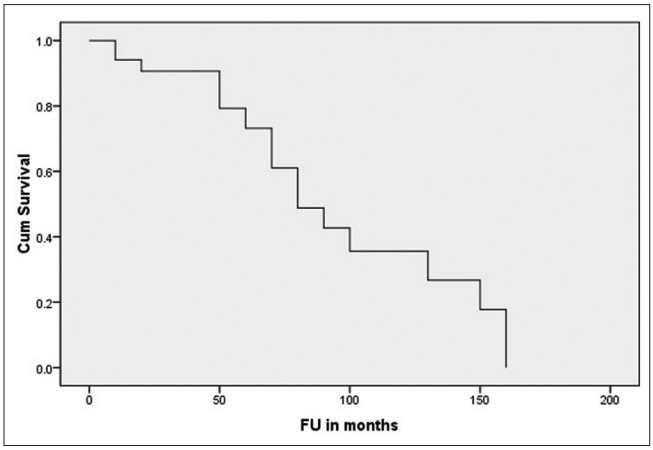

Figure 4: Survival function curve of cases of GCT (X axis: Follow-Up (FU) in months, Y axis: Cumulative survival)

recurrent disease. Therefore, serum inhibin may be considered as a prognostic marker of tumors of granulosa cell origin.

GCTs are usually detected in early stages due to their overt clinical symptoms and, hence, are mostly curable surgically alone.[10-12] Stage of the tumor is an established prognostic parameter.[13-18] Most of the patients in the present study also were in stage I disease. There was significant association of this stage group with no recurrence. The few cases with recurrence in the stage I disease group mostly staged Ic and were offered chemotherapy also. All patients of stage II disease and beyond (18/60; 30%) were given chemotherapy. Three patients of this subset had no evidence of disease progression on follow-up. Interestingly, one of them had metastatic disease after 4 years of initial detection but was clinically stable even 5 years postchemotherapy. The above findings of this study highlight the good prognostic characteristics of these tumors along with their chemosensitive nature.

GCTs are usually unilateral and have a wide range of tumor size varying from 3–24 cm.[9] They have varied architectural patterns and may show combinations of macrofollicular, microfollicular, trabecular, insular, tubular, cysts, or solid sheet patterns, of which the microfollicular pattern is the most common. We had similar divergent patterns among our cases with the diffuse sheet pattern being the commonest. In addition, the unusual pseudopapillary pattern which can often be confused with other tumors of the ovary[19] were also seen in five of our cases. We could not establish any prognostic significance of the histologic patterns of GCT similar to what Miller *et al.* had mentioned in their editorial.[20] GCTs are characterized by the typical Call-Exner bodies which are considered sine-qua-non of this entity and is reportedly present in 30–50% of these tumors.[3,10] The Call-Exner bodies were present in 64% of our cases but were abundant in only 6.2% cases. The absence of Call-Exner bodies has been reported to be associated with worse prognosis by some authors.[21] We found no such association. In addition, we insist that its absence does not completely rule out a GCT and they should form a part of the differential diagnoses while evaluating the poorly differentiated tumors of the ovary. On the other hand, the coffee-bean appearance of nuclei with longitudinal grooves was seen in 98.8% of our cases, thereby indicating the fact that a GCT should be considered if grooving is seen even focally. Based on the histology, the important differential diagnoses that can be considered while evaluating adult GCTs include ovarian endometrioid adenocarcinoma, endometrial stromal sarcoma, carcinoid tumor, desmoplastic small round cell tumor, Brenner tumor, germ cell neoplasms, malignant lymphoma, and metastatic carcinoma.[22,23] The other SCSTs also need to be excluded before labeling a case as GCT. Similarly, the endodermal sinus tumor, clear cell carcinoma, and small cell carcinoma of hypercalcaemic type need to be differentiated from juvenile GCTs.[22] The poorly differentiated carcinomas form an important differential of GCTs, especially those having a diffuse sheet pattern. The difference in the nuclear appearance of such cases helps in clinching the diagnosis. While the GCTs possess monomorphic grooved coffee bean nuclei, the poorly differentiated tumors exhibit hyperchromatic nuclei of varying shapes and sizes without grooves.[24]

Furthermore, the presence of anisonucleosis, necrosis, and associated inflammation in our cases were not associated with any prognostic parameter. Increased mitotic activity in GCTs has been associated with poorer prognosis in some studies,[17,18,21] while others have reported no such association.[12,20,25] Leuverink *et al.* in their study of 35 cases of GCT did not find any correlation with any of the proliferation indices (mitotic count/Ki-67 index) with clinical outcomes.[26] Our series had 93% cases with <10 mitoses/10 HPF and no association with survival characteristics. Therefore, we do not recognize mitotic activity as a prognostic indicator. The IHC for Ki-67 labeling index, when performed on our cases, showed increased counts even in some with low mitotic counts on hematoxylin-eosin sections. High Ki-67 index was more frequent in cases with recurrence but had no statistical significance which could be attributed to the small sample size with available follow-up. Therefore, the assumption that a high Ki-67 index might act as a predictive and prognostic marker in GCTs[27-30] remained doubtful, requiring studies with a larger cohort for validation.

GCTs are mostly diagnosed morphologically without any requirement of immunohistochemical stains. However, with the existing myriad of differential diagnoses, a panel of different IHC stains to rule out other tumor types is essential. Studies have reported >90% of GCT cases expressing inhibin.[31] We observed 5 (11.6%) of them in our series to be negative for inhibin. Calretinin is also as sensitive a marker for GCTs as inhibin.[32] None of our cases were negative for calretinin. Similar result of inhibin and calretinin positivity has been reported earlier where the former was found to be less sensitive.[33] The importance lies when GCTs have to be distinguished from other epithelial neoplasms when cytokeratins are positive in both the tumors. Inhibin positivity in GCTs is stronger and more diffuse in comparison. In addition, GCTs are negative for epithelial membrane antigen, cytokeratins 10/13, 19, and 20, carcinoembryonic antigen, CA 125 and CA 19–9. These markers will help in distinguishing them from anaplastic/poorly differentiated carcinomas.[23] However, the same

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

cannot be definitely used to differentiate between the various SCSTs as most of them are inhibin positive. In these cases, the morphology helps in the differentiation. The IHC findings in our study reiterate the fact that GCTs cannot be definitely ruled out in inhibin negative cases and a panel of antibodies instead of a single IHC should be utilized while evaluating such tumors. The GCTs are usually positive for vimentin, inhibin, calretinin, MIC-2, and also Melan A.

Of late, there has been an emerging trend of characterizing the molecular landscapes of different tumors. Whole-genome analysis of GCTs have found recurrent somatic mutation of the forkhead box L2 (FOXL2) gene in adult GCT in high frequencies. However, this mutation is not exclusive for GCTs and is also seen in other SCSTs such as thecomas.[34] The other genetic mutations seen in these tumors are expression of Müllerian inhibiting substance, p53, proto-oncogene such as c-erbB2 and c-myc. These tumors are also associated with chromosomal aberrations such as trisomy 12 and 14 and monosomy 22.[3]

These tumors have an unpredictable behavior with sometimes even stage I tumors presenting with late recurrences. There have been studies trying to correlate prognosis with various histomorphological features and mitotic activity. Although no correlation has been found with the histomorphology of the tumor, some studies have reported a direct association with the mitotic activity.[17,30] Similarly, our study shows no association of survival characteristics with the tumor architectural patterns and an increased frequency of recurrences in lesions with high Ki-67 proliferation index. However, these findings may not be truly representative as the follow-up was available only in a limited number of cases.

CONCLUSION

This study comprises one of the largest cohorts of GCTs from India. It was performed keeping in mind the diverse histomorphology of GCTs and the existing predicaments regarding its prognostic parameters. We tried to accomplish a comprehensive assessment of the clinical and histopathological features along with their predictive and prognostic importance. Our findings restate the frequent occurrence of these tumors in lower stages with late recurrences. The occurrence of grooves on histopathology is an indicator toward granulosa cell origin of the ovarian tumor under evaluation, and the presence of Call-Exner bodies is not a necessity. We did not find any definite association of the histomorphological findings of GCTs with prognosis; however, its probable association with Ki-67 proliferation index cannot definitely be ruled out. We also emphasize the use of an antibody panel for a definite diagnosis of these tumors. We propose further studies on a larger cohort of GCTs to verify our findings.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Diddle AW. Granulosa-and theca-cell ovarian tumors: Prognosis. Cancer 1952;5:215-28.
2. Ranganath R, Sridevi V, Shirley SS, Shantha V. Clinical and pathologic prognostic factors in adult granulosa cell tumors of the ovary. Int J Gynecol Cancer 2008;18:929-33.
3. Geetha P, Nair MK. Granulosa cell tumors of the ovary. Aust N Z J Obstet Gynaecol 2010;50:216-20.
4. Huang BS, Sun HD, Hsu YM, Chang WH, Horng HC, Yen MS, *et al*. Clinical presentation and outcome of adult-type granulosa cell tumors: A retrospective study of 30 patients in a single institute. J Chin Med Assoc 2014;77:21-5.
5. Stine JE, Suri A, Gehrig PA, Chiu M, Erickson BK, Huh WK, *et al*. Pre-operative imaging with CA125 is a poor predictor for granulosa cell tumors. Gynecol Oncol 2013;131:59-62.
6. Yesilyurt H, Tokmak A, Guzel AI, Simsek HS, Terzioglu SG, Erkaya S, *et al*. Parameters for predicting granulosa cell tumor of the ovary: A single center retrospective comparative study. Asian Pac J Cancer Prev 2014;15:8447-50.
7. Mom CH, Engelen MJ, Willemse PH, Gietema JA, Ten Hoor KA, de Vries EG, *et al*. Granulosa cell tumors of the ovary: The clinical value of serum inhibin A and B levels in a large single center cohort. Gynecol Oncol 2007;105:365-72.
8. Färkkilä A, Koskela S, Bryk S, Alfthan H, Bützow R, Leminen A, *et al*. The clinical utility of serum anti-müllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors–A comparative study with inhibin B. Int J Cancer 2015;137:1661-71.
9. Koukourakis GV, Kouloulias VE, Koukourakis MJ, Zacharias GA, Papadimitriou C, Mystakidou K, *et al*. Granulosa cell tumor of the ovary: Tumor review. Integr Cancer Ther 2008;7:204-15.
10. Kottarathil VD, Antony MA, Nair IR, Pavithran K. Recent advances in granulosa cell tumor ovary: A review. Indian J Surg Oncol 2013;4:37-47.
11. Khosla D, Dimri K, Pandey AK, Mahajan R, Trehan R. Ovarian granulosa cell tumor: Clinical features, treatment, outcome, and prognostic factors. N Am J Med Sci 2014;6:133-8.
12. Mangili G, Ottolina J, Gadducci A, Giorda G, Breda E, Savarese A, *et al*. Long-term follow-up is crucial after treatment for granulosa cell tumors of the ovary. Br J Cancer 2013;109:29-34.
13. Wang PH, Sun HD, Lin H, Wang KL, Liou WS, Hung YC, *et al*. Outcome of patients with recurrent adult-type granulosa cell tumors–A Taiwanese gynecologic oncology group study. Taiwan J Obstet Gynecol 2015;54:253-9.
14. Vani BR, Geethamala K, Geetha RL, Srinivasa MV. Granulosa cell tumor of ovary: A clinicopathological study of four cases with brief review of literature. J Midlife Health 2014;5:135-8.
15. Uygun K, Aydiner A, Saip P, Basaran M, Tas F, Kocak Z, *et al*. Granulosa cell tumor of the ovary: Retrospective analysis of 45 cases. Am J Clin Oncol 2003;26:517-21.
16. Sekkate S, Kairouani M, Serji B, Tazi A, Mrabti H, Boutayeb S, *et al*. Ovarian granulosa cell tumors: A retrospective study of 27 cases and a review of the literature. World J Surg Oncol 2013;11:142.
17. Sehouli J, Drescher FS, Mustea A, Elling D, Friedmann W, Kühn W, *et al*. Granulosa cell tumor of the ovary: 10 years follow-up data of 65 patients. Anticancer Res 2004;24:1223-9.
18. Fujimoto T, Sakuragi N, Okuyama K, Fujino T, Yamashita K, Yamashiro S, *et al*. Histopathological prognostic factors of adult granulosa cell tumors of the ovary. Acta Obstet Gynecol Scand 2001;80:1069-74.
19. Irving JA, Young RH. Granulosa cell tumors of the ovary with a pseudopapillary pattern: A study of 14 cases of an unusual

[Downloaded free from http://www.ijpmonline.org on Thursday, April 2, 2020, IP: 106.192.203.92]

morphologic variant emphasizing their distinction from transitional cell neoplasms and other papillary ovarian tumors. Am J Surg Pathol 2008;32:581-6.
20. Miller K, McCluggage WG. Prognostic factors in ovarian adult granulosa cell tumor. J Clin Pathol 2008;61:881-4.
21. Miller BE, Barron BA, Wan JY, Delmore JE, Silva EG, Gershenson DM. Prognostic factors in adult granulosa cell tumor of the ovary. Cancer 1997;79:1951-5.
22. Hildebrandt RH, Rouse RV, Longacre TA. Value of inhibin in the identification of granulosa cell tumors of the ovary. Hum Pathol 1997;28:1387-95.
23. McCluggage WG, Maxwell P. Immunohistochemical staining for calretinin is useful in the diagnosis of ovarian sex cord–stromal tumours. Histopathology 2001;38:403-8.
24. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol 2003;21:1180-9.
25. Horny HP, Marx L, Kröber S, Lüttges J, Kaiserling E, Dietl J. Granulosa cell tumor of the ovary. Gynecol Obstet Invest 1999;47:133-8.
26. Leuverink E, Brennan BA, Crook ML, Doherty D, Hammond IG, Ruba S, *et al*. Prognostic value of mitotic counts and Ki-67 immunoreactivity in adult-type granulosa cell tumor of the ovary. J Clin Pathol 2008;61:914-9.
27. Jurić G, Žarković N, Nola M, Tillian M, Jukić S. The value of cell proliferation and angiogenesis in the prognostic assessment of ovarian granulosa cell tumors. Tumori 2001;87:47-53.
28. King LA, Okagaki T, Gallup DG, Twiggs LB, Messing MJ, Carson LF. Mitotic count, nuclear atypia, and immunohistochemical determination of Ki-67, c-myc, p21-ras, c-erbB2, and p53 expression in granulosa cell tumors of the ovary: Mitotic count and Ki-67 are indicators of poor prognosis. Gynecol Oncol 1996;61:227-32.
29. Wabersich J, Fracas M, Mazzer S, Marchetti M, Altavilla G. The value of the prognostic factors in ovarian granulosa cell tumors. Eur J Gynaecol Oncol 1998;19:69-72.
30. Costa MJ, Walls J, Ames P, Roth LM. Transformation in recurrent ovarian granulosa cell tumors: Ki67 (MIB-1) and p53 immunohistochemistry demonstrates a possible molecular basis for the poor histopathologic prediction of clinical behavior. Hum Pathol 1996; 27: 274-81.
31. Deavers MT, Malpica A, Liu J, Broaddus R, Silva EG. Ovarian sex cord-stromal tumors: An immunohistochemical study including a comparison of calretinin and inhibin. Mod Pathol 2003;16:584-90.
32. Costa MJ, Ames PF, Walls J, Roth LM. Inhibin immunohistochemistry applied to ovarian neoplasms: A novel, effective, diagnostic tool. Hum Pathol 1997;28:1247-54.
33. Cathro HP, Stoler MH. The utility of calretinin, inhibin, and WT1 immunohistochemical staining in the differential diagnosis of ovarian tumors. Hum Pathol 2005;36:195-201.
34. Kim MS, Hur SY, Yoo NJ, Lee SH. Mutational analysis of FOXL2 codon 134 in granulosa cell tumour of ovary and other human cancers. J Pathol. 2010;221:147-52.