

Juvenile Granulosa Cell Tumors of the Testis: A Clinicopathologic Study of 70 Cases with Emphasis on Its Wide Morphologic Spectrum

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Abstract

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The clinical and pathologic features of 70 juvenile granulosa cell tumors of the testis are presented. The patients were from 30-weeks gestational age to 10 years old; 60 of 67 (90%) whose age is known to us were ≤ 6 months old. Sixty-two underwent gonadectomy, 6 wedge excision, and 2 only biopsy. Twenty-six tumors were left-sided, and 22 right-sided. Six occurred in an undescended testis and 2 in dysgenetic gonads. The most common presentation was a testicular mass (65%) followed by an “enlarging testis” (25%). Six of 14 patients in whom it was measured had “elevated” serum AFP, likely physiologically, and 1 had gynecomastia. The tumors measured 0.5 to 5 cm (mean, 1.7; median, 1.5) and were most commonly well-circumscribed and typically yellow-tan; approximately 2/3 had a cystic component, while 1/3 were entirely solid. Microscopic examination typically showed a lobular growth, punctuated in 67 cases by variably-sized and shaped follicles containing material that was basophilic (21%), eosinophilic (44%), or of both characters (35%); 3 lacked follicles. In non-follicular areas, the tumor cells typically grew diffusely, but occasionally had a corded arrangement (26%) or reticular appearance (29%). The stroma was either fibrous or fibromyxoid; hemorrhage associated with hemosiderin-laden macrophages was focally seen in 16%. The tumor cells were mostly small to medium sized with round to oval nuclei containing inconspicuous nucleoli and moderate to abundant, but occasionally scant, pale to lightly eosinophilic, sometimes vacuolated, cytoplasm; nuclear grooves were infrequent (6%). Focal columnar morphology was seen in 27% of the tumors. Mitoses were plentiful in 37% and apoptosis was prominent in 46%. Intratubular tumor was seen in 43% and entrapped seminiferous tubules in 70%. Lymphovascular invasion was present in 2 cases, rete testis involvement in 4, and necrosis in 1. Rare features/patterns included: regressed tumor with hyalinization and prominent blood vessels (13%), papillary (4%), basaloid (1%), spindle cell predominant (1%), microcystic (1%), adult granulosa cell-like (1%)

patterns, and hyaline globules (1%). Inhibin (16/18), calretinin (8/9), WT1 (6/7), FOXL2 (12/12), SF-1 (12/12), and SOX9 (6/11) were positive, while SALL4 and glypican-3 were consistently negative in the neoplastic granulosa cells. Only one tumor was focally positive for AFP. Juvenile granulosa cell tumor is a rare neoplasm with a wide morphologic spectrum that also occurs rarely in undescended testes and dysgenetic gonads. The solid and reticular patterns may pose diagnostic challenges but the lobular appearance and follicular differentiation are characteristic. Immunohistochemical stains may aid in its distinction from other tumors of young males, particularly yolk sac tumor, a neoplasm that peaks at a somewhat later age. Twenty-four patients with follow-up, including 4 of 6 patients treated with wedge resection /biopsy, had no evidence of disease (2-348 months; mean, 83; median, 61). One additional patient was alive at 260 months but disease status is unknown. The benign clinical course of all cases of juvenile granulosa cell tumor with follow-up, despite often frequent mitotic activity, supports testis sparing surgery when technically feasible.

Keywords: Testis, juvenile granulosa cell tumor, sex cord-stromal tumor, infants, immunohistochemistry.

Introduction

In the late 1960s – early 1970s, the late Dr. Robert E. Scully became aware that in the ovary granulosa cell tumors in the young often had different characteristics from those occurring in the more typical older patient and coined the designation “juvenile granulosa cell tumor” for them. He first widely popularized the term in his first fascicle on ovarian tumors, published in 1979.¹ Circa the time of publication of that work, he began to observe a similar profile (more varied follicular architecture and immature nuclei with greater mitotic activity) in testicular granulosa cell tumors in the very young. Logically he referred to the testicular tumors by the same name. Soon afterwards the first example of juvenile granulosa cell tumor of the testis was reported in the literature,² Dr. Scully’s experience with 14 cases was described two years later.³ Over the years it has become apparent that criteria for the diagnosis of this neoplasm in the testis are not applied uniformly by individual investigators and the spectrum acceptable for this designation has been debated. To explore this aspect and record our own now significantly expanded experience with juvenile granulosa cell tumors of the testis, we report our experience to date herein.

Materials and Methods

A search of the consultation files at the Massachusetts General Hospital uncovered 51 cases of juvenile granulosa cell tumor of the testis, many from the consultation collection of the late Dr. Robert E. Scully; 14 of them were previously reported.^{3, 4} A computer-based text search of the surgical pathology files of Indiana University revealed 19 more cases. Clinical data including age, presentation, serum tumor markers, and follow-up information were recorded. The gross features, histologic patterns, cytologic features, presence of intratubular component, mitotic rate, apoptotic activity, lymphovascular invasion, necrosis, and nature of the stroma were

assessed. All cases with available material were stained with antibodies directed against inhibin, calretinin, Wilms' tumor 1 (WT1), SOX9, FOXL2, and steroidogenic factor-1 (SF-1).

Additionally, all immunostains previously performed were reviewed and results documented.

The study was approved by the Institutional Review Board of Indiana University.

The antibody sources, dilutions, antigen retrieval methods, and incubations are summarized in Table 1. Immunostains of whole sections of formalin-fixed, paraffin-embedded tissue directed against SF-1, inhibin, calretinin, and WT1 were conducted using a polymer based method (EnVision FLEX or FLEX+, Dako, Carpinteria, CA), diaminobenzidine as the chromogen, and a Dako automated immunostaining instrument. Those directed against SOX9 and FOXL2 were conducted using a different polymer based method (donkey-anti-goat, Jackson ImmunoResearch Labs and LSAB2-SA, Dako, Carpinteria, CA), diaminobenzidine as the chromogen, and a Dako automated immunostaining instrument. Negative and positive controls were performed for each immunohistochemical stain. Only nuclear reactivity was considered positive for SOX9, FOXL2, SF-1, and WT1; the presence of cytoplasmic staining without nuclear reactivity was considered negative. Both nuclear and cytoplasmic reactivity was required for calretinin.

Results

Clinical features

The patients ranged from 30-weeks gestational age to 10 years old; 34 \leq 1 month, eight $>$ 1 but \leq 2 months, eight $>$ 2 but \leq 3 months, four $>$ 3 but \leq 4 months, five $>$ 4 but \leq 5 months, one $>$ 5 but \leq 6 months, three $>$ 6 months but \leq 1 year-old, and four $>$ 1 year old (14 months, 21 months, 6 and 10 years). One patient had gynecomastia, and 6 of 14 had an "elevated", likely

physiologically, serum AFP level. Forty-one patients were noted to have a testicular mass and 16 "testicular swelling"; 2 of the latter had torsion. The remaining six patients presented with extratesticular "masses" later revealed to be neoplasms in undescended testes. Two tumors were found in dysgenetic gonads (karyotype showed 46XX and 45XO/46XY mosaic), and were previously reported.⁴ The tumor was slightly more commonly located in the left testis (n=26) than the right (n=22) in cases in which laterality is known to us.

Pathologic features

The tumors measured 0.5 to 5 cm (mean, 1.7 cm; median, 1.5 cm) in maximum dimension and were mostly well-circumscribed (94%). Of the 41 cases with an available gross description, 26 were cystic (13 multilocular) and 15 solid (Fig. 1). The latter component varied from yellow-tan to grey-white; 7 had a cut surface that was sometimes described as mucoid, gelatinous or glistening (Fig. 1). Microscopic examination showed that all had at least a focal lobular appearance on low-power with the lobules separated by a variably cellular stroma (Fig. 2, 3A). Sixty-seven (96%) were punctuated by variably-sized and shaped follicles (Figs. 2, 3B, 4-6) containing basophilic material (21%), eosinophilic material (44%), or both (35%). Mixed follicular and solid patterns occurred in 55 cases (79%) with follicular predominance in 33 (47%) and solid predominance in 22 (32%). The follicles ranged from small and round to large, irregular and cystically dilated (Figs. 2, 4-6). Purely follicular or purely solid (Fig. 3A) appearances were less common, 12 (17%) and 3 (4%), respectively. The follicles were lined by either a single layer or multiple layers of rounded cells (Fig. 5). In non-follicular areas, the tumor cells typically grew diffusely, but occasionally grew as cords (26%) or had a reticular appearance (29%) (Fig. 7). The stroma was fibrous or fibromyxoid in an equal number of cases (Figs. 8-9)

and occasionally had hemorrhage associated with hemosiderin-laden macrophages (16%). Occasionally myxoid stroma merged imperceptibly with similarly staining follicular fluid (Fig. 9B).

The tumor cells were mostly small to medium sized (91%) with round to oval nuclei (63%) containing inconspicuous nucleoli (94%) and moderate to abundant (59%), but occasionally scant (41%), pale to lightly eosinophilic (80%), sometimes vacuolated (17%), cytoplasm (Figs. 8-10). The nuclei varied from pale to hyperchromatic (Fig. 10). Cells with columnar morphology and basally located nuclei lined some follicles in 19 cases (27%) (Fig. 11). Occasional tumors had minor foci where the cells were somewhat spindled (Fig. 12). Rare nuclear grooves were observed in 4 (6%). The mitotic count ranged from 0 to > 100/10 high-power fields (HPF). Mitoses were abundant (≥ 10 mitosis/10 HPFs) in 26 cases (37%) and apoptosis was prominent (> 20 apoptotic bodies in 1 HPF) in 32 (46%). Intratubular JGCT was seen in 43% and entrapped seminiferous tubules were frequent (70%) at the periphery of the tumor. Lymphovascular invasion was present in 2 cases, rete testis involvement in 4, and necrosis in 1.

Uncommon to rare features or patterns included: regressed tumor foci with confluent hyalinization and prominent blood vessels (13%) (Fig. 13A), papillary growth (4%) (Figs. 2B and 13B), basaloid morphology (1%) (Fig. 13C), spindle cell predominance (1%), microcystic foci (1%) (Fig. 6), adult granulosa cell-like patterns (1%) (Fig. 13D), and hyaline globules (1%). The papillary pattern was characterized by tumor cells lining fibrovascular cores. The basaloid pattern comprised of nests of small cells with scant cytoplasm with peripheral palisading. The adult granulosa cell-like pattern consisted of cells with oval to angulated nuclei with scant cytoplasm and occasional nuclear grooves.

Inhibin (16/18), calretinin (8/9), WT1 (6/7), FOXL2 (12/12), SF-1 (12/12), and SOX9 (6/11) were positive, while SALL4 (9 cases) and glypican-3 (1 case) were consistently negative in the neoplastic granulosa cells; SALL4 occasionally highlighted the residual germ cells (Fig. 14). AFP was mostly negative (9/10); the one positive case showed only focal reactivity. Other commonly positive markers were vimentin (7/7) and pancytokeratin (8/13).

Treatment and follow-up

Sixty-two patients underwent gonadectomy, while 6 had wedge excision, and 2 only biopsy. None underwent lymph node dissection or received adjuvant therapy. Follow-up was available for 25 patients: 24, including 4 managed by wedge resection (3) or biopsy (1) and one case with necrosis, showed no evidence of disease (2-348 months; mean, 83; median, 61) while one was alive at 260 months but disease status is unknown. Of our 24 cases with no evidence of disease, 12 had mitotic counts $\geq 10/10$ HPFs; five of the 12 had counts in the range of 40 to more than 100/10HPFs.

Discussion

Prior to the 1985 series of juvenile granulosa cell tumor (JGCT) of the testis,³ the characteristics of this tumor were not well defined, and the collective experience with this tumor remains limited.⁵⁻¹² We have encountered patterns and cytologic features that have not been described in the literature or only to a minimal degree, which may potentially cause confusion with other neoplasms, most often yolk sac tumor (YST) or, rarely, other sex cord stromal tumors.^{13, 14} We therefore undertook a comprehensive morphological analysis of testicular JGCT

to highlight not only the classic features but also unusual aspects and those useful in differentiating it from other neoplasms.

Testicular JGCTs most frequently occur in the first 6 months of life and rarely arise in boys older than 1 year old; only four in our series occurred beyond one year. The oldest patient reported with testicular JGCT was 27 years old.⁸ They usually lack clinically evident endocrine manifestations; only 1 patient in our series had gynecomastia. Most are at least focally cystic grossly but some are uniformly solid and may be tan, white to yellow. One microscopic finding that has not been emphasized in the literature is the characteristic lobular arrangement; this is especially helpful in cases that are afollicular or paucifollicular (Fig. 3A). The predominant histologic patterns are a combination of follicular and solid; as in the ovary the follicles are variable in size and shape. The granulosa cells have moderate amounts of pale to lightly eosinophilic or vacuolated cytoplasm with round nuclei without grooves.

We encountered a few patterns that have not been previously described. Tumor cells lining fibrovascular cores formed a papillary architecture (4%). Basaloid foci (1%) showed nests of primitive "blue" tumor cells with peripheral palisading, resembling somewhat basal cell carcinoma. Predominance of spindle cells (1%) created a sarcomatoid appearance, and sheets of cells punctuated by small cysts resulted in a microcystic appearance (1%). The adult granulosa cell-like pattern (1%), although focal, had cells with oval to angulated nuclei with occasional grooves and scant cytoplasm.

Two types of stroma were seen in JGCT: fibrous and fibromyxoid. The latter type typically is somewhat basophilic occasionally imparting a chondroid appearance. In addition, foci of hemorrhage associated with hemosiderin-laden macrophages were seen in 16%; this and areas of hyalinization and prominent blood vessels (13%), which we consider regressed tumor,

are previously unemphasized features of JGCT (Fig. 13A). We have seen both in the ovarian JGCT sporadically. Another feature not previously described is the presence of columnar cells (Fig. 11). These were found lining cystic spaces and had basally located nuclei in 19 cases (27%). We hypothesize these are of Sertoli cell origin, which is supported by their positivity for SOX9, a marker expressed in the (pre-)Sertoli cells of the testis.^{15, 16}

Although an intratubular component is reportedly rare,¹⁷ we found it in 43% of our cases. This suggests that neoplastic proliferation of intratubular sex cord cells progress to an invasive tumor, simultaneously acquiring granulosa cell differentiation and losing Sertoli cell differentiation as reflected in their FOXL2 reactivity (100%) (Fig. 14C) and diminishing SOX9 reactivity (55%) (Fig. 14E). At least some follicles may, therefore, represent expansion of this intratubular growth; this is supported by SALL4 occasionally highlighting residual germ cells at the base of these follicles (Fig. 14F). Our FOXL2 staining result is in accordance with the reported consistent immunohistochemical expression of FOXL2 in JGCTs^{18, 19}; however, our experience has been that other testicular sex cord stromal tumors may also express FOXL2, including Sertoli cell tumor, fibrothecoma, and myoid gonadal stromal tumor, so FOXL2 positivity should not be considered specific.

Occasional JGCTs arise in undescended testes; the 3 in our series were previously included in the series of Lawrence et al,³ and other rare reports exist.^{20, 21} This is of course a phenomenon much more typical of germ cell tumors.²²⁻²⁴ Another uncommon association is with a disorder of sexual development⁴; we have only encountered four additional cases since the initial report.⁴

The differential diagnosis of the JGCT may include a number of entities in the sex cord-stromal category as well as other categories. As the best known testicular tumor of the young is

the YST,¹⁴ we consider it first, and then discuss the differential with other sex cord-stromal tumors, and then, briefly, other entities less often an issue.

In the differential with YST, the age is helpful as most boys with JGCT are less than six months old whereas the majority of children with YST are older.^{14, 25, 26} In the largest series of testicular YSTs, only 9% were less than 6 months old, and another 15% 6 months or older but less than 1 year old.¹⁴ One pitfall is that the typical serum AFP elevation seen in cases of YST is occasionally seen in patients with JGCT due to the physiologic elevation seen in the early months of life; however, the levels are almost invariably lower than the pathologic levels associated with YST.^{25, 27} Grossly, JGCTs more often exhibit a solid and cystic appearance, whereas the prepubertal YST usually lacks conspicuous cystic areas, but frequently the gross appearance is indistinguishable. On microscopic examination, the overt follicular differentiation of most JGCTs is very helpful. Follicles are not a feature of YSTs although rarely cysts in the polyvesicular vitelline variant may simulate follicles. The rare polyvesicular YST²⁸ has not been reported in pure form in the testis and even in minor part is rare. However, cysts in YSTs may be misconstrued as dilated follicles of a JGCT, one of several problematic overlapping appearances of the two tumors (Fig. 6). True follicles are diagnostic of JGCT. When follicles are inconspicuous or absent in a JGCT, the differential with YST may arise when the former has foci that have a lace-like arrangement in a myxoid stroma resembling the reticular pattern of YST (Fig. 7B). Potential confusion between JGCT and YST is compounded by the presence in each of them solid foci. In a recent paper on YST of the infant testis 64% had solid foci.¹⁴ Although a low-power lobular arrangement is highly suggestive of JGCT it may be seen in some YSTs. Despite the overlap just noted in individual tumors careful evaluation of well sampled neoplasms will show one or more features indicative of the correct diagnosis whether it be typical follicles

of JGCT or Schiller-Duval bodies in yolk sac tumor. Brisk mitotic activity can be observed in both, and is not a helpful differential feature. In difficult cases, IHC is helpful. Sex cord-stromal tumor markers such as inhibin, calretinin, and SF-1 are almost always positive in JGCT, while SALL4, glypican-3, and AFP are negative in the neoplastic granulosa cells. It is important to keep in mind, however, that not all JGCTs are conspicuously positive for inhibin, and one case (10%) in our series showed focal reactivity for AFP.

Although greater difficulty in differential diagnosis of the JGCT occurs with other sex cord tumors, particularly Sertoli cell tumor, it is worth briefly pointing out at this juncture the important differences from the adult type of testicular granulosa cell tumor. The latter occurs at a much older age, average 40 years,^{12, 29} and has the spectrum of differences in morphology that have been elaborated in detail in discussion of these two tumors in the ovary,³⁰ so will not be repeated here.

The differential diagnosis of JGCT with Sertoli cell tumor and even unclassified sex cord-stromal tumor may be problematic and indeed it must be noted that the inherent subjectivity that plays a role in tumor subclassification exists in this circumstance. There is a marked contrast in the morphology of the JGCT with the usual Sertoli cell tumor typically seen in adults.³¹ However, some might interpret the corded patterns seen in some of our JGCTs as belonging in the Sertoli cell group, which may explain why some have reported “Sertoli cell tumors” as more common than JGCTs in the testis of children.⁷ The follicles observed in JGCTs are typically larger than the lumens of tubules in Sertoli cell tumors; the former is also commonly multilayered in contrast to the single cell lining of the latter. In our opinion, an immature nuclear appearance and brisk mitotic rate are much more typical of JGCT than Sertoli cell tumor as is the lobular arrangement of tumor cells and myxoid stroma.

In cases that are paucifollicular, unclassified sex cord-stromal tumor enters the differential diagnosis. The latter, however, typically occurs in patients who are older than those with JGCTs,^{6, 32} shows non-specific solid and nested patterns without the lobular growth characteristic of JGCT, often has a more prominent and integral spindle cell component, and lacks distinct follicles with a circumferential arrangement of epithelioid tumor cells.³³

A rare, but important differential is with a sarcoma, particularly embryonal rhabdomyosarcoma given the primitive nuclei, mitotic activity, occasional spindle cell component in JGCTs and sometimes a “small round blue cell tumor”-like appearance. However, sarcomas are most commonly located in the paratestis, although the testis may become secondarily involved. Furthermore, although primary testicular sarcomas of non-germ cell tumor origin rarely occur,^{33, 34} none has been reported in infants. Other features of JGCT include follicular differentiation, absence of rhabdomyoblasts, and lack of myogenin reactivity, although there may be focal actin and desmin positivity.³⁵

One might think the JGCT would have a malignant potential given its frequent brisk mitotic activity and prominent apoptosis. In all of the reported cases with follow-up, however, the tumor has behaved in a benign fashion.^{3, 6, 7, 36} Although follow-up was unavailable in many of our patients, that which is available showed no evidence of disease after long-term followup (12 > 5 years); furthermore, we suspect we would have been made aware of bad outcomes had they transpired. The standard treatment of JGCT is radical orchiectomy; however, based on its benign outcome, testis sparing surgery is now advocated.³⁶ Six patients in our series had wedge excision, and the three with follow-up showed no evidence of disease at 7, 30, and 68 months, respectively. One of the two patients who had biopsy had no evidence of disease at 16 months. The collective experience is supportive of testis sparing surgery.

In conclusion, testicular juvenile granulosa cell tumor is a distinctive tumor that most commonly occur in patients less than 6 months old and may occur in undescended testes and dysgenetic gonads. Its wide morphologic spectrum may potentially lead to a variety of issues in differential diagnosis, but awareness of its particular tendency to occur in the very young, the spectrum elaborated herein, and if necessary immunohistochemistry should enable the correct diagnosis to be made. Based on current experience, the prognosis seems very good, despite a frequently brisk mitotic rate.

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Figure legends:

Fig.1: Solid lobulated creamy-white tumor (top). Tumor with glistening focally lobulated brown-orange sectioned surface and cysts (bottom).

Fig. 2: Well-circumscribed lobules with variably sized follicles. B shows a more conspicuous solid nests and a papillary focus at the left.

Fig. 3: Cellular lobules of neoplastic cells separated by a fibrous stroma (A). High-power view of similar region from another case showing diffuse growth of neoplastic cells, some of them spindled, and rare follicles (B).

Fig. 4: Prominent follicular differentiation with striking macrofollicles. Solid paucifollicular regions are also seen.

Fig. 5: Irregularly shaped follicles containing basophilic material and lined by one to several layers of cells with pale cytoplasm. The lining is flattened around some follicles.

Fig. 6: Reticular-cystic pattern mimicking yolk sac tumor.

Fig. 7: Strands and cords of neoplastic cells separated by prominent stroma (A). Follicles (seen best at top and right) and central area in which there is a focal “reticular” appearance (B).

Fig. 8: Nests and clusters of tumor cells within a fibrous stroma. Note focal limited follicular differentiation (A). Immature cells with ill-defined cytoplasmic membranes in a fibromyxoid stroma (B).

Fig. 9: Prominent myxoid stroma and cells with vacuolated cytoplasm (A). Myxoid stroma (top right) merges imperceptibly with the basophilic staining material within follicles (B).

Fig. 10: Solid growth of cells with pale cytoplasm. Several mitotic figures are visible (A).

Primitive appearing neoplastic cells with hyperchromatic nuclei, scant cytoplasm, and apoptosis (B).

Fig. 11: Large follicle lined by columnar cells.

Fig. 12: Admixture of typical rounded cells and spindle-shaped cells.

Fig. 13: Regressed tumor characterized by extensive sclerosis with interspersed blood vessels

(A). Papillary pattern (B). Large aggregates of tumor cells with peripheral palisading (C). Tumor cells with scant cytoplasm resulting in an appearance reminiscent of adult granulosa cell tumor (D).

Fig. 14: Positive immunoreactivity of JGCT for inhibin (A), calretinin (B), FOXL2 (C), SF-1

(D), and SOX9 (E). SALL4 is negative in the granulosa cells but highlights residual germ cells at the base of the granulosa cells lining a follicle (F).

Table 1. Antibodies used for immunohistochemistry staining.

Antibody	Vendor	Source (Clone)	Pretreatment	Dilution	Incubations (min)¹
Calretinin	DAKO	Mouse (monoclonal)	High pH	RTU ²	10/10/10/10
FOXL2	Imgenex ³	Rabbit (Polyclonal)	High pH	1:100	20/10/10/5
Inhibin	DAKO ⁴	Mouse (monoclonal)	High pH	RTU	10/10/10/10
SF-1	R&D Systems ⁵	Mouse (Monoclonal)	EDTA	1:100	20/10/10/10
SOX9	R&D Systems	Goat (Polyclonal)	Low pH	1:200	20/10/10/10
WT1	DAKO	Mouse (monoclonal)	High pH	RTU	25/15/15/10

¹primary antibody/secondary antibody/labeled polymer/DAB development

²Ready to use

³San Diego, CA

⁴Carpinteria, CA

⁵Minneapolis, MN

FIGURE 1. Solid lobulated creamy-white tumor (top). Tumor with glistening focally lobulated brown-orange sectioned surface and cysts (bottom).

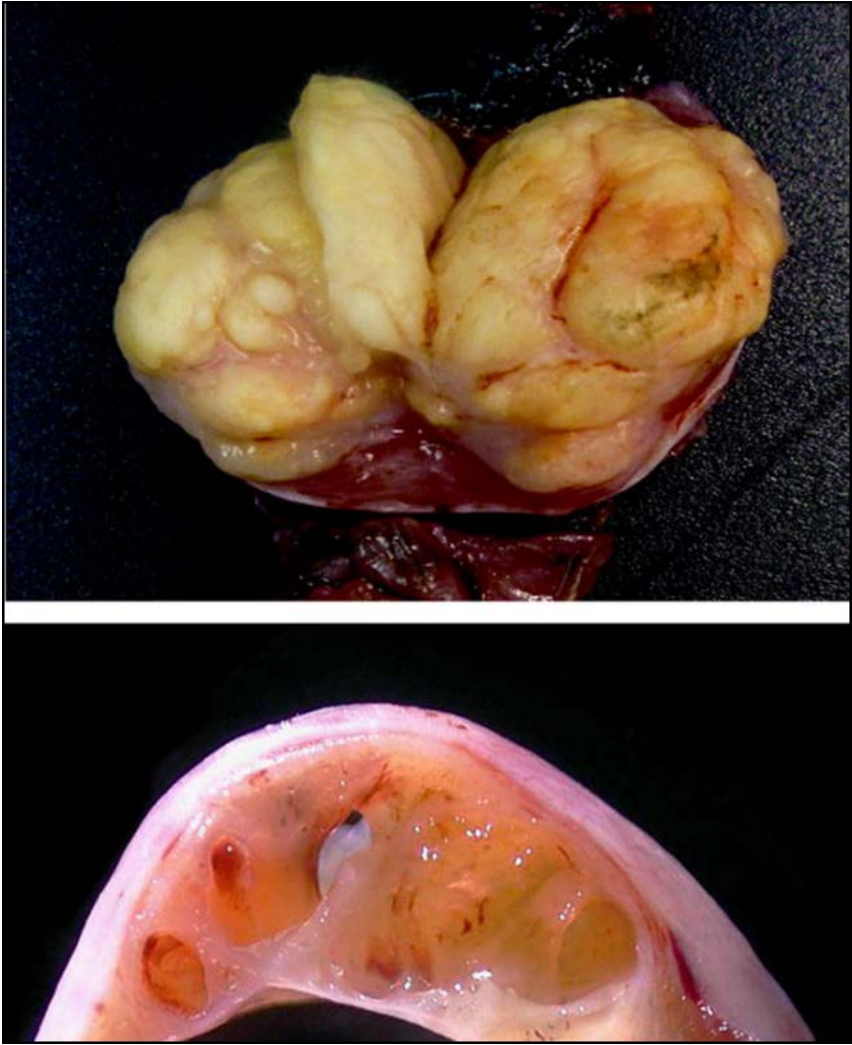


FIGURE 2. A, Well-circumscribed lobules with variably sized follicles. B, More conspicuous solid nests and a papillary focus at the left.

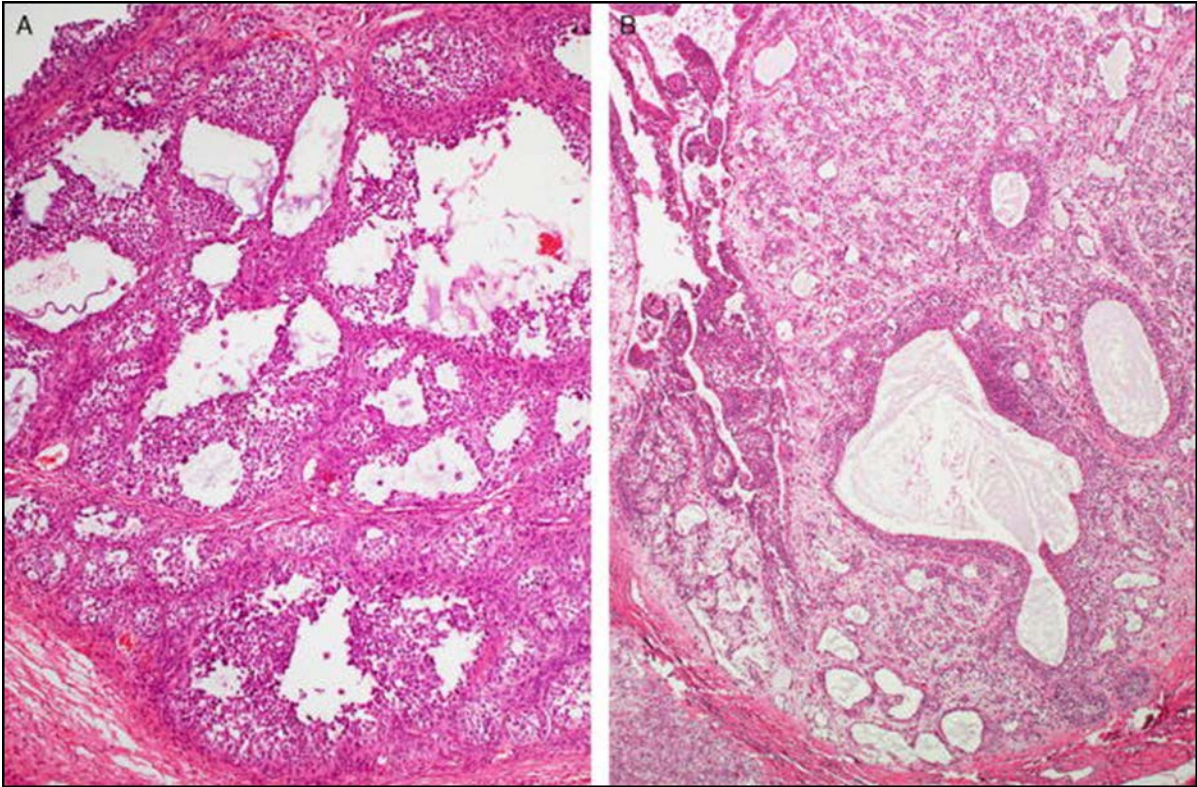


FIGURE 3. A, Cellular lobules of neoplastic cells separated by a fibrous stroma. B, High-power view of a similar region from another case showing diffuse growth of neoplastic cells, some of them spindled, and rare follicles.

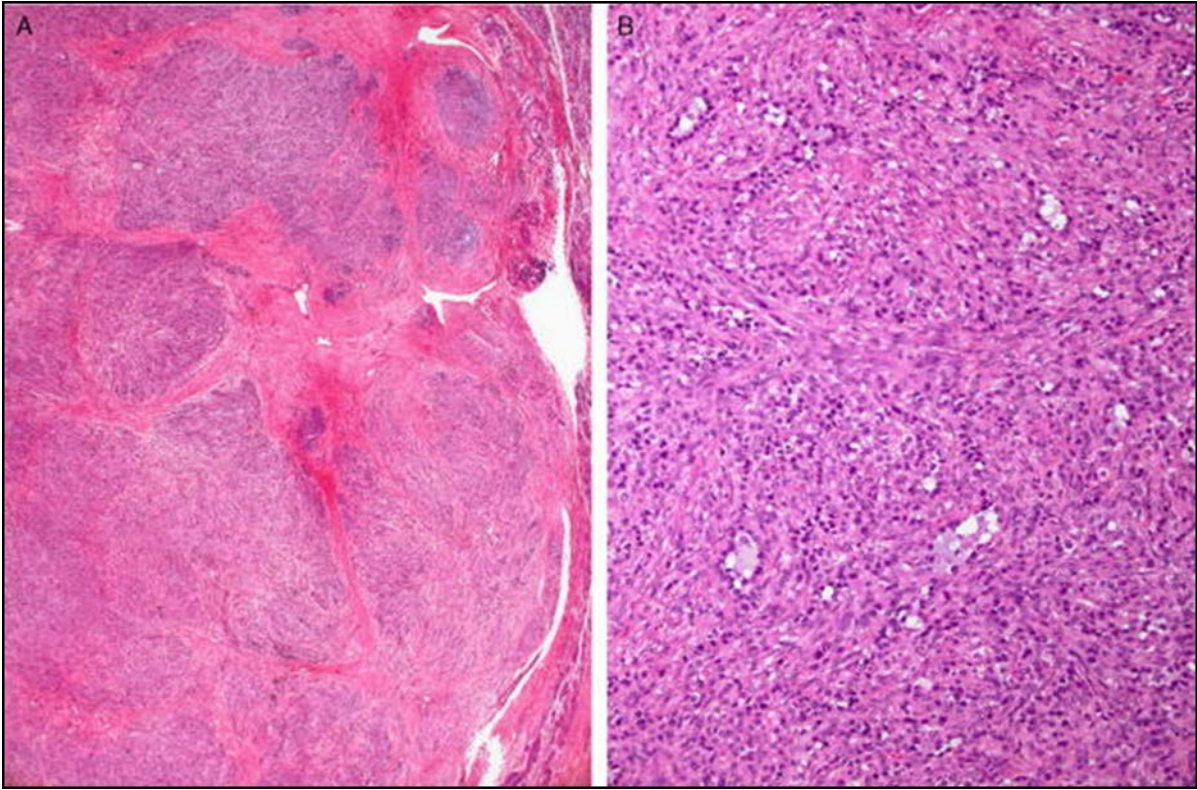


FIGURE 4 . Prominent follicular differentiation with striking macrofollicles. Solid paucifollicular regions are also seen.

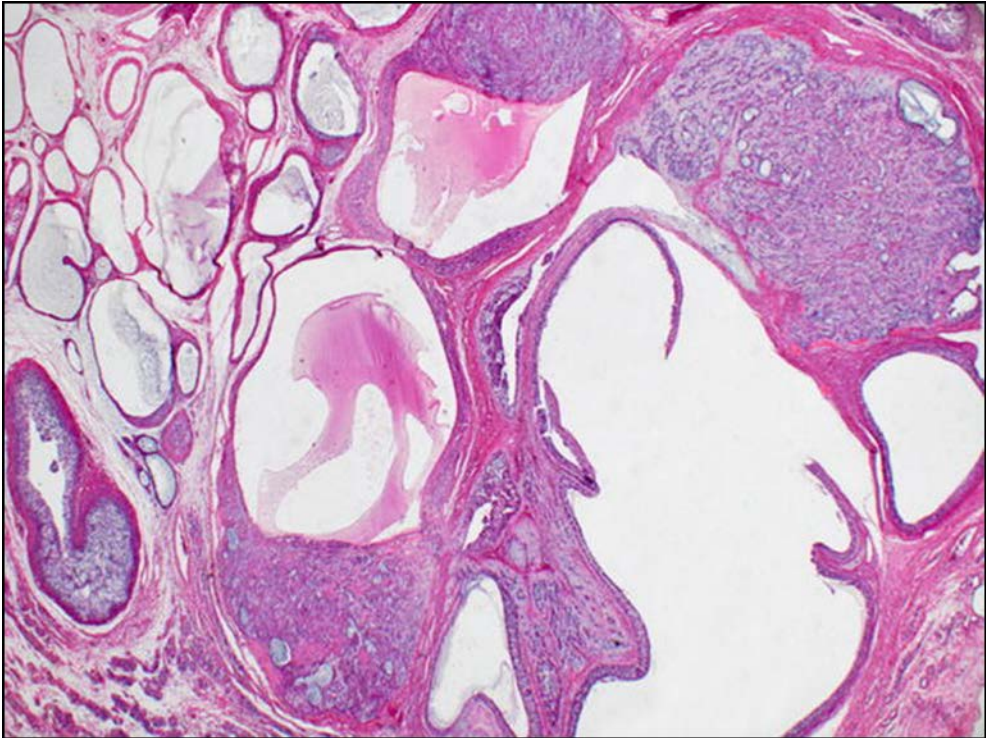


FIGURE 5 . Irregularly shaped follicles containing basophilic material and lined by 1 to several layers of cells with pale cytoplasm. The lining is flattened around some follicles.

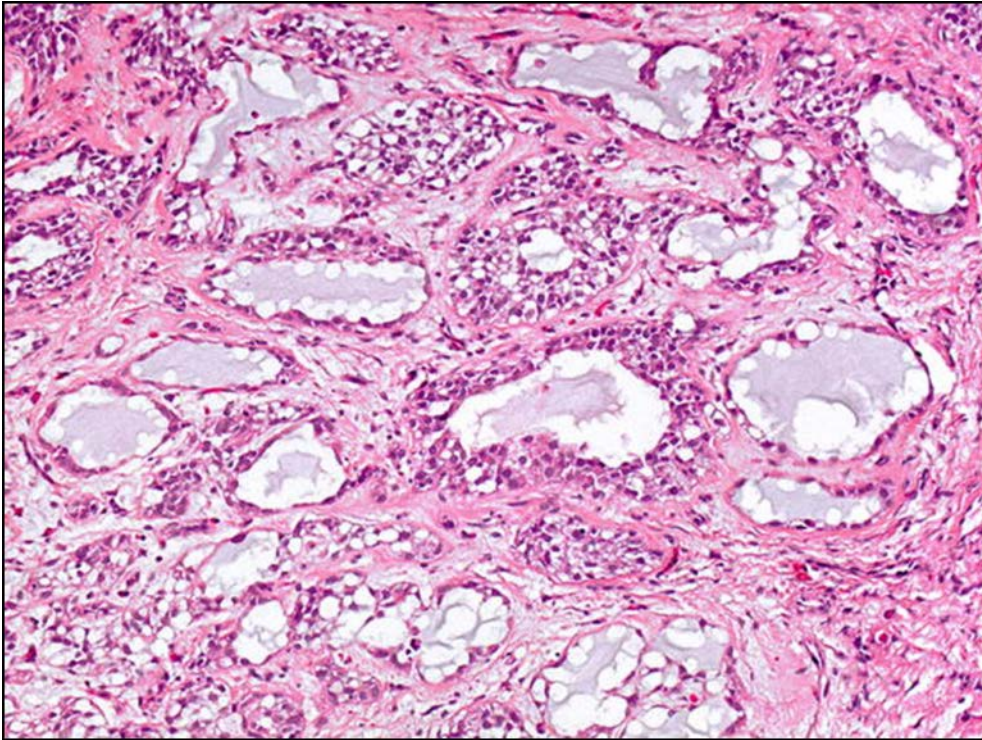


FIGURE 6 . A reticular-cystic pattern mimicking YST.

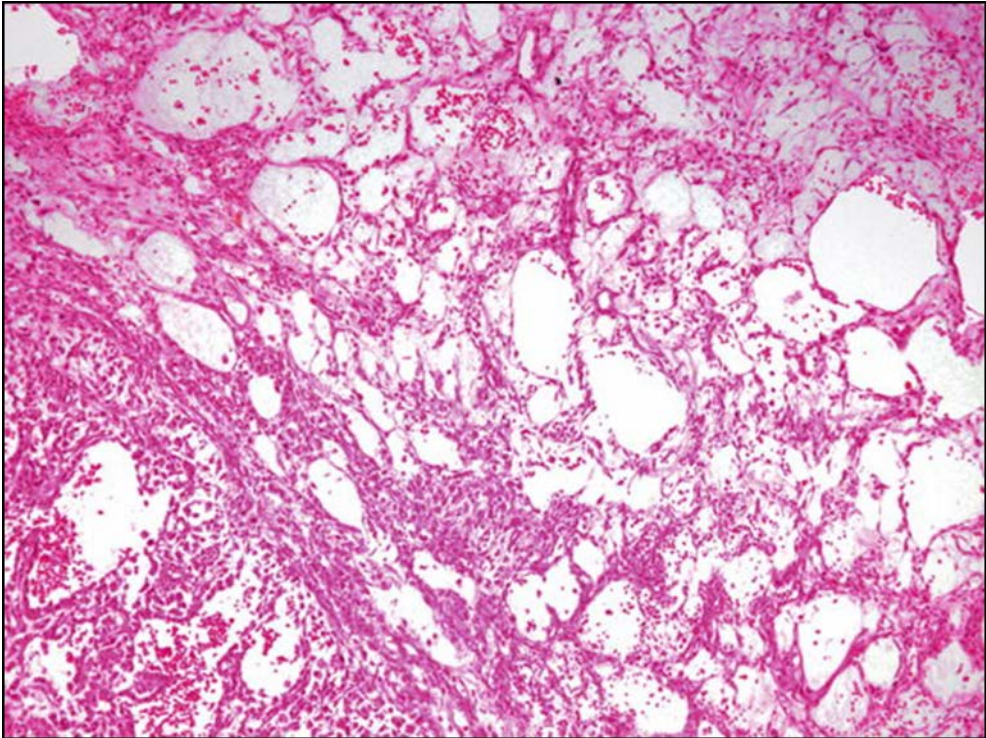


FIGURE 7 . A, Strands and cords of neoplastic cells separated by prominent stroma. B, Follicles (seen best at top and right) and central area in which there is a focal "reticular" appearance.

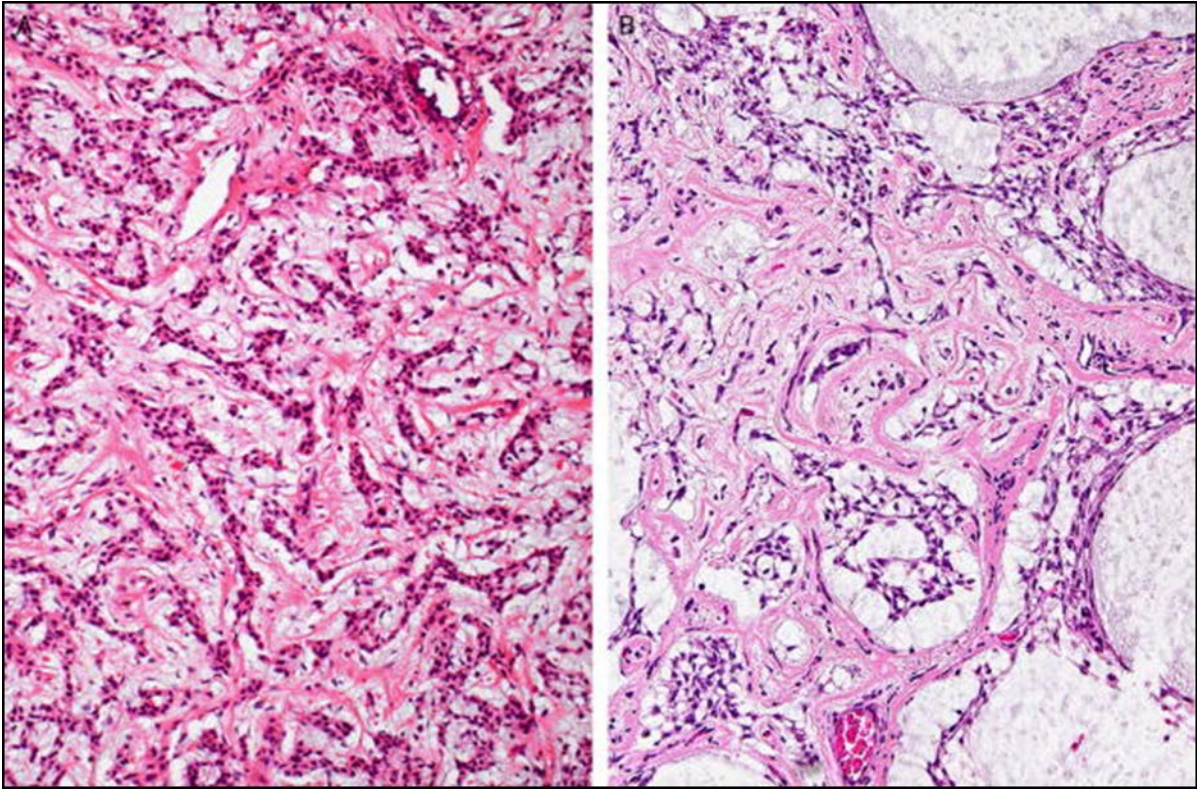


FIGURE 8 . A, Nests and clusters of tumor cells within a fibrous stroma. Note focal limited follicular differentiation. B, Immature cells with ill-defined cytoplasmic membranes in a fibromyxoid stroma.

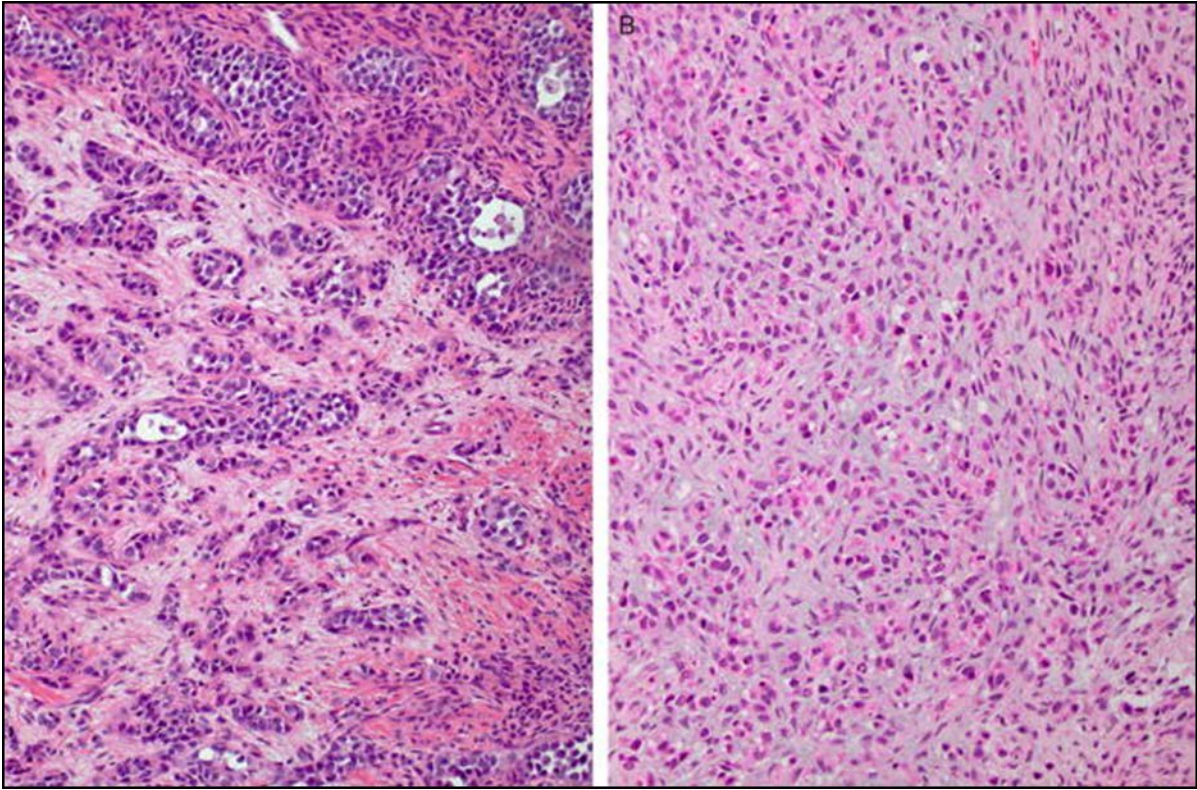


FIGURE 9 . A, Prominent myxoid stroma and cells with vacuolated cytoplasm. B, Myxoid stroma (top right) merges imperceptibly with the basophilic staining material within follicles.

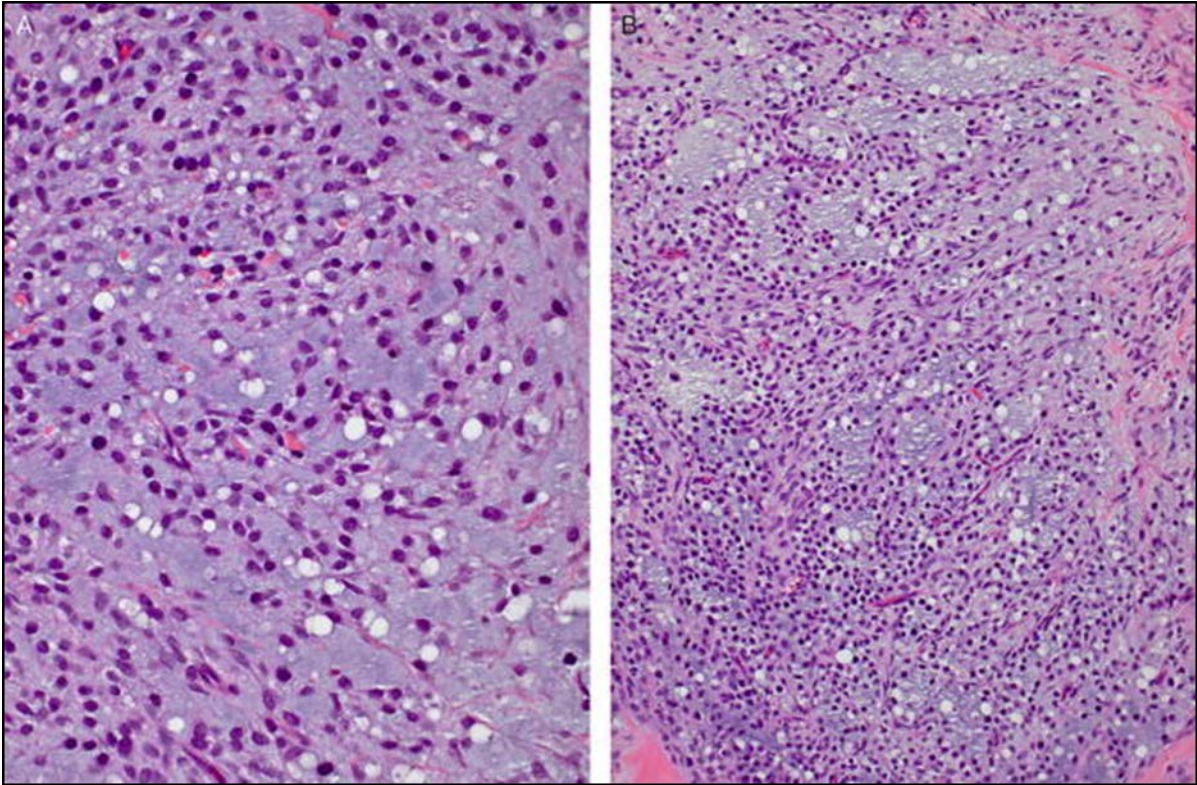


FIGURE 10 . A, Solid growth of cells with pale cytoplasm. Several mitotic figures are visible. B, Primitive-appearing neoplastic cells with hyperchromatic nuclei, scant cytoplasm, and apoptosis.

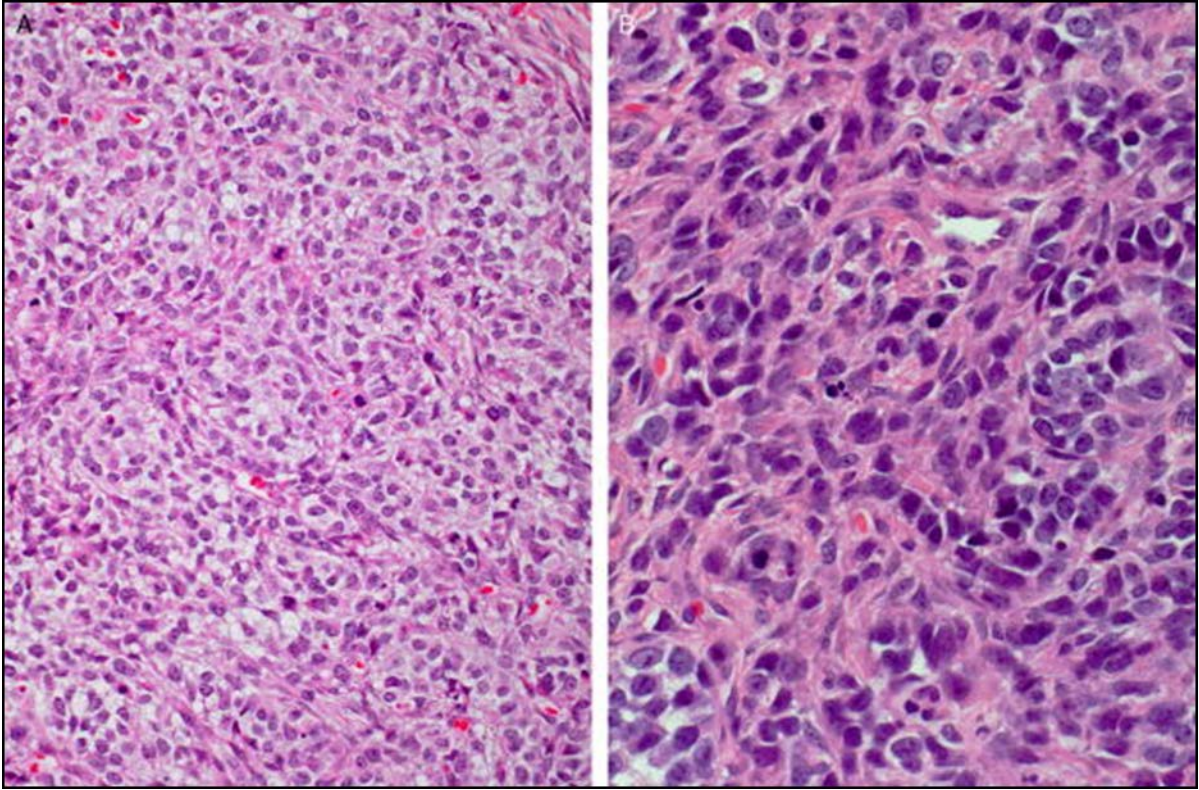


FIGURE 11 . Large follicle lined by columnar cells.

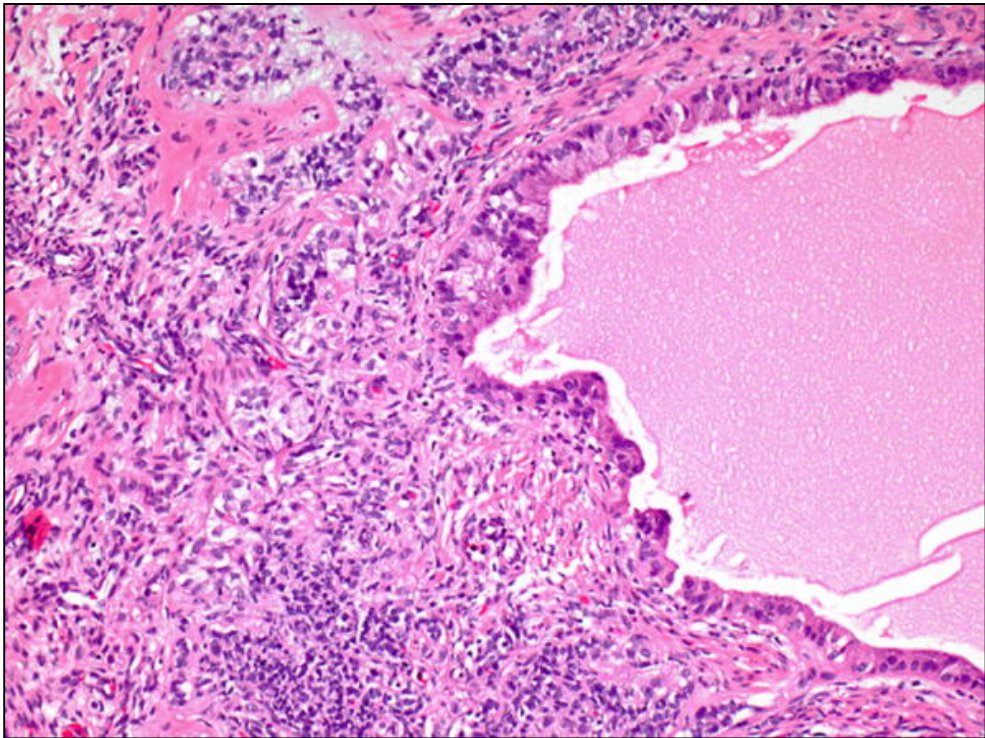


FIGURE 12 . Admixture of typical rounded cells and spindle-shaped cells.

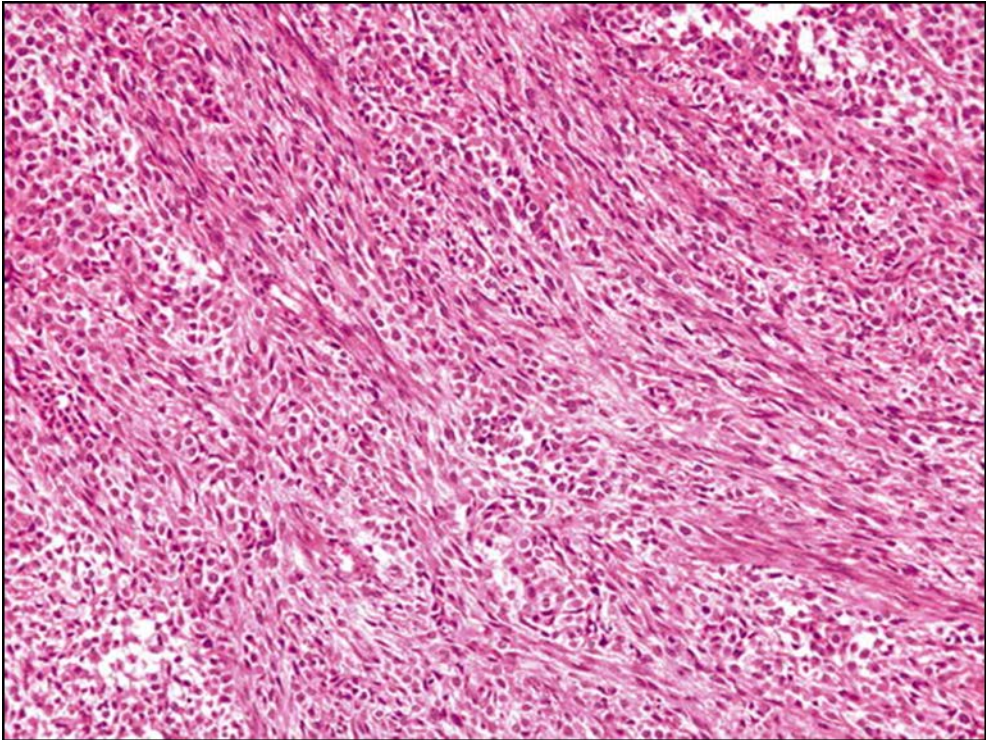


FIGURE 13 . A, Regressed tumor characterized by extensive sclerosis with interspersed blood vessels. B, Papillary pattern. C, Large aggregates of tumor cells with peripheral palisading. D, Tumor cells with scant cytoplasm resulting in an appearance reminiscent of adult granulosa cell tumor.

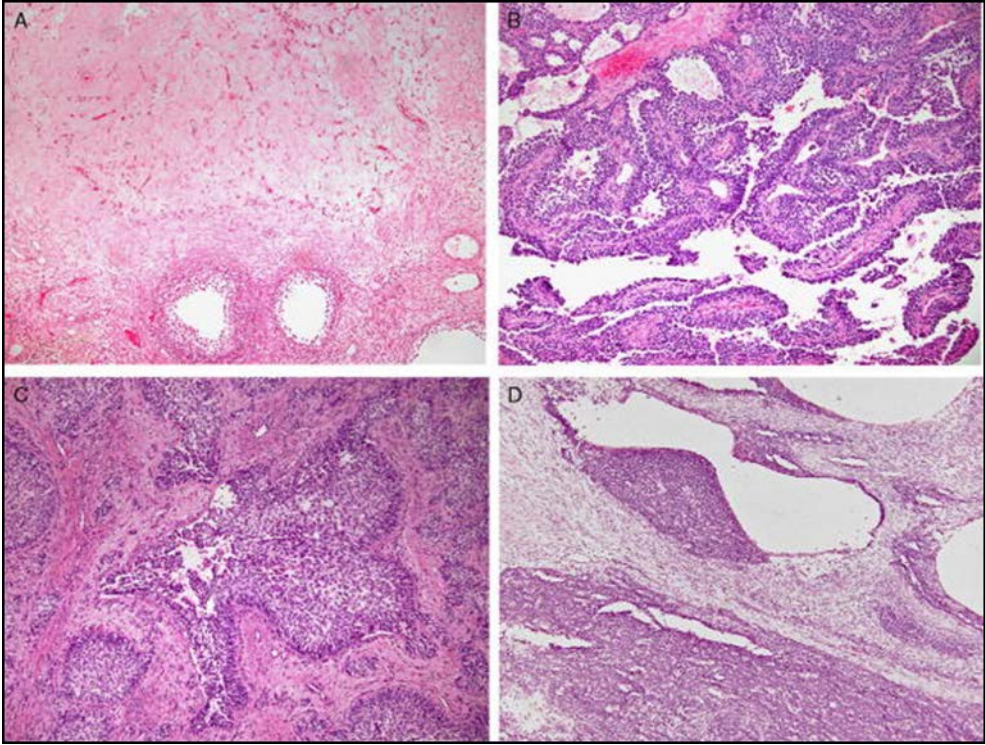


FIGURE 14 . Positive immunoreactivity of JGCT for inhibin (A), calretinin (B), FOXL2 (C), SF-1 (D), and SOX9 (E). F, SALL4 is negative in the granulosa cells but highlights residual germ cells at the base of the granulosa cells lining a follicle.

