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Adult Granulosa Cell Tumor With High-grade Transformation

Report of a Series With FOXL2 Mutation Analysis

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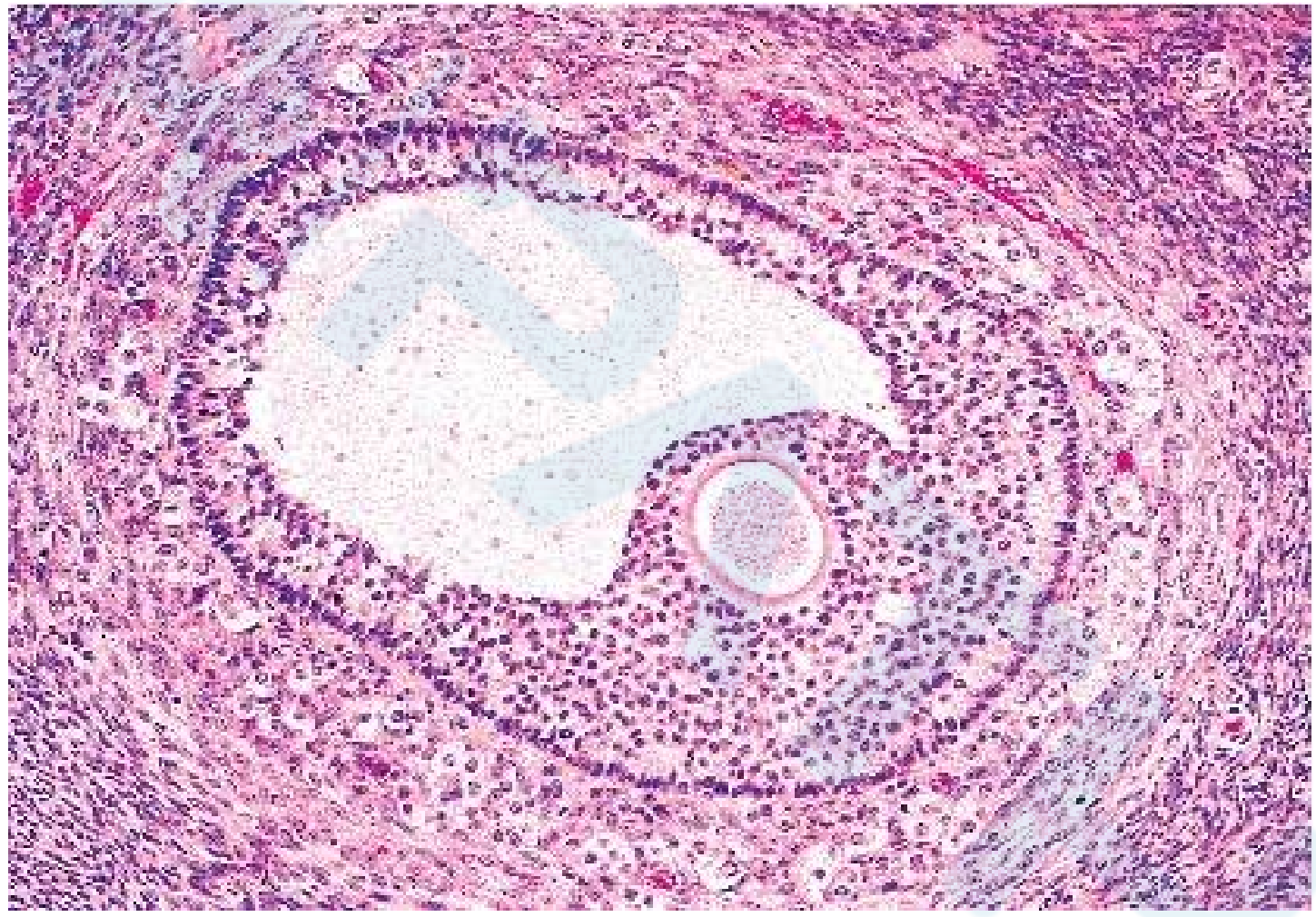
汇报人：李擒龙

Sex cord-stromal tumours	
Pure stromal tumours	
Fibroma	8810/0
Cellular fibroma	8810/1
Thecoma	8600/0
Luteinized thecoma associated with sclerosing peritonitis	8601/0
Fibrosarcoma	8810/3
Sclerosing stromal tumour	8602/0
Signet-ring stromal tumour	8590/0
Microcystic stromal tumour	8590/0
Leydig cell tumour	8650/0
Steroid cell tumour	8760/0
Steroid cell tumour, malignant	8760/3
Pure sex cord tumours	
Adult granulosa cell tumour	8620/3
Juvenile granulosa cell tumour	8622/1
Sertoli cell tumour	8640/1
Sex cord tumour with annular tubules	8623/1
Mixed sex cord-stromal tumours	
Sertoli-Leydig cell tumours	
Well differentiated	8631/0
Moderately differentiated	8631/1
With heterologous elements	8634/1
Poorly differentiated	8631/3
With heterologous elements	8634/3
Retiform	8633/1
With heterologous elements	8634/1
Sex cord-stromal tumours, NOS	8590/1



Adult granulosa cell tumour (AGCT)

Definition

A low-grade malignant, sex cord-stromal tumour composed of granulosa cells often with a variable number of fibroblasts and theca cells.

ICD-O code 8620/3

Epidemiology

Adult granulosa cell tumour accounts for about 1 % of all ovarian tumours.

Clinical features

- occur over a wide age range with an average age of 53 years.
- postmenopausal bleeding in older women,
- menorrhagia(月经过多), metrorrhagia(子宫不规则出血), or amenorrhea(闭经) in younger patients.
- Rupture or torsion of the tumour causes acute abdominal symptoms in about 10% of patients.
- The tumour is typically unilateral and confined to the ovary at diagnosis.

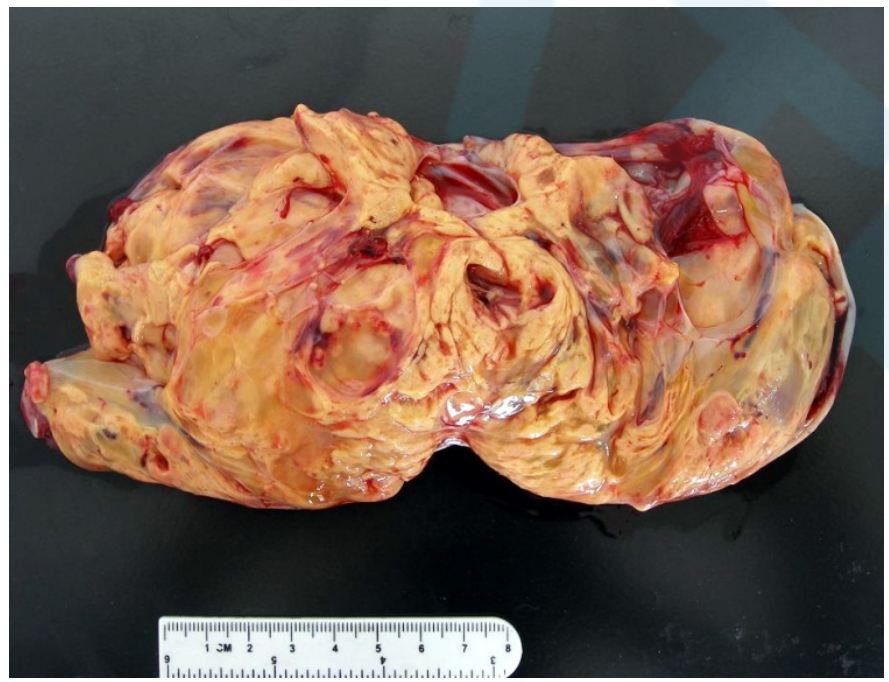
Macroscopy

•AGCT vary greatly in size, but the average diameter is about 10 cm.

•most typically solid and cystic , but may be solid or rarely entirely cystic

•The solid areas are usually soft and tan to yellow.

•The cysts typically contain clotted blood and some tumours, particularly those associated with rupture , exhibit conspicuous haemorrhage.



Histopathology

- A variety of growth patterns occur and are often admixed.
- The most common pattern is diffuse.
- Tumour cells often grow in cords and trabeculae, in undulating ribbons and in nests (insular pattern). A pseudopapillary architecture may be seen.
- A microfollicular pattern (Call-Exner bodies) is seen in a minority of tumours and is uncommonly conspicuous. Occasionally larger follicles are seen (macrofollicular pattern).
- The tumour cells usually have scant pale cytoplasm, but rarely the cytoplasm is abundant and eosinophilic (luteinized), The nuclei are typically uniform, pale and round to oval.
- Nuclear grooves are a characteristic feature but in many tumours are not conspicuous.
- Nuclear atypia is usually absent except for occasional (about 2%) cases which show bizarre nuclei, unassociated with increased mitotic activity. Mitotic activity is variable, and sometimes brisk.

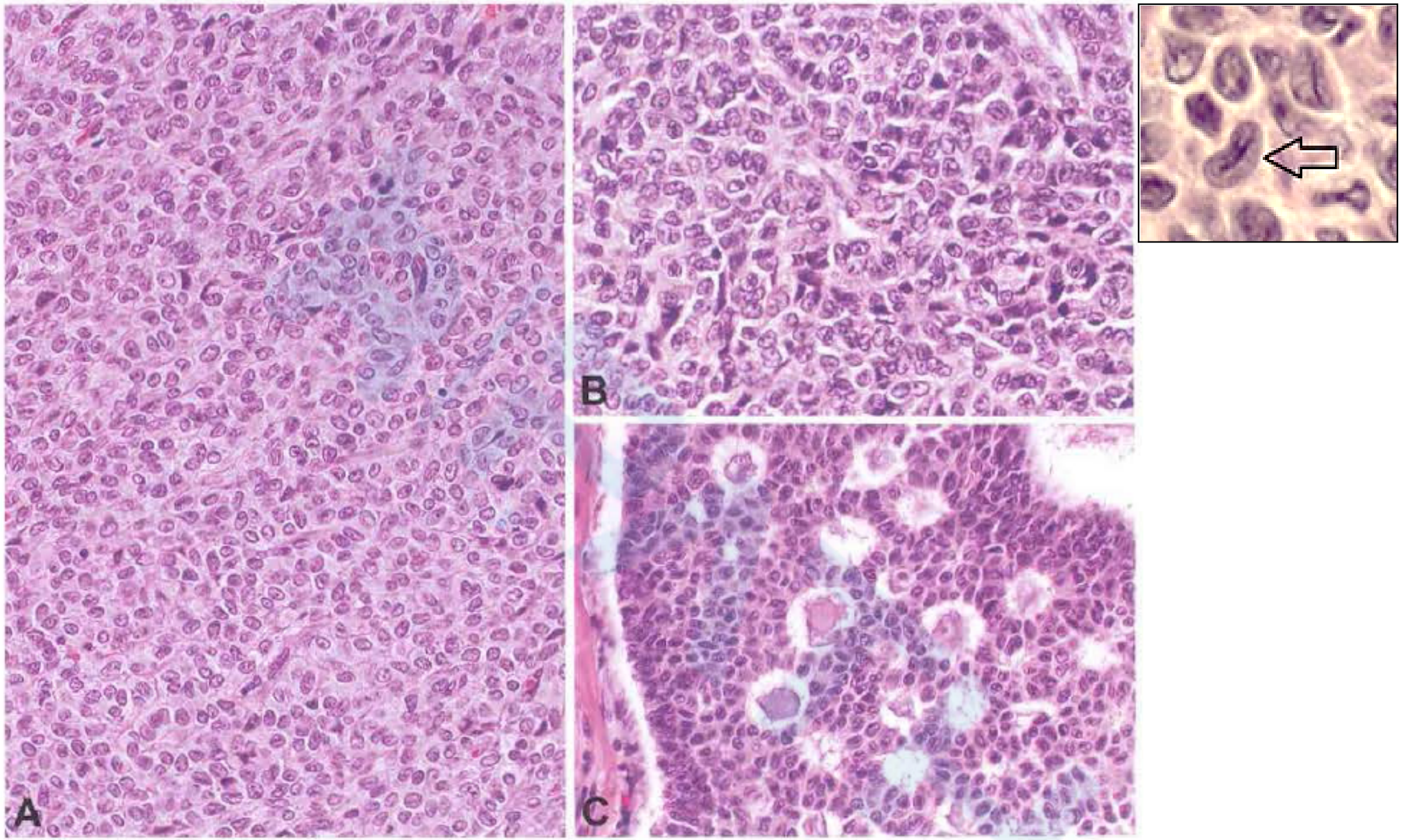
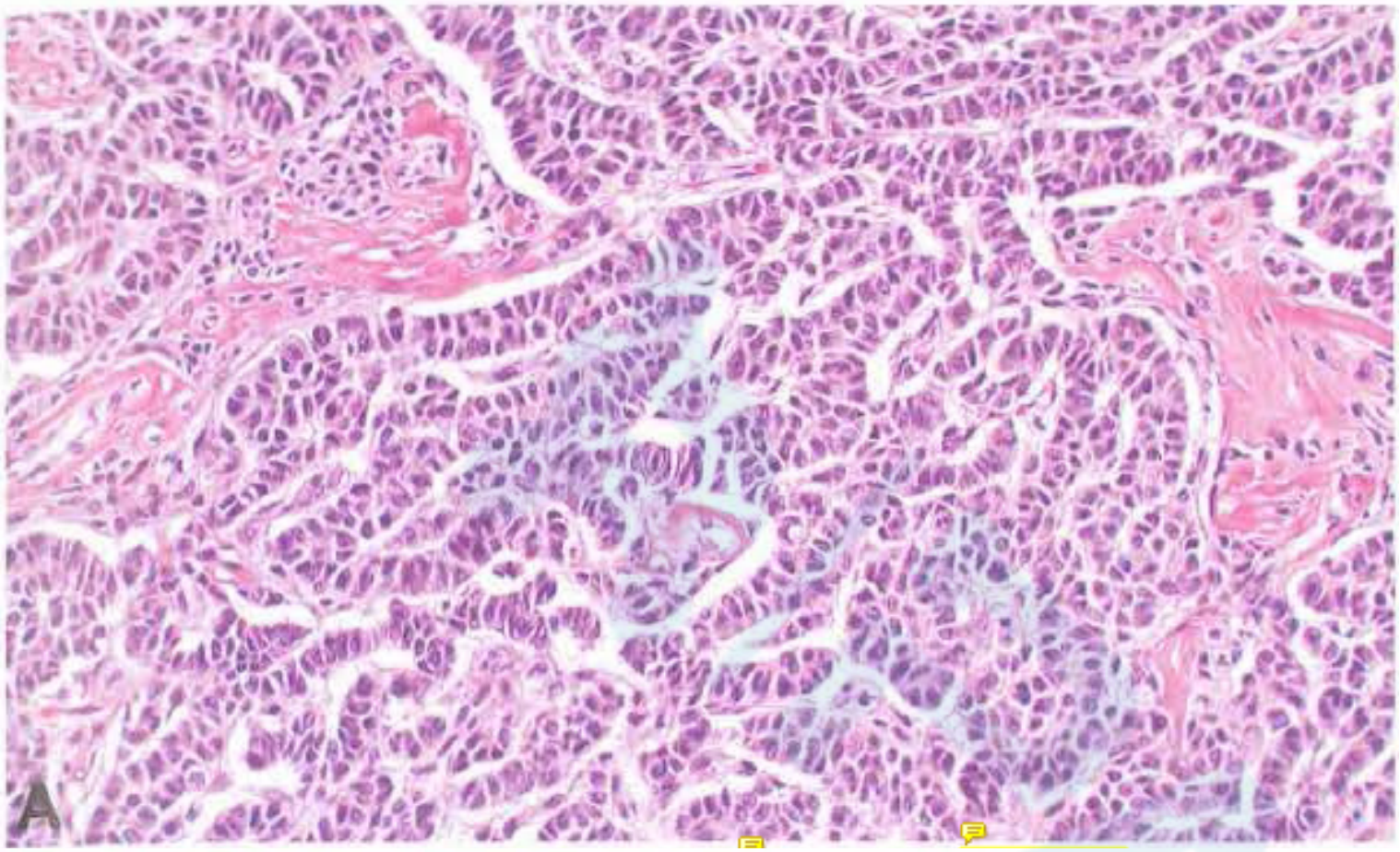


Fig.1.45 AGCT. **A** Tumour cells show a diffuse growth pattern.
B Sheets of monotonous small cells with scant cytoplasm and nuclei with occasional longitudinal grooves are seen. **C** In the microfollicular pattern (Call-Exner bodies), the tumour cells surround small, rounded spaces filled with eosinophilic material.



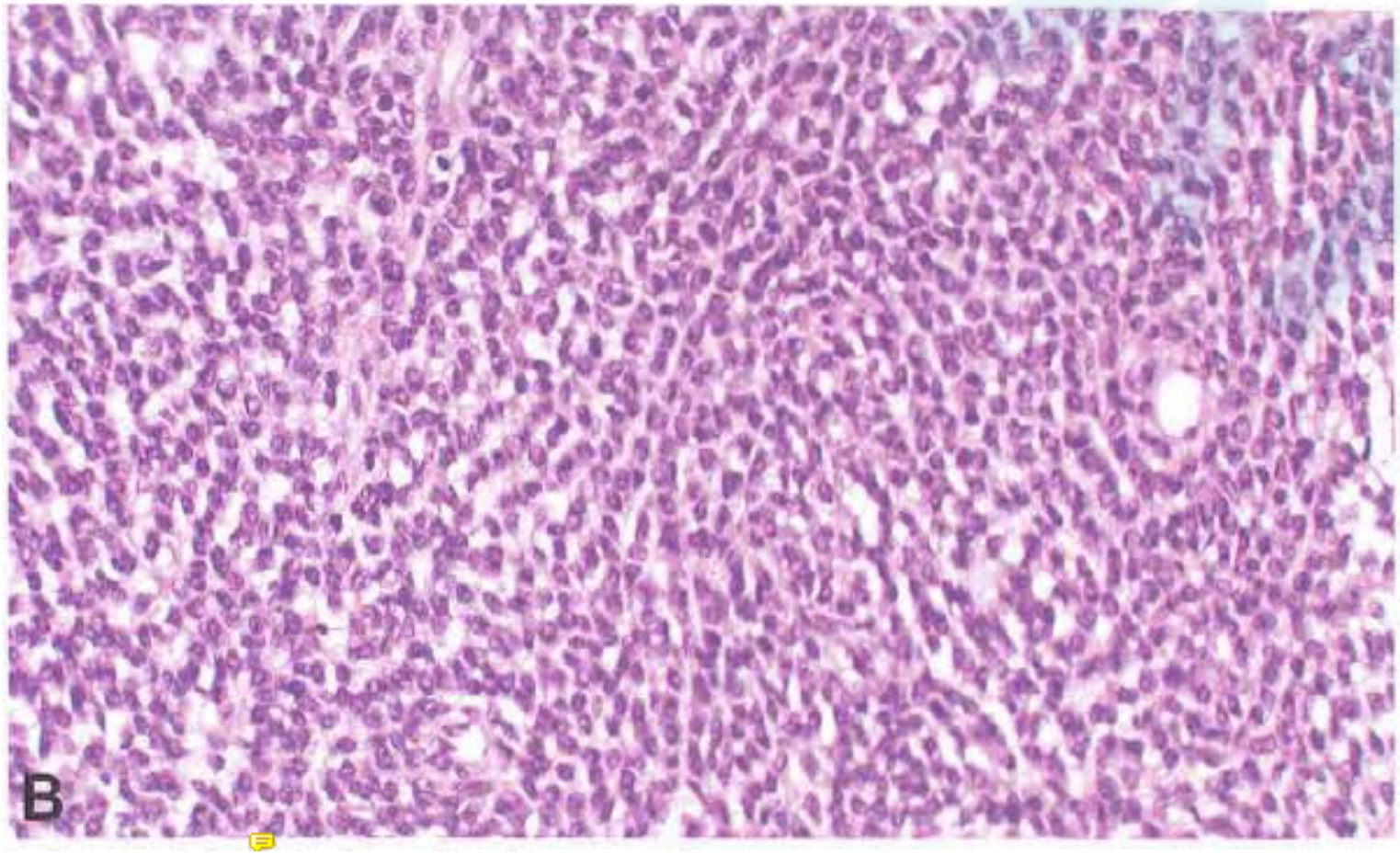


Fig. 1.46 AGCT
A Inter-anastomosing trabeculae in a collagenous background.
B Delicate cords of tumour cells are present.

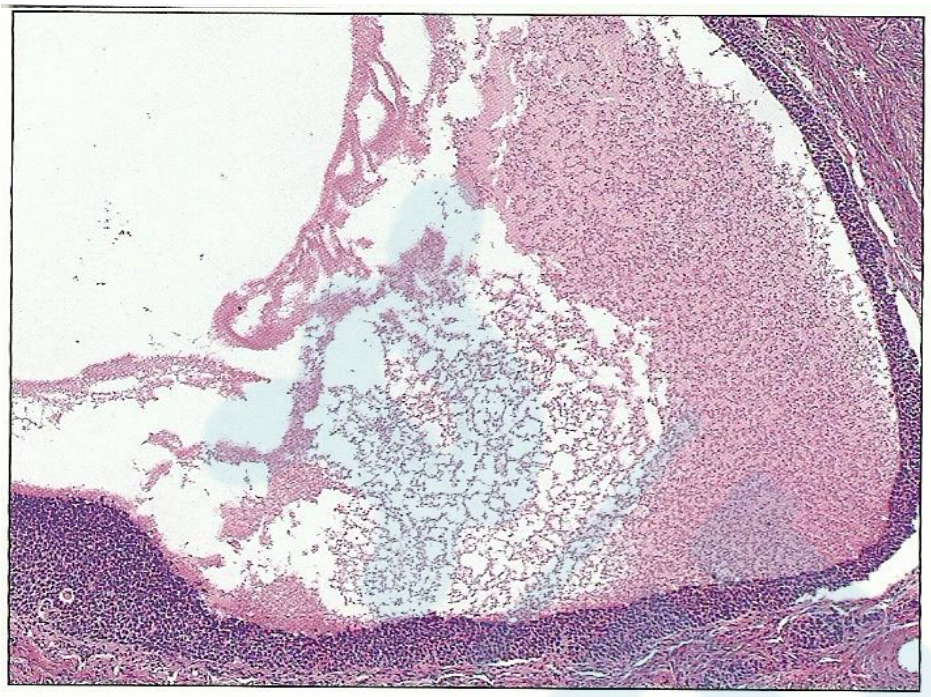


Fig. 26.6 Well-differentiated granulosa cell tumor, macrofollicular pattern. Lining cells closely resemble those of normal preovulatory follicles. No thecal layer is present in this example.

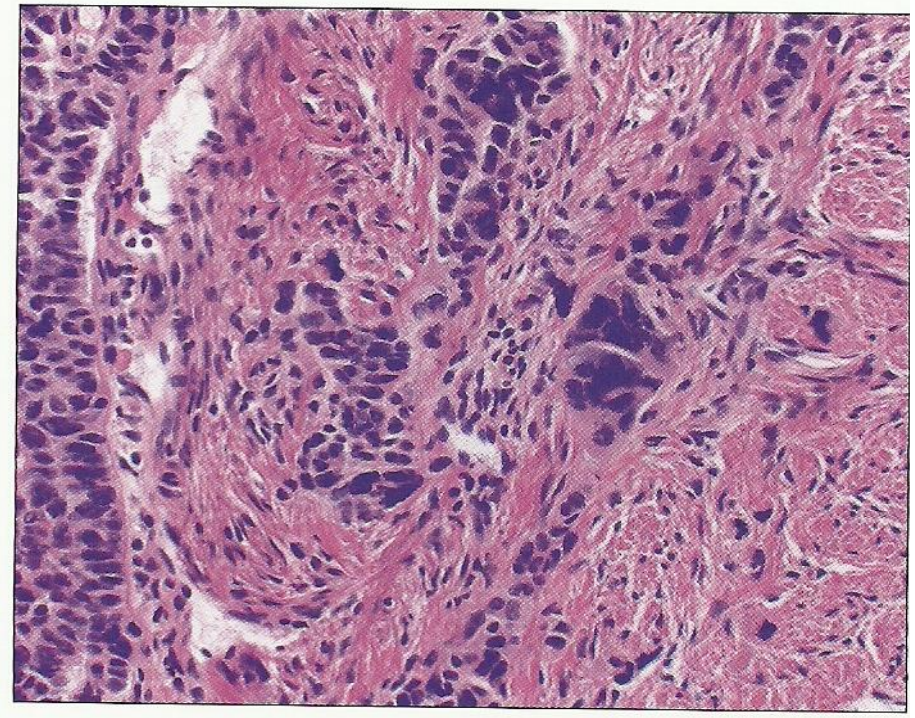


Fig. 26.11 Well-differentiated granulosa cell tumor with focally bizarre nuclei. They may occur in any of the histologic variants of this tumor. Isolated bizarre nuclei seen here in small trabecular of granulosa cells.

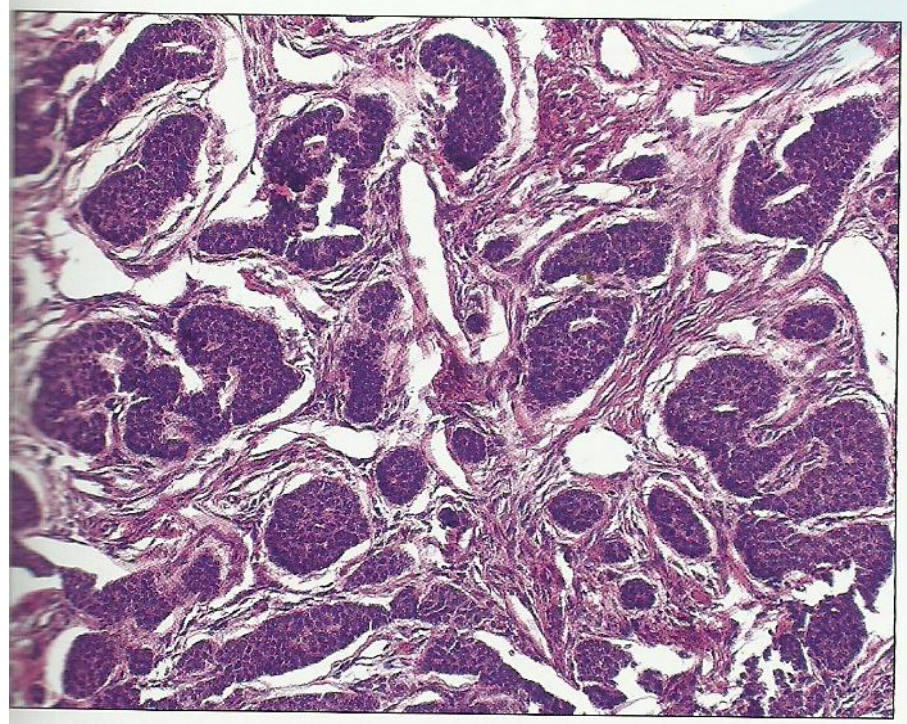


Fig. 26.10 'Insular' variant of microfollicular granulosa cell tumor. This pattern is important only in the difficulty it may present in being distinguished from ovarian carcinoid tumors.

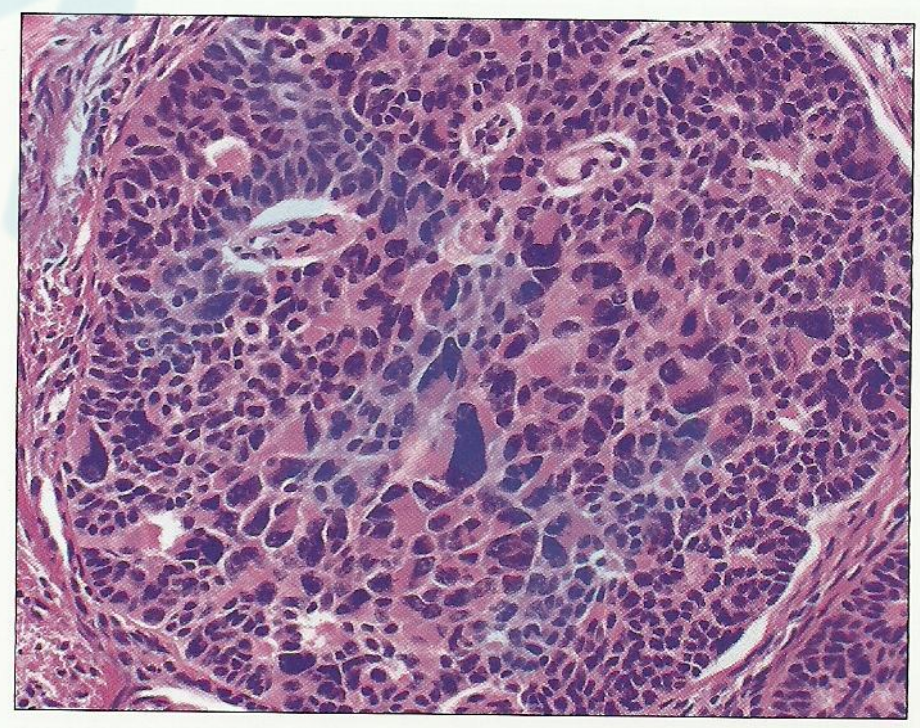


Fig. 26.12 Well-differentiated granulosa cell tumor with focally bizarre nuclei. Bizarre nuclei seen within cell nest of microfollicular tumor.

Immunohistochemistry

•Granulosa cell tumours usually exhibit inhibin， calretinin， FOXL2, steroidogenic factor-1 (SF-1), WT1 and CD56 positivity.

•They may be positive for pan-CK and CK8/18, but are typically negative for CK7 and EMA.

•They may be positive for SMA, desmin, CD99 (membranous) and S-100 protein.

Genetic profile

•The most common abnormalities reported have been trisomy 12, trisomy 14, monosomy 16 or deletion of 16q and monosomy 22.

•There is a missense somatic point mutation in the *FOXL2* gene (C402G) in more than 90% of AGCT.

Prognosis and predictive factors

•The recurrence rate is 10-15% for stage Ⅰa tumours and 20-30% overall. Metastases/ recurrences are often detected > 5 years after initial treatment, sometimes after intervals of > 20 years.

•Extraovarian spread is to the peritoneum and omentum and rarely to liver or lungs. Lymph node metastases are uncommon.

•Unfavourable factors include advanced stage (most important), large size (> 15 cm), bilaterality and tumour rupture.

•There is no correlation between microscopic appearance, including mitotic activity, and outcome.

Juvenile granulosa cell tumour (JGCT)

Definition

A distinctive type of granulosa cell tumour that occurs mainly in children and young adults.

ICD-O code 8622/1

Epidemiology

It accounts for 5% of granulosa cell tumours.

Clinical features

- This variant occurs usually in the first three decades (average age is 15 years), but can be seen in older patients.
- Young girls typically have isosexual pseudoprecocity(同性假性性早熟).
- Older children and premenopausal women present with menorrhagia(月经过多) or amenorrhea(闭经) or with nonspecific symptoms such as abdominal or pelvic pain, distension or a palpable mass.
- Torsion or rupture of the tumour causes acute abdominal symptoms.
- Juvenile granulosa cell tumours are typically unilateral, and more than 95% of them are confined to the ovary (stage 1).

Macroscopy

The average size is about 12 cm and most are solid and cystic, but some are uniformly solid or cystic. The solid areas are yellow or tan. Haemorrhage may be conspicuous within cysts and solid foci of the neoplasm, particularly in tumours that have ruptured.

Histopathology

•The tumour has a nodular or diffuse growth punctuated, in most cases, by follicles of varying sizes and shapes. Sometimes they are round and uniform but they more often have irregular shapes. They contain secretions that may be eosinophilic but are, more often, basophilic and may stain for mucin.

•The cells lining the follicles and in the solid areas characteristically have abundant eosinophilic but occasionally pale amphophilic cytoplasm.

•The nuclei are round and lack grooves with rare exceptions.

•Mitotic figures are typically frequent and striking nuclear atypia is seen in 10-15% of the tumours.

•The stroma is generally less conspicuous in these tumours compared to adult granulosa cell tumours but it is occasionally prominent and in rare cases there is striking sclerosis which may obscure the underlying neoplastic cells.

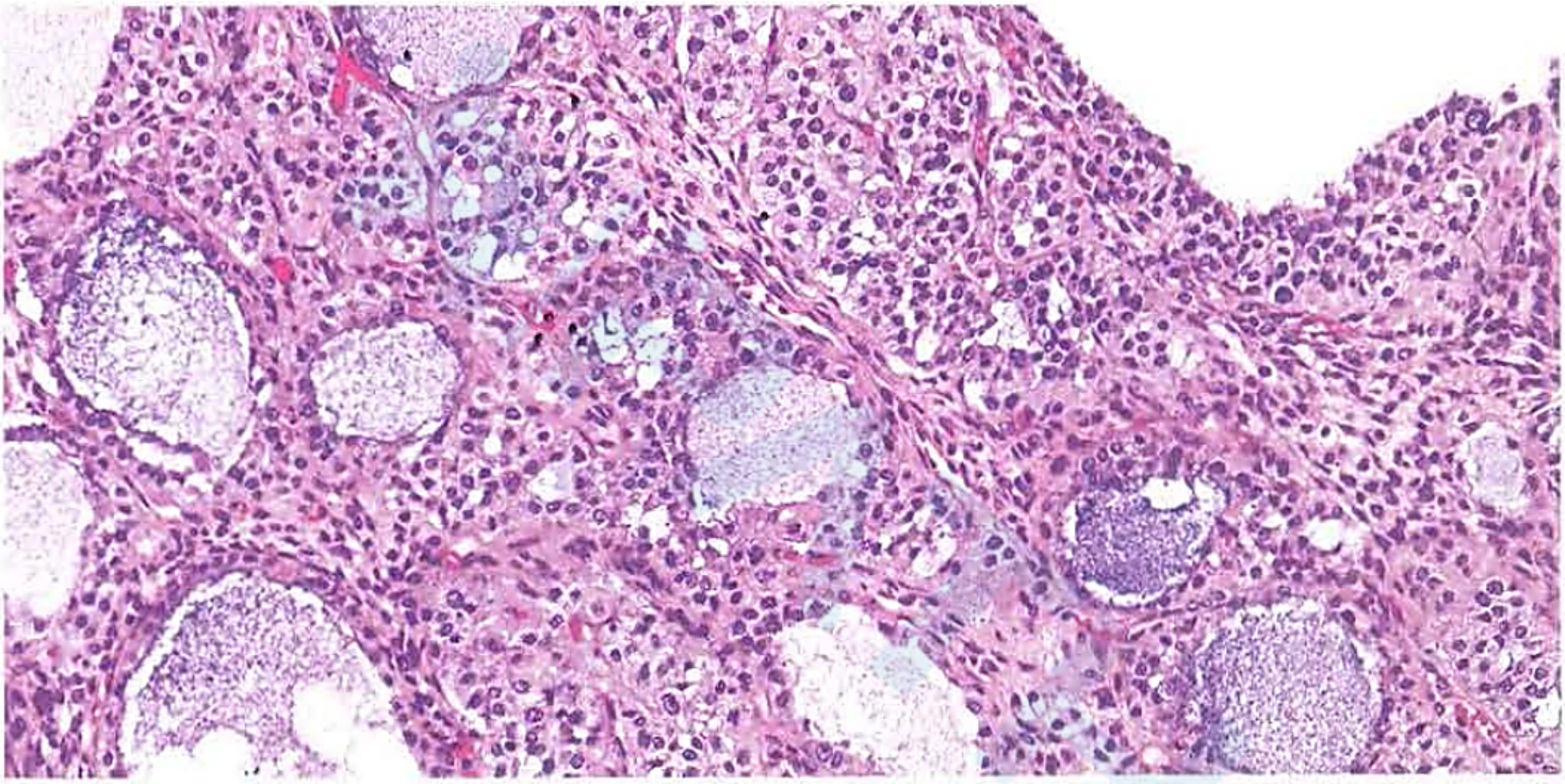


Fig. 1.47 Juvenile granulosa cell tumour. The tumour has many follicles that vary in size and shape and are filled with basophilic secretion.

Immunohistochemistry

- These tumours are usually positive for inhibin , calretinin, SF-1， CD99 and CD56.
- A small minority express FOXL2.
- Low molecular weight cytokeratin may be positive while EMA is only rarely weakly and focally positive.

Genetic profile

- The most common cytogenetic abnormality associated with this tumour is trisomy 12, which is present in most cases.
- ***FOXL2* (C402G) mutation is absent in these neoplasms.**

Genetic susceptibility

JGCT has been associated with the hereditary conditions Ollier disease (enchondromatosis) and Mafucci syndrome (enchondromatosis and multiple subcutaneous haemangiomas).

Prognosis and predictive factors

- Juvenile granulosa cell tumour is typically limited to the ovary at diagnosis and has a good prognosis.
- Recurrences usually occur within three years of diagnosis. Patients with ruptured tumour, positive peritoneal cytology or extra-ovarian tumour spread have a higher risk of recurrence.

Aim

Most AGCTs are composed of cells with bland nuclear features and even when these tumors recur or metastasize, the nuclear features are almost always bland and low-grade. There have been occasional case reports of typical AGCT with areas of "high-grade" malignant morphology, either in the original neoplasm or in the recurrence; this has generally been referred to as sarcomatous transformation. In this study, we report a small series of AGCTs with high-grade transformation.

FOXL2

- located in 3q22.3 area, which belongs to the large family of forkhead/winged-helix transcription factors.
- One of first genes expressed in female gonad development, required for proper granulosa cell differentiation during folliculogenesis.
- Expression strongly maintained in granulosa cells throughout life.

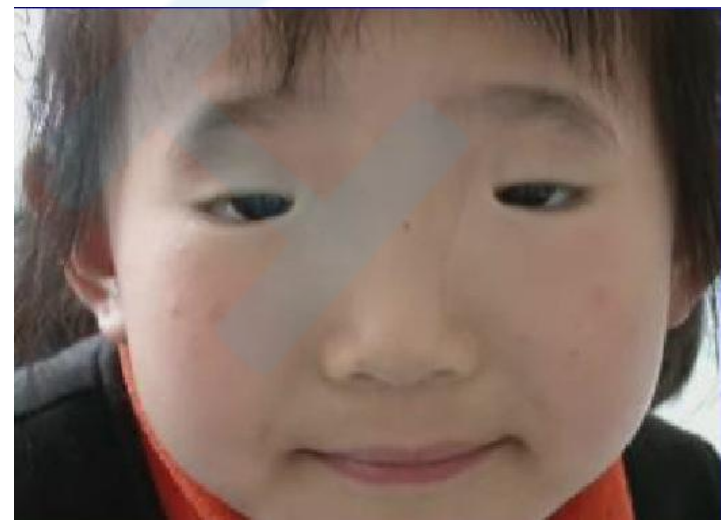
FOXL2 mutation

•FOXL2 mutation (402C→G / C134W) present in 70 - 95% of ovarian AGCTs but not in ovarian fibromas and JGCTs;

•present in 2 of 5 men with AGCTs.

•Germline mutations lead to disorders of ovarian function ranging from premature follicle depletion (卵泡枯竭) and ovarian failure (卵巢早衰) to unregulated granulosa cell proliferation leading to tumor formation.

•Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES,小睑裂综合征) cases may have different mutations.



Uses by pathologists
FOXL2 mutation analysis distinguishes diffuse AGCT(402C→G mutation present) from cellular fibroma (mutation absent).

IHC Positive staining - normal
Nuclear stain Ovary: granulosa cells

IHC Positive staining - disease
Ovary: most sex cord stromal tumors (>95% of AGCT, JGCT, fibromas, and sclerosing stromal tumors; 50% of Sertoli-Leydig cell tumors, 9% of steroid cell tumors
Pituitary adenoma: gonadotropin-subunit-producing adenomas (87%), null cell adenoma cases (73%)
Testis: granulosa cell tumors
Breast cancer

IHC Negative staining
Ovary: most non sex cord stromal tumors
Ovary: gonadoblastoma - germ cells in gonadoblastoma and dysgerminoma components.

MATERIALS AND METHODS

The cases derived from the pathology archives of the institutions to which the authors are affiliated together with the consultation practice of one of the authors (W. Glenn McCluggage).

Immunohistochemistry for p53, MIB1, inhibin and p16

•Inhibin staining was classified as negative, focal (<50%) or diffuse (⩾50%).

•p16 staining was classified as negative, non–block-type (patc hy positive staining involving <90% of tumor cells) or block-type (involving at least 90% and essentially all of the tumor cells).

•The MIB1 proliferation index was subjectively assessed in areas which exhibited the highest staining.

•P53 staining was classified as mutation-type (diffuse strong positive staining in >80% of cells or completely negative) or wild-type (heterogenous staining of variable intensity in <80% of cells).

FOXL2 Mutation Methods

- FOXL2 mutation analysis was undertaken in 4 cases (cases 2, 3, 4, 5).
- A H.E. stained section cut from each block was reviewed by pathologists involved in the study and tumor tissue from both the low-grade and high-grade components was selected for analysis.
- Tumor tissue from the blocks was scraped off with coring (1mm diameter) with a uni-core (Sigma-Aldrich, St Louis, MO) or slide scraping.
- After an overnight proteinase K digestion step at 70° C, DNA extraction was performed with Maxwell RSC DNA FFPE kit according to the manufacturer's protocols on a Maxwell RSC device from Promega (Promega, Madison, WY).
- DNA was quantified using QuantiFluor ONE dsDNA System (Promega).

- The detection of mutations within exon 1 of the FOXL2 gene was performed using Sanger sequencing. A part of FOXL2 exon 1 (the amplicon size was 182 pb) was amplified by PCR.
- Direct sequencing was performed with the above primers using the Big-Dye DyeDeoxy terminator cycle sequencing kit (Applied Biosystems, Foster City, CA).
- Sequencing reactions were carried out on the ABI Prism 3100 Genetic Analyzer (Applied Biosystems). As a reference for the FOXL2 gene, NM_023067.3 aligned on a sequence of chromosome 3 (hg19) was used.

TP53 Mutation Methods

•TP53 mutation analysis was undertaken in 4 cases (cases 2, 3, 4, 5).

•DNA was extracted from four 10 μm sections from each case from both the low-grade and high-grade components.

•Standard procedures were used according to the manufacturer's protocol for DNA extraction (QIAampDNA FFPE Tissue Kit; Qiagen, Manchester, UK), except that incubation at 56° C was extended to 3 days to optimize the purification of genomic DNA.

•Quantification of DNA was performed by an absorbance method using the NanoDrop 2000c spectrophotometer.

•Exons 4 to 10 were amplified with primers as previously described.

•PCR products were directly sequenced by Sanger sequencing with Big-Dye terminators version 3.1 (Applied Biosystems), using both forward and reverse primers.

•Mutations were confirmed by amplifying a duplicated PCR product.

•Polymorphism status was assessed and the presence of mutations were confirmed with reference to the IARC TP53 database.

RESULTS

TABLE 1. Clinicopathologic Features of Cases Included in Study

Case No.	Age (y)	Tumor site	Clinical Presentation	Operative Procedure	Tumor Size (cm)	Adjuvant Treatment	FIGO Stage	Site of Metastatic Disease at Diagnosis	Follow-up
1	59	Right ovary	48 h history of acute abdominal pain	Hysterectomy and BSO	16.5	Carboplatin, ifosfamide and etoposide chemother-apy	IA	None	Mediastinal, peritoneal and pulmonary metastasis 17 mo after diagnosis; alive with disease 19 mo after diagnosis
2	51	Right ovary	Pelvic pain and bloating	Hysterectomy, BSO, omentectomy, pelvic lymphadenectomy	21	None	IA	None	No evidence of recurrence at 9 mo
3	37	Left ovary	6 wk history of PV bleeding. Left adnexal mass identified on imaging	Hysteroscopy, left salpingo-oophorectomy, omental biopsy, pelvic and para-aortic lymph node sampling	9	None	IA	None	No evidence of recurrence at 6 mo
4	87	Large right adnexal mass but ovary never removed	Intestinal obstruction	Small intestinal bypass and omental resection	NA	None	IIIC	Sigmoid colon and omentum	Referred to palliative case and then lost to follow-up
5	52	Left ovary	Found to have large ovarian mass on imaging	Hysterectomy, BSO, omentectomy	28	None	IA	None	No evidence of recurrence at 6 mo

BSO indicates bilateral salpingo-oophorectomy; NA, not available.

Pathologic Features

•Where **the gross description** was available, the tumors were described as predominantly solid with minor cystic foci and with a yellow/gray cut surface.

•The omentum in case 4 measured 30 cm in maximum dimension and was almost totally involved by tumor.

low-grade areas

- **Histologically** all the tumors had areas of typical AGCT with low-grade cytologic features and scant cytoplasm.
- In these areas, tumor cells with angulated nuclei, some containing grooves, and scant cytoplasm were arranged in various architectural patterns, including solid, nested, and corded/trabecular. Microfollicles and Call-Exner bodies were identified in some cases.
- The mitotic count per 10 HPF in these low-grade areas was 30, 1, 6, 1, and 1 in cases 1 to 5, respectively.
- Necrosis was not identified in these areas, except in 1 case (case 2) where there were areas of infarct type necrosis.

high-grade areas

- In all cases, there was an abrupt transition between the low-grade areas and foci where the tumor cells exhibited marked nuclear atypia, often with bizarre multinucleate forms.
- In these foci, the tumor cells were predominantly arranged in diffuse sheets but in some cases, there was a focal nested and/or corded/trabecular architecture.
- The tumor cells in these morphologically high-grade areas had abundant eosinophilic, and sometimes focally clear, cytoplasm.
- In cases 1, 2, and 3, intermediate sized follicles, some containing eosinophilic material, were present.

(low-grade: 30, 1, 6, 1, and 1)

- The mitotic count per 10 HPF in these areas was 50, 3, 6, 4, and 1 in cases 1 to 5, respectively, and atypical mitoses were identified in some cases.
- Areas of necrosis were typically present.

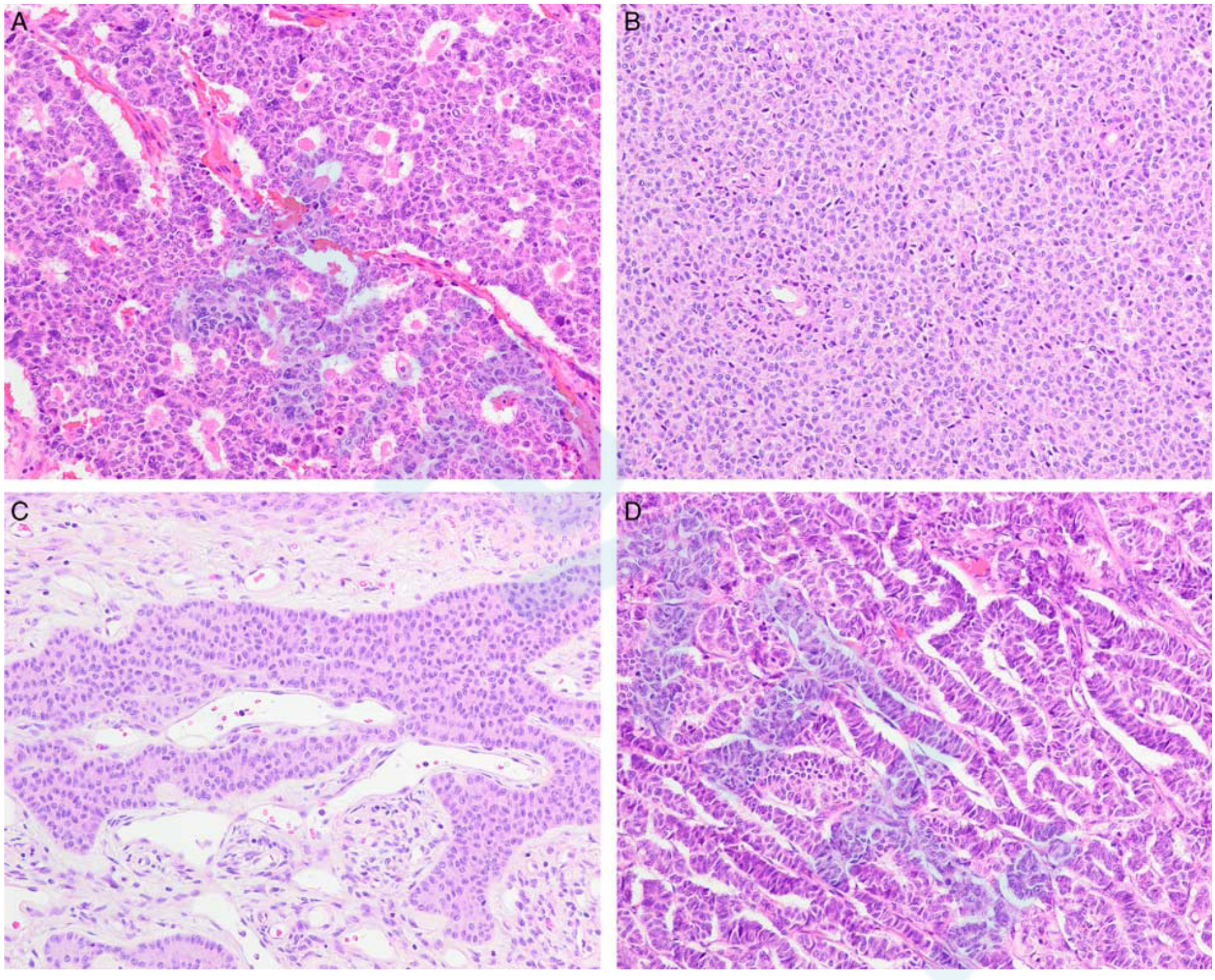


FIGURE 1. Representative areas of AGCT with typical low-grade morphology from the various cases. Various architectural patterns are present, including trabecular, diffuse and microfollicular (A–D).

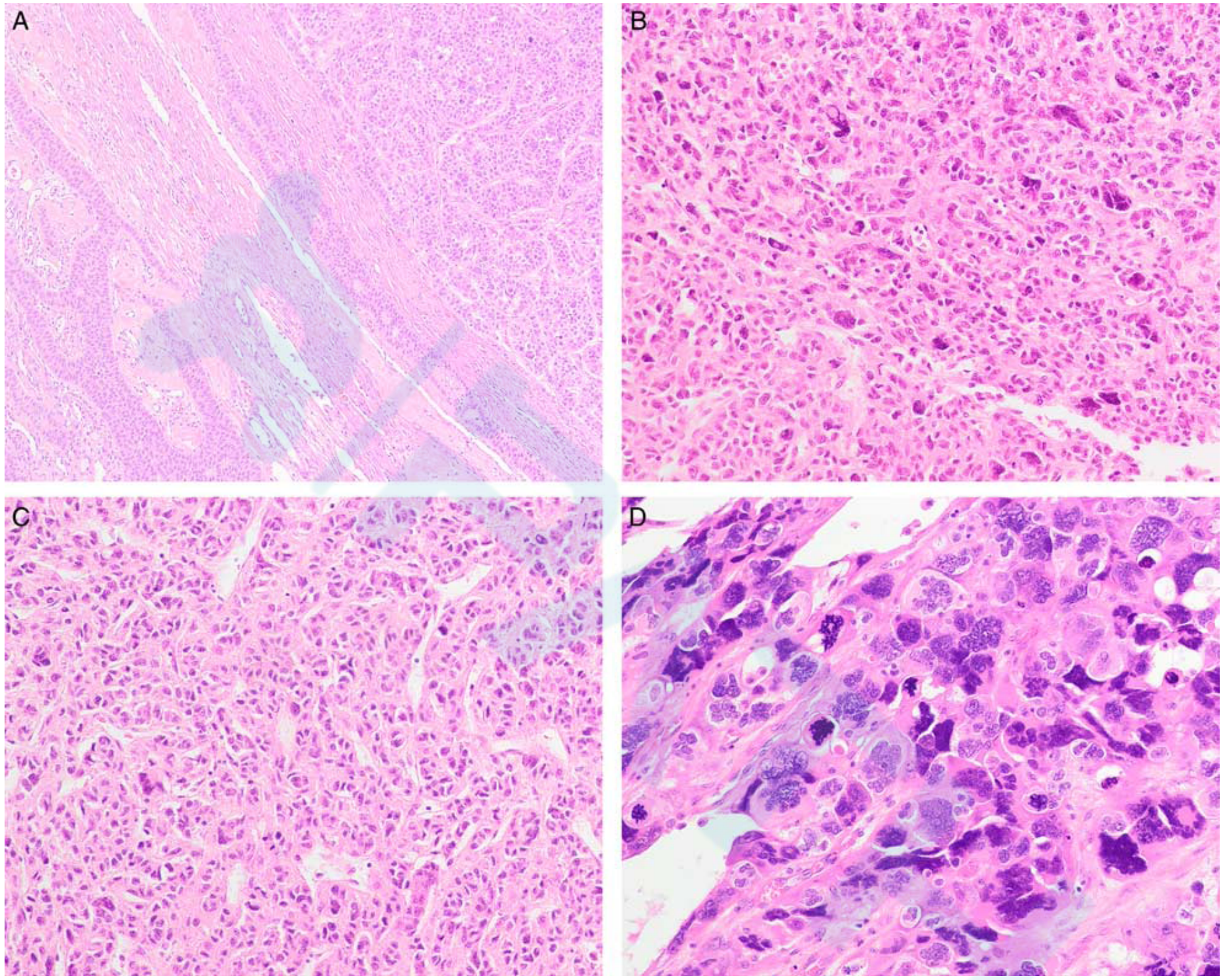


FIGURE 2. Representative areas of AGCT with high-grade morphology. There is a sharp demarcation between a morphologically low-grade area (bottom left) and a high-grade area (top right) (**A**). High-grade area with marked nuclear atypia, including multinucleate cells (**B**). High-grade area where the tumor cells have abundant eosinophilic cytoplasm (**C**). High-grade areas with bizarre nuclear atypia and abundant mitotic activity, including atypical mitoses (**D**).

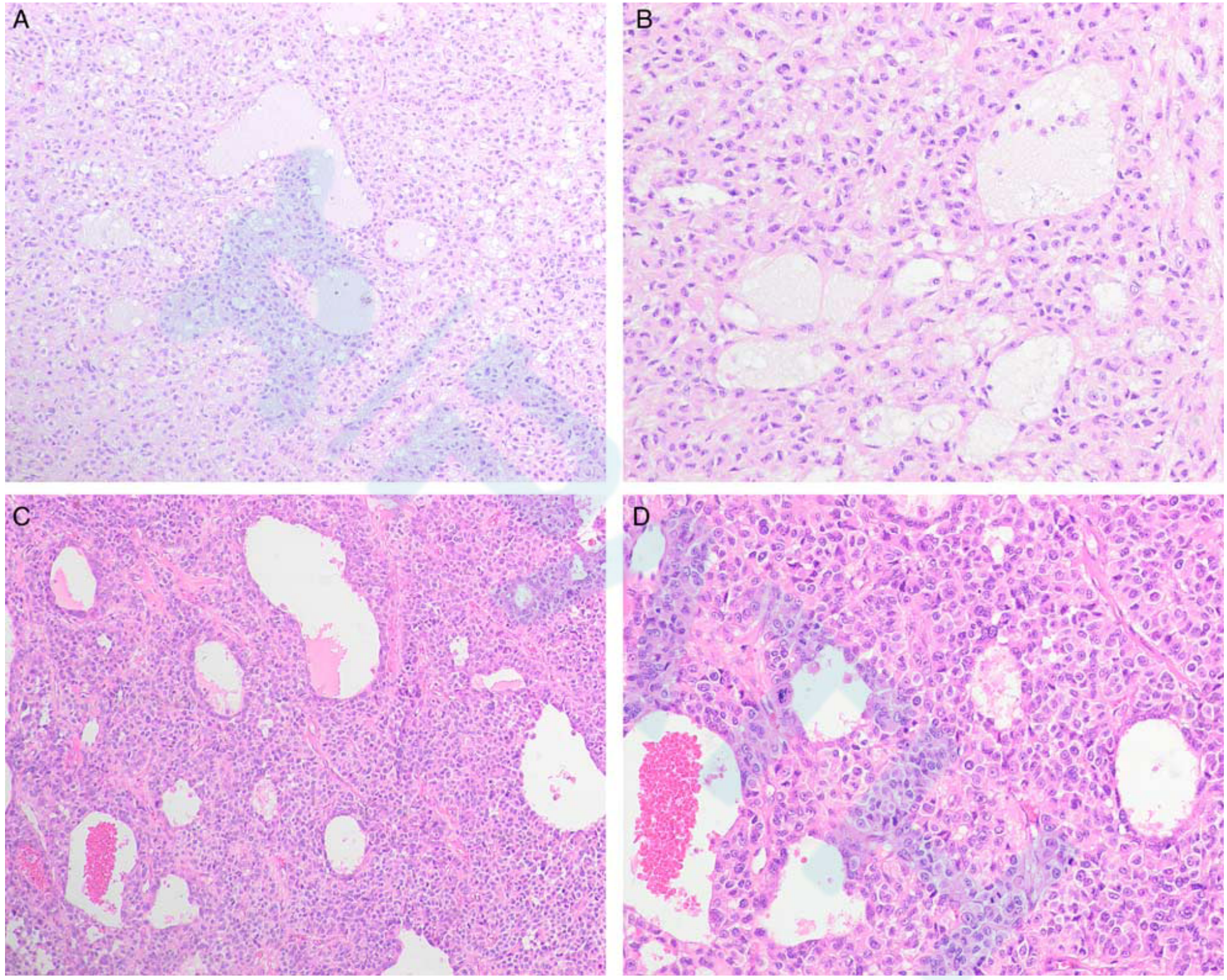


FIGURE 3. **High-grade areas resembling JGCT** with tumor cells with abundant eosinophilic cytoplasm forming follicles, some containing eosinophilic fluid (A–D).

Immunohistochemical Results

TABLE 2. Immunohistochemical Findings

Case No.	MIB1 Low-grade Areas	MIB1 High-grade Areas	p53 Low-grade Areas	p53 High-grade Areas	Inhibin Low-grade Areas	Inhibin High-grade Areas	p16 Low-grade Areas	p16 High-grade Areas
1	Not done	Not done	Not done	Not done	Diffuse	Diffuse	Not done	Not done
2	1%	10%	Wild-type	Diffuse mutation-type	Diffuse	Diffuse	Focal	Diffuse
3	1%	30%	Wild-type	Diffuse mutation-type	Focal	Focal	Focal	Diffuse
4	1%	50%	Wild-type	Wild-type	Diffuse	Focal	Focal	Focal
5	1%	1%	Wild-type	Diffuse mutation-type	Focal	Diffuse	Focal	Diffuse

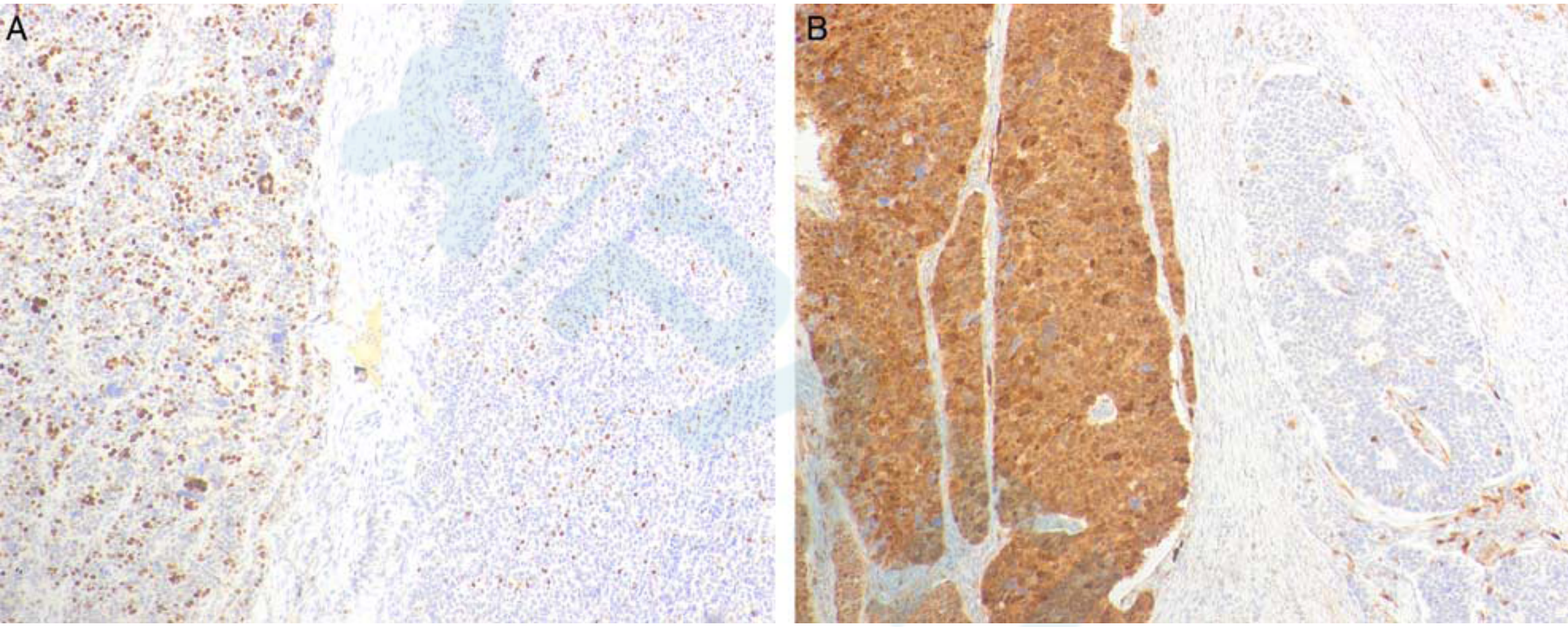


FIGURE 4. Case 3.
Ki67 stain showing low proliferation index in low-grade area (right) and high proliferation index in high-grade area (left) (A).
p16 stain showing largely negative staining in low-grade area (right) and diffuse staining in high-grade area (B).

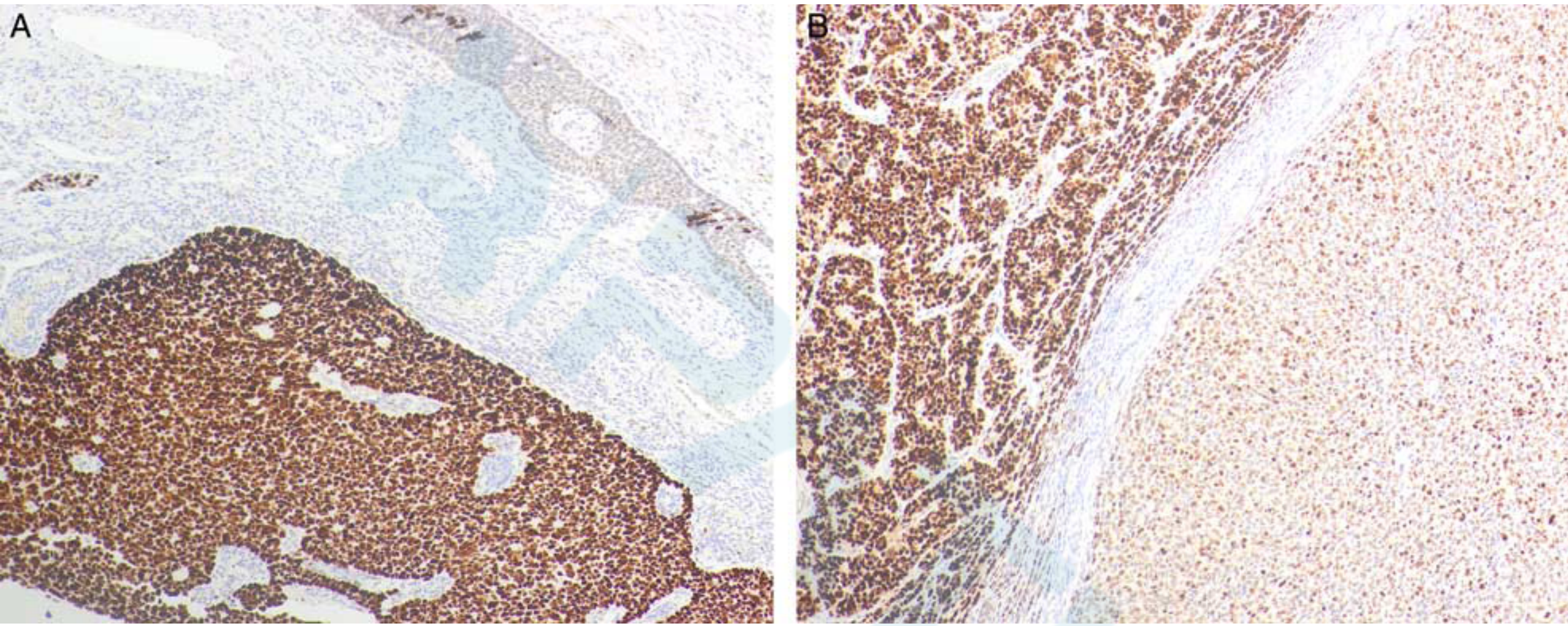
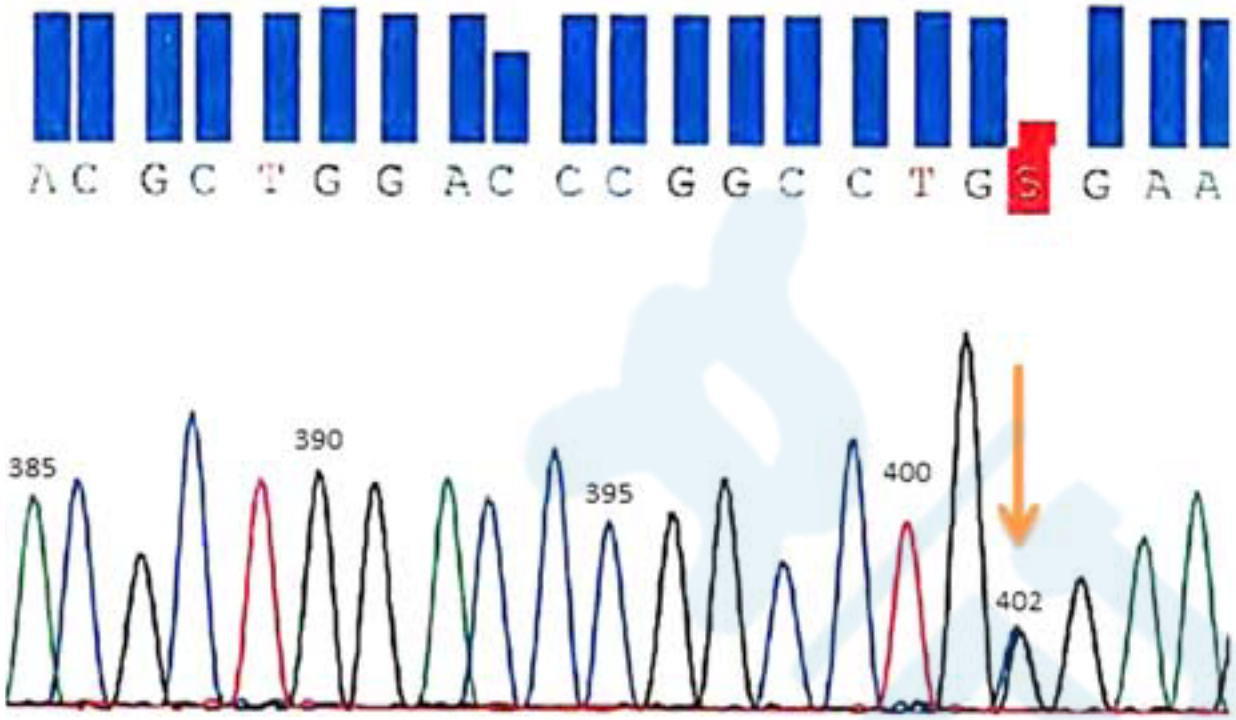


FIGURE 5.
p53 stain showing sharp demarcation between wild-type staining in low-grade area (top) and diffuse mutation-type immunoreactivity in high-grade area (bottom) (A) (case 5).
Another case (case 2) showing sharp demarcation between wild-type staining in low-grade area (right) and diffuse mutation-type immunoreactivity in high-grade area (left) (B).

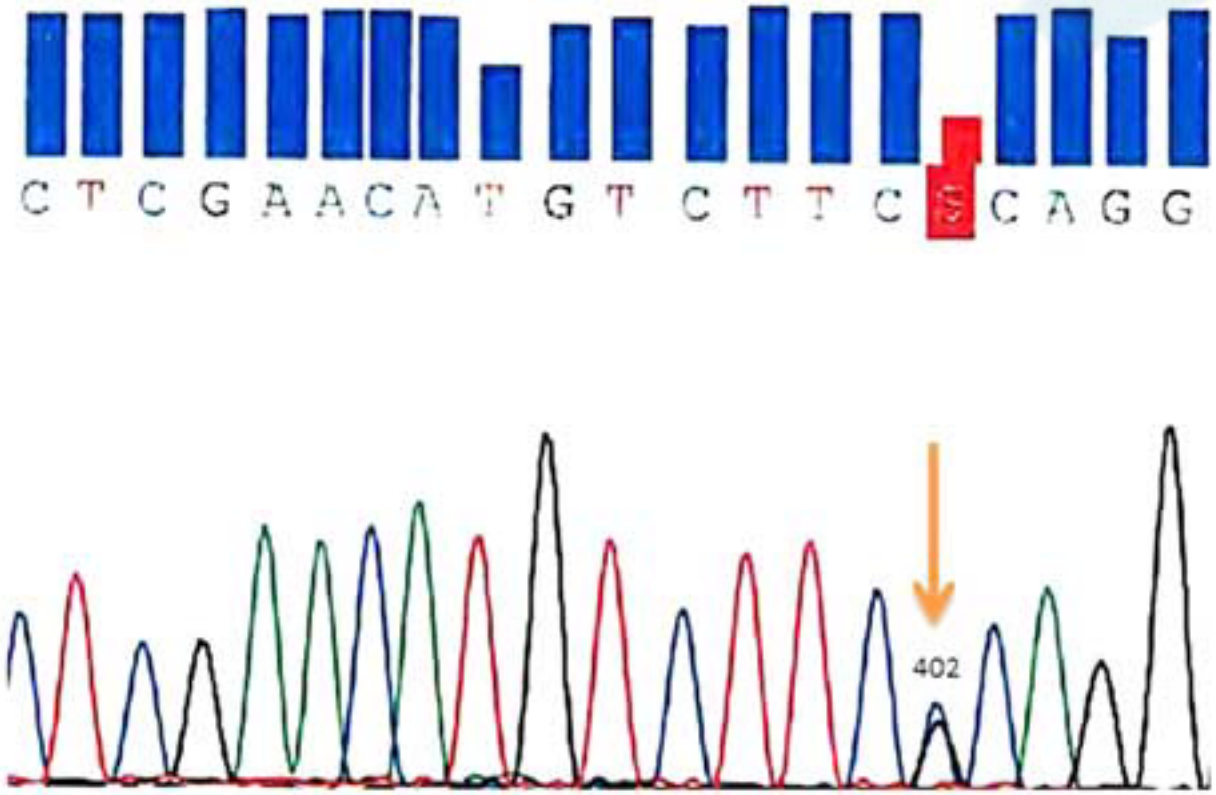
FOXL2 Mutation Results

- All cases where molecular testing was undertaken harbored the missense point mutation, c.402C > G, p. (Cys134Trp), which is characteristic of AGCT;
- the same mutation was present in the low-grade and high-grade components (Fig. 6).



FOXL2 exon 1
(forward)

c.402C>G
p.(Cys134Trp)
C134W



FOXL2 exon 1
(reverse)

FIGURE 6. Electropherogram of one of the cases. Note the presence of the FOXL2 missense point mutation.

TP53 Mutation Results

- TP53 mutations were detected in the high-grade components of cases 2 and 3.
- A missense mutation (c.659A > C, p.Y220S) was detected in exon 6 of case 2 and a nonsense mutation (c.916C >T, p.R306*) in exon 8 of case 3.
- No mutations were detected in the low-grade components in cases 2 and 3 or the low-grade or high-grade components in cases 4 and 5.

TABLE 2. Immunohistochemical Findings

Case No.	MIB1 Low-grade Areas	MIB1 High-grade Areas	p53 Low-grade Areas		p53 High-grade Areas		Inhibin Low-grade Areas	Inhibin High-grade Areas	p16 Low-grade Areas	p16 High-grade Areas
1	Not done	Not done	Not done		Not done		Diffuse	Diffuse	Not done	Not done
2	1%	10%	Wild-type	-	Diffuse	+	Diffuse	Diffuse	Focal	Diffuse
					mutation-type					
3	1%	30%	Wild-type	-	Diffuse	+	Focal	Focal	Focal	Diffuse
					mutation-type					
4	1%	50%	Wild-type	-	Wild-type	-	Diffuse	Focal	Focal	Focal
5	1%	1%	Wild-type	-	Diffuse	-	Focal	Diffuse	Focal	Diffuse
					mutation-type					

TP53 Mutation Results

DISCUSSION

- In this study, we report 5 AGCTs exhibiting an abrupt transition from areas of typical morphologically low-grade neoplasm to areas of high-grade tumor.
- In reporting these unusual cases, we compare the immunophenotype and FOXL2 mutation status between the 2 components and discuss the underlying mechanisms behind the high-grade transformation.

- In all cases, the low-grade areas were morphologically typical of AGCT. The high-grade areas were composed of markedly atypical bizarre cells, often with multinucleate cells and areas of necrosis. There was usually significant mitotic activity, often with atypical mitoses.
- To our knowledge, this is the first series reporting high-grade transformation within AGCT, although there have been occasional case reports of “sarcomatous” change with marked nuclear atypia in these neoplasms. These may represent similar tumors to those we report.

Two other points:

•**Luteinized AGCT** is an uncommon variant of AGCT in which the tumor cells have abundant eosinophilic or clear cytoplasm, in contrast to the usual scant cytoplasm of typical AGCT. It has arbitrarily been recommended that at least 50% of the tumor cells should be luteinized before rendering a diagnosis of luteinized AGCT. Luteinized AGCTs are characterized by slightly enlarged nuclei and a relative lack of nuclear grooves, as compared with typical AGCT.

•**Although the high-grade areas in our cases had abundant eosinophilic cytoplasm, the nuclear features were much more atypical than in seen in luteinized AGCTs.**

- **Small collections of cells with bizarre nuclei, but without significant mitotic activity,** may occur in various sex cord-stromal tumors. They may be seen in Sertoli-Leydig cell tumors, AGCTs, thecomas, fibromas, and other sex cord-stromal tumors and can be regarded as analogous to bizarre/symplastic cells in uterine leiomyomas. They are probably degenerative in nature and are not thought to be of any clinical significance, although this is based on follow-up in a limited number of cases.

- As discussed, in one of our cases the mitotic count was low and similar between the low-grade and high-grade components raising the possibility of symplastic change; however, given the large confluent areas of markedly atypical cells with tumor cell necrosis and diffuse mutation-type staining with p53, **we excluded symplastic change as an explanation for this morphology.**

AGCT ? JGCT ?

- In 3 of our cases, the morphology of the high-grade areas strongly raised the possibility of JGCT due to the significant nuclear atypia, obvious mitotic activity, abundant eosinophilic cytoplasm, and the presence of intermediate sized follicles.
- We only identified a single reported case of combined AGCT and JGCT in the literature; this occurred in a 12-year-old girl and the tumor was reported to contain areas of AGCT, JGCT (with areas of marked atypia) and Sertoli cell tumor.
- In spite of the paucity of reports, many authorities believe that combined AGCT and JGCT exists (W. Glenn McCluggage, personal oral communication).
- **However, given that the underlying molecular events differ between AGCT and JGCT, we believe it is likely that mixed tumors with components of both are extremely uncommon if they exist at all; / it is likely that neoplasms reported as mixed AGCT and JGCT represent a single neoplastic type with morphologic mimicry of the other.**

FOXL2 mutation

- FOXL2 mutation was first identified in 90 of 93 (97%) AGCTs in a study in 2009; in that study, 3 of 14 thecomas (21%) and 1 of 10 JGCTs (10%) also harbored the mutation. Mutations were not found in 49 other ovarian sex cord-stromal tumors or in an additional 329 neoplasms comprising ovarian tumors of non–sex cord stromal lineage or breast carcinomas.
- In another study, 52 of 56 (93%) AGCTs harbored FOXL2 mutation; morphologic reappraisal of the 4 cases exhibiting wild-type FOXL2 sequences suggested that they may have been misclassified at diagnosis.
- **It may be that the small percentage of JGCTs exhibiting FOXL2 mutation in some studies represent misclassified AGCTs, perhaps similar to the cases we report.**
- In the 4 cases we report where mutational analysis was undertaken, FOXL2 was mutated in both the low-grade and high-grade components providing convincing evidence that these represent AGCTs with high-grade transformation rather than mixed neoplasms.

- We compared the **immunophenotype** between the low-grade and high-grade areas in our cases. There was no obvious difference in the expression of **inhibin**.

- In all but 1 case, the **MIB1** proliferation index was, as expected, elevated in the high-grade as compared with the low-grade areas.

- In our study, there was generally increased expression of **p16** in the high-grade compared with the low-grade areas. In 1 of our cases, the high-grade component exhibited block-type p16 immunoreactivity. This is an interesting phenomenon and analogous to what occurs in some mesenchymal neoplasms. For example, p16 expression is typically markedly elevated in uterine leiomyosarcomas, as compared with leiomyomas and there is markedly increased expression in areas of atypia or sarcomatous transformation in cellular angiofibromas.
- Our study adds to the list of gynecological neoplasms which may exhibit block-type p16 immunoreactivity.

In 3 of 4 cases, the **p53** staining pattern was different in the low-grade and high-grade areas. In these cases, the low-grade areas exhibited wild-type staining while the high-grade areas exhibited mutation-type immunoreactivity.

This strongly suggests that TP53 mutation is important in high-grade transformation in AGCTs.

The high-grade component in the cases we report could potentially be **confused** with a wide range of other neoplasms, especially if only this component is biopsied or represented. Awareness of the fact that AGCT may undergo high-grade transformation is crucial to the diagnosis.

We will not discuss the **differential diagnosis** in detail but mention that as high-grade foci in AGCT may be positive with WT1 and exhibit mutation-type staining with p53 and block-type immunoreactivity with p16, a high-grade serous carcinoma might enter into the differential diagnosis. In such cases, the demonstration of positivity with sex cord markers, such as inhibin, and of a FOXL2 mutation will assist in establishing a correct diagnosis.

- In all cases, except case 4, the tumors were FIGO stage IA at diagnosis.
- We only have short follow-up (ranging from 6 to 9 mo) in 3 of our stage IA cases with no evidence of tumor recurrence. The other stage IA case exhibited widespread metastatic disease 17 months after diagnosis.
- There have also been occasional case reports of "sarcomatous" change with marked nuclear atypia in AGCTs which have exhibited an aggressive clinical course.
- **This suggests that high-grade transformation in AGCTs may herald an aggressive clinical course.**

Summary

- We report a small series of AGCTs with high-grade transformation.
- FOXL2 mutation analysis suggests that the high-grade component represents transformation of typical AGCT rather than the coexistence of another sex cord-stromal tumor, such as JGCT.
- TP53 mutation is likely to play a role in the transformation from typical low-grade AGCT to a high-grade neoplasm.
- This high-grade transformation may herald an aggressive clinical course.

Thanks!