Myoid Gonadal Stromal Tumor

A Clinicopathologic Study of Three Cases of a Distinctive Testicular Tumor

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ABSTRACT

Objectives: *To report three new cases of testicular myoid gonadal stromal tumor to better characterize its features.*

Methods: *The clinicopathologic findings (including follow-up) were evaluated and a review of the literature was performed.*

Results: *The patients were 38, 43, and 59 years old, and tumor sizes were 1.2, 1.3, and 3.2 cm. All were unilateral, well circumscribed, adjacent to the rete testis, and composed exclusively of spindled cells with elongated nuclei and occasional nuclear grooves arranged in fascicles with admixed variably ectatic blood vessels. Nucleoli were inconspicuous, and the cytoplasm was scant, ill-defined, and pale/lightly eosinophilic. No sex cord component was present. Mitotic figures ranged from zero to five per 10 high-power fields. Significant atypia, lymphovascular invasion, and necrosis were absent. All were consistently positive for smooth muscle actin, S100 protein, FOXL2, and steroidogenic factor 1 but negative for h-caldesmon, calretinin, and SOX9. Inhibin and calponin were focally positive. All patients were alive and well at 5, 31, and 58 months postorchiectomy. Combining our cases with those previously reported (n = 6) shows that this neoplasm occurs mostly in younger men (mean, 37 years), and all follow-up thus far (mean, 25 months) has been benign.*

Conclusions: *Myoid gonadal stromal tumors are small (<4 cm) indolent testicular tumors distinctly different from other sex cord–stromal tumors and are adequately managed by orchiectomy.*

Myoid gonadal stromal tumor of the testis is an uncommon spindle cell tumor hypothesized to arise from peritubular myoid cells or intertubular primitive mesenchymal cells.[1-4] To our knowledge, there are only six previously documented cases in the literature, including those reported by Weidner[3] and Du et al,[4] who together defined this rare, yet distinctive, testicular tumor.[1-5] It is characterized by uniform, cytologically bland spindled cells forming short, interwoven fascicles with intervening collagen and coexpression of S100 protein and smooth muscle actin (SMA). All have been small, circumscribed, nonencapsulated masses with no reports of metastasis. In this study, we examined three previously unreported myoid gonadal stromal tumors of the testis to better characterize their clinicopathologic features, including their immunoreactivities for a comprehensive panel of sex cord–stromal markers.[5-15] We also provide additional follow-up concerning this rare entity as well as a review of the literature.

Materials and Methods

We reviewed H&E-stained slides from all cases of testicular sex cord–stromal tumors from our surgical pathology files at Indiana University Health Pathology Laboratory between 1990 and 2013 and identified three cases of myoid gonadal stromal tumor that were previously diagnosed as "unclassified sex cord tumor with prominent spindle cells," "unclassified gonadal stromal tumor," and "unclassified spindle cell sex cord–stromal tumor." All were evaluated prior to the study that characterized the immunohistochemical features of myoid gonadal stromal tumor.[4] All three were consultation cases of orchiectomy

Table 1
Antibodies Used for Immunohistochemistry Staining

Antibody	Vendor	Pretreatment	Dilution	Incubations (min)[a]
Actin, SMA	Dako[b]	High pH	RTU	20/15/10
h-Caldesmon	Dako	High pH	RTU	20/20/20/10
Calponin	Dako	Low pH	1:80	20/10/10/10
Calretinin	Dako	High pH	RTU	10/10/10/10
Desmin	Dako	High pH	RTU	20/10/10
FOXL2	Imgenex[c]	High pH	1:100	20/10/10/5
Inhibin	Dako	High pH	RTU	10/10/10/10
SF-1	R&D Systems[d]	EDTA	1:100	20/10/10/10
SOX9	R&D Systems	Low pH	1:200	20/10/10/10
S100	Dako	High pH	RTU	20/10/10
WT1	Dako	High pH	RTU	20/15/15/10

RTU, ready to use; SMA, smooth muscle actin.
[a] Primary antibody/labeled polymer/DAB development or primary antibody/secondary antibody/labeled polymer/DAB development.
[b] Carpinteria, CA.
[c] San Diego, CA.
[d] Minneapolis, MN.

specimens. The diagnosis was confirmed by the senior author (T.M.U.); we required positive reactivity for both S100 protein and SMA according to the criteria of Du et al,[4] as well as the absence of any sex cord component. All cases showing any sex cord differentiation were excluded since they are more appropriately categorized as unclassified sex cord–stromal tumors. In one case, this was further confirmed by absence of a nested pattern on a reticulin stain.

The tumors were analyzed for various histopathologic features, including size (maximum dimension), necrosis, mitotic rate, cytologic atypia, lymphovascular invasion, encapsulation, and circumscription vs infiltrative margins. Cytologic atypia was defined as a combination of nuclear enlargement, irregularity, pleomorphism, and nucleolar prominence. Additional features assessed were cell shape, nuclear shape, nuclear grooves, perinuclear vacuoles, the quantity and quality of cytoplasm, nature of blood vessels, relationship to the rete testis, and entrapped seminiferous tubules at the periphery.

The results of all immunohistochemical stains performed at the time of diagnosis were recorded, and cases with available material were stained with antibodies directed against S100 protein, SMA, h-caldesmon, desmin, calponin, SOX9, FOXL2, steroidogenic factor 1 (SF-1), inhibin, WT1, and/or calretinin if information was lacking. 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 S100 protein, SMA, h-caldesmon, desmin, calponin, SF-1, inhibin, WT1, and calretinin 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 Laboratories, West Grove, PA] and LSAB2-SA [Dako]), 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 S100 protein and calretinin.

All available clinical history and follow-up information were recorded. A review of the previously reported myoid gonadal stromal tumors from the literature (six cases fulfilling our diagnostic criteria) was undertaken.[1-5] This study was approved by the institutional review board at Indiana University.

Results

Clinical Features

The patients were aged 38, 43, and 59 years, and each had a single testicular mass. All tumors were unilateral with one left-sided and two right-sided. Serum tumor markers (α-fetoprotein and β–human chorionic gonadotropin) obtained prior to surgery in one patient were within normal limits. No patient was known to have hormonal abnormalities or clinical syndromes occasionally associated with some types of sex cord–stromal tumors.[16-23]

Pathologic Features

A summary of pathologic features is provided in **Table 2**. On gross examination, all were unifocal and well circumscribed with a yellow/tan appearance. The sizes were 1.2, 1.3, and 3.2 cm in the greatest dimension. On low-power examination, all were circumscribed and nonencapsulated, focally contained medium- to large-sized ectatic blood vessels and were adjacent to the rete testis **Image 1A**. The tumor cells were spindled and mostly arranged in short intersecting

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Table 2
Pathologic Features of Testicular Myoid Gonadal Stromal Tumor (n = 3)

Case No.	Gross Findings	Growth Pattern	Cell Shape	Nuclear Shape	Nuclear Grooves	Perinuclear Vacuole	Cytoplasm	Atypia	Mitosis per 10 hpf	Necrosis	LVI	IHC Profile
1	Subcapsular, well-circumscribed 1.2-cm golden yellow nodule	Short fascicles	Spindled	Fusiform	Occasional	No	Scant, ill-defined, eosinophilic	No	5	No	No	S100+, SMA+, FOXL2+, SF-1+, vimentin+, inhibin+ (focal weak), desmin–, h-caldesmon–, calretinin–, WT1–, SOX9–, CD34–
2	Well-circumscribed 3.2-cm tan, whorled nodule	Short and broad fascicles	Spindled	Elongated	Occasional	No	Moderate, ill-defined, pale to lightly eosinophilic	Mild	3	No	No	S100+, SMA+, FOXL2+, SF-1+, vimentin+, inhibin+ (focal), calponin+ (focal weak), desmin+ (focal), h-caldesmon–, calretinin–, WT1–, SOX9–
3	Well-circumscribed 1.3-cm yellow-white nodular mass focally contiguous with tunica albuginea	Short fascicles	Spindled	Fusiform	Occasional	No	Scant, ill-defined, pale to lightly eosinophilic	No	<1	No	No	S100+, SMA+, FOXL2+, SF-1+, vimentin+, inhibin+ (focal), calponin+ (focal weak), desmin+, WT1+, h-caldesmon–, calretinin–, SOX9–, CD34–, chromogranin–, synaptophysin–, AE1/3–

hpf, high-power field; IHC, immunohistochemistry; LVI, lymphovascular invasion; –, negative; +, positive.

fascicles (n = 2) **Image 1B** with varying degrees of thin collagen bands in the background **Image 1C**; one case contained short, broad tumor fascicles. The nuclei ranged from elongated to fusiform with inconspicuous to small nucleoli and occasional grooves **Image 1D**. The cytoplasm was scant (n = 2) to moderate (n = 1) and ill-defined, ranging from pale to lightly eosinophilic; none had perinuclear vacuoles (Image 1D). No significant cytologic atypia was present. The number of mitotic figures varied from zero to five per 10 high-power fields. All lacked tumor necrosis and lymphovascular invasion. Two had entrapped seminiferous tubules at the periphery **Image 1E**. The seminiferous tubules adjacent to the tumor showed normal spermatogenesis. A sex cord component was absent in all cases, verified by pericellular reticulin staining in one case.

The tumor was positive for the following immunohistochemical stains: S100 protein (three of three) **Image 2A**, SMA (three of three) **Image 2B**, FOXL2 (three of three) **Image 2C**, SF-1 (three of three), vimentin (three of three), inhibin (focal, three of three), desmin (two of three), calponin (focal and weak, two of two), and WT1 (one of three). Staining for h-caldesmon **Image 2D**, calretinin, SOX9, and CD34 (two cases) was consistently negative. Synaptophysin, chromogranin, and cytokeratin AE1/3 were negative in one case. The peritubular myoid cells in the adjacent seminiferous tubules were positive for SMA, desmin, h-caldesmon (Image 2D), and calponin but negative for S100 protein (Image 2A), inhibin, calretinin, WT1, SOX9, FOXL2, and SF-1.

Treatment and Clinical Follow-up

Clinical follow-up showed all three patients were alive with no evidence of recurrent or metastatic disease at 5, 31, and 58 months postorchiectomy. Two patients had follow-up computed tomography scans of the abdomen and pelvis, which showed no retroperitoneal disease; one of these patients (whose tumor was 1.2 cm) underwent "virgin" retroperitoneal lymph node dissection 1 month after orchiectomy, which confirmed the absence of metastatic disease. None received any other form of adjuvant therapy. A summary of testicular myoid gonadal stromal tumors, including those previously reported in the literature, is provided in **Table 3**.[1-5]

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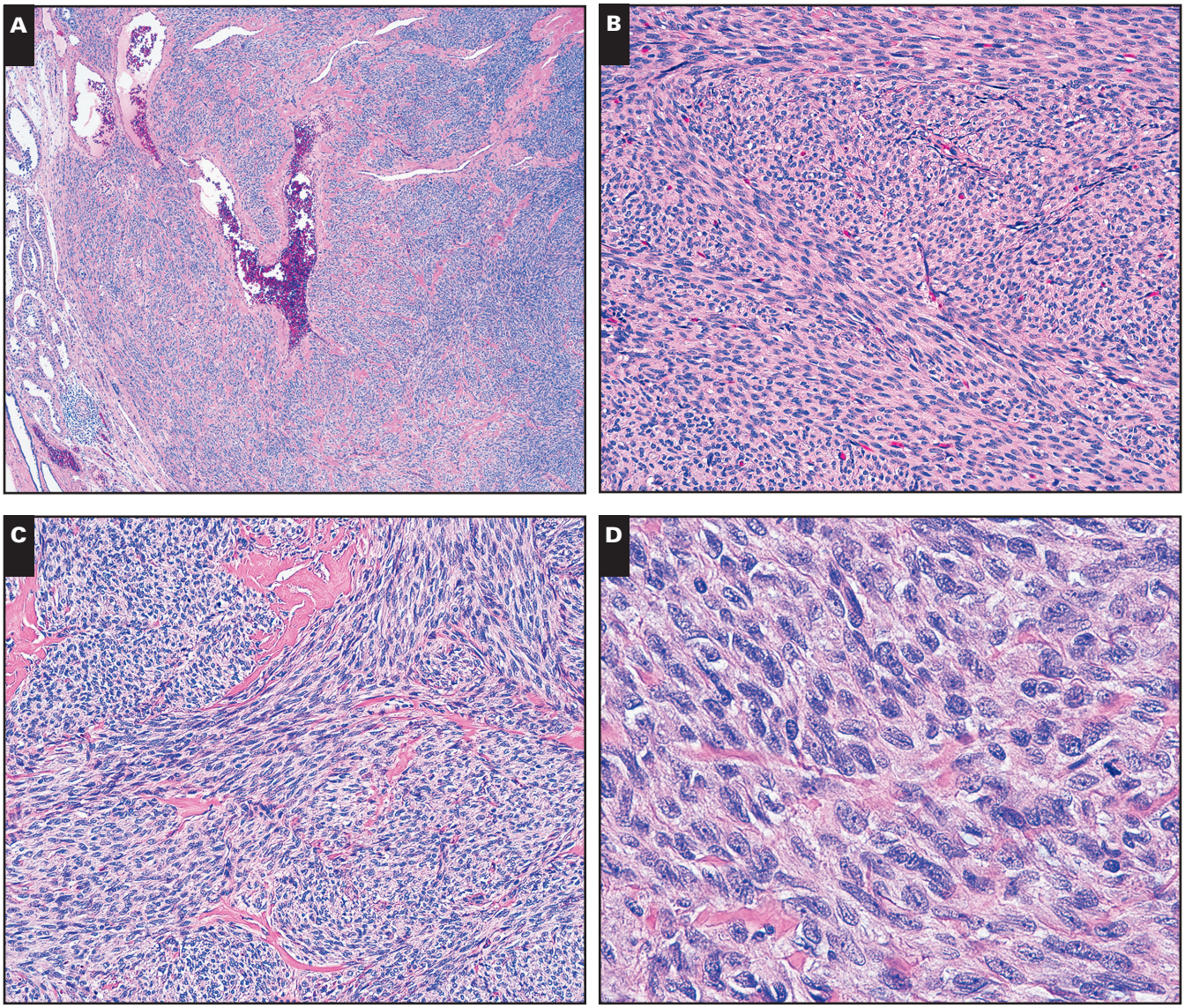

Image 1 **A**, Low-power view shows a well-circumscribed, nonencapsulated myoid gonadal stromal tumor adjacent to the rete testis (left) and focally containing ectatic blood vessels and scattered thin collagen bands (H&E, ×40). **B**, The spindled tumor cells are arranged in short intersecting fascicles (H&E, ×150). **C**, There are patchy collagen deposits in the background (H&E, ×150). **D**, Nuclear grooves are occasionally present (center). Note the mitotic figure at the right and occasional small nucleoli (H&E, ×400).

Discussion

Sex cord–stromal tumors of the testis are rare, representing approximately 4% to 6% of all adult testicular tumors.[24-26] Even rarer are pure spindle cell tumors, lacking a sex cord component and showing myofilaments, pinocytic vesicles, and lipid droplets on electron microscopy as well as SMA and S100 protein immunoreactivity.[1-5] Weidner,[3] after ultrastructural study, proposed the term *myoid gonadal stromal tumor* for this neoplasm based on its myogenic differentiation (thin filaments with focal densities and α-SMA immunoreactivity), similar to peritubular myoid cells present in the normal testis, which also contain subplasmalemmal micropinocytotic vesicles, thin filaments with focal densities, and reactivity for α-SMA and desmin. Given the rarity of this tumor, previous reports were restricted to one or two cases each, and all were clinically benign.[1-5] In addition, the nomenclature for this tumor varied from "unusual gonadal stromal tumor" and "testicular stromal tumor with myofilaments" to "unclassified sex cord–stromal tumor with predominance of spindle cells." To our knowledge, our study is the largest contribution regarding this rare entity and provides additional clinicopathologic information concerning this neoplasm.

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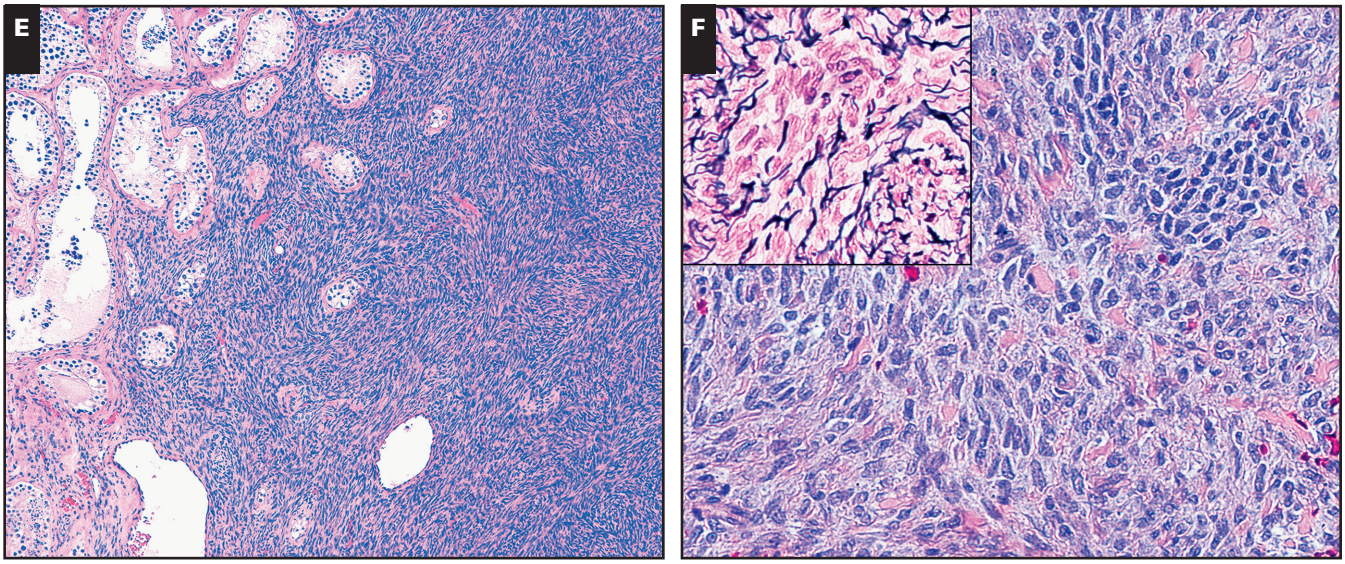

Image 1 (cont) **E**, Entrapped seminiferous tubules are at the periphery of the tumor (H&E, ×150). **F**, An unclassified, spindle cell–predominant sex cord–stromal tumor with small, tight clusters of sex cord cells with dark nuclei and scant cytoplasm (top right) (H&E, ×200). Inset: reticulin stain shows the nested arrangement of sex cord cells lacking reticulin fibers (×300).

Our three patients all had single testicular masses without serum tumor marker elevations or hormonal dysfunction. The gross appearance was a well-circumscribed mass with a yellow or tan appearance. The tumor cells were spindled or fusiform and arranged in tight, short, and occasionally broad, intersecting fascicles. The nuclei were uniform and elongated with inconspicuous to small nucleoli and had occasional grooves. The cytoplasm was ill-defined and pale to lightly eosinophilic. Follow-up of our patients showed all were alive with no evidence of disease.

Immunohistochemistry demonstrated consistent strong and diffuse positive reactivity for SMA, S100 protein, and FOXL2; positivity for the first two was considered one of the defining criteria for this neoplasm.[4] SF-1 was also diffusely positive in all three cases but with less intensity, and there was variable positivity for desmin and WT1. Inhibin and calponin were both focally and weakly positive. SOX9, h-caldesmon, and calretinin, on the other hand, were consistently negative. The only similarities between the tumors and the peritubular myoid cells of the adjacent nonneoplastic testis were reactivities for SMA, calponin, and desmin (variable). The peritubular myoid cells were consistently negative for S100 protein, FOXL2, SF-1, inhibin, and WT1 but positive for h-caldesmon. The difference in immunostaining pattern argues against myoid gonadal stromal tumors showing peritubular myoid cell differentiation.

Aside from peritubular myoid cells, the origin from primitive gonadal stromal cells—more specifically, intertubular mesenchymal cells that underwent myogenic differentiation—has also been hypothesized.[2,4,27-29] The tumor's consistent strong and diffuse positivity for FOXL2, together with its negative reactivity for SOX9, provides support that myoid gonadal stromal tumor is a pure stromal neoplasm rather than of mixed sex cord–stromal lineage since SOX9 is a relatively sensitive and specific marker for sex cord tumor elements compared with FOXL2, which is a better marker for "stromal" tumors in addition to granulosa cell tumors (C.S. Kao, T.M. Ulbright, and M.T. Idrees, unpublished observations).[11,12,14] SF-1, on the other hand, is a very sensitive but less specific "general" marker for both sex cord and stromal elements.[15] Our findings support the proposition made initially by Greco et al[2] that myoid gonadal stromal tumors are derived from intertubular primitive mesenchymal cells that undergo myogenic differentiation.

Even though myoid gonadal stromal tumors have been shown to contain myofilaments and desmosomes on electron microscopy, similar to smooth muscle tumors or those with myoepithelial differentiation, h-caldesmon was consistently negative while calponin was only focally and weakly positive. Its S100 protein reactivity also contrasts with the negativity of leiomyoma. These findings provide further support that myoid gonadal stromal tumor is a distinct entity separate from leiomyoma and most likely not of myoepithelial origin.

The differential diagnosis of myoid gonadal stromal tumor includes leiomyoma, testicular fibrothecoma, and unclassified sex cord–stromal tumor; **Table 4** provides a summary of their individual immunohistochemical properties. The main differential between myoid gonadal stromal tumor and leiomyoma has been presented in detail by Du et al[4] and is only briefly discussed here. Myoid gonadal stromal tumor lacks the diffuse broad fascicles, abundant eosinophilic cytoplasm, and cigar-shaped nuclei often accompanied by perinuclear vacuoles seen in leiomyoma (Table 2). Furthermore, myoid gonadal stromal tumor shows

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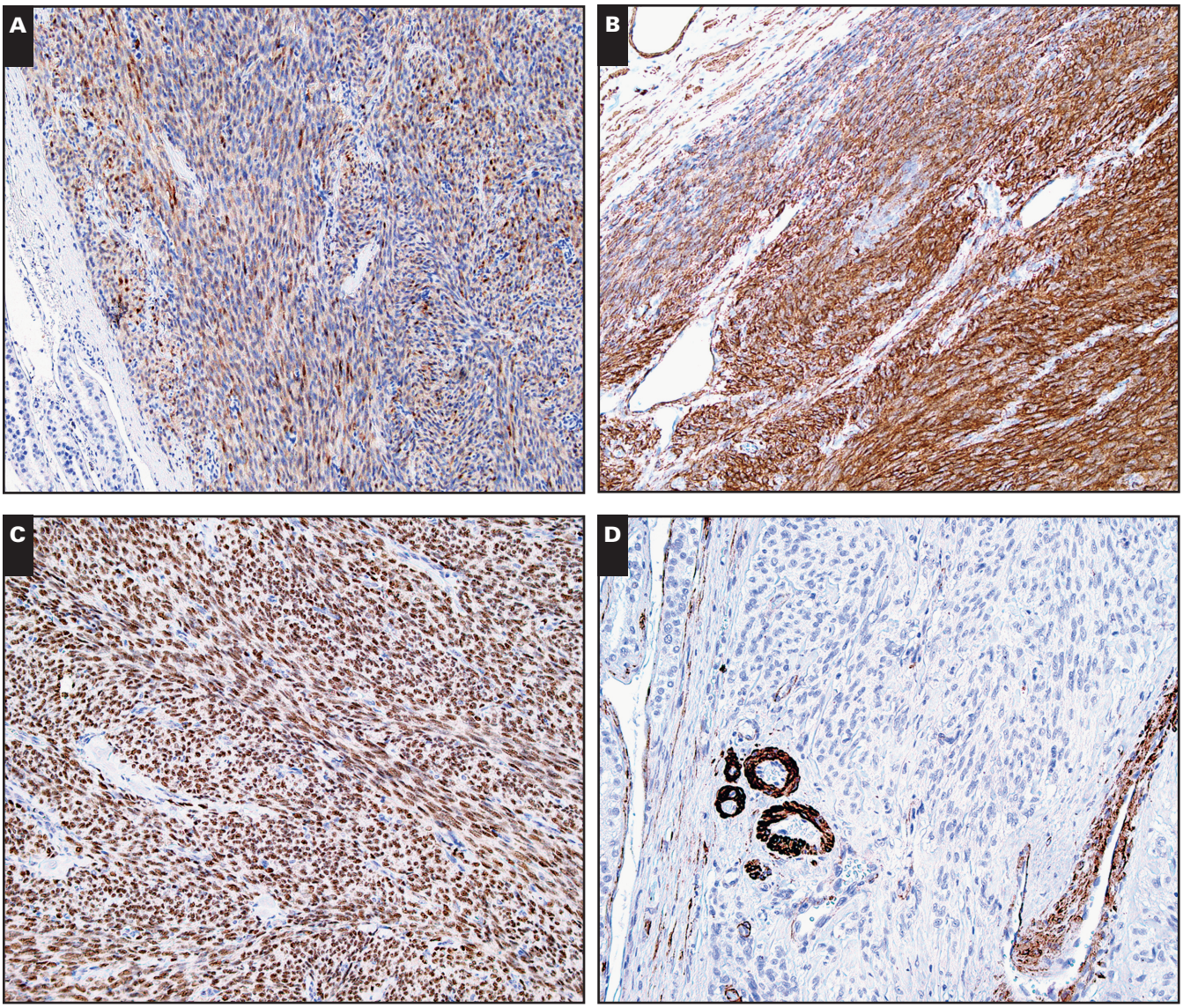

Image 2 Myoid gonadal stromal tumor showing diffuse, strong positivity for S100 (**A**, ×150), smooth muscle actin (**B**, ×150), and FOXL2 (**C**, ×150). The tumor is negative for h-caldesmon (**D**, ×150), whereas the peritubular myoid cells are positive.

S100 protein positivity and lacks h-caldesmon reactivity, while the opposite profile is observed in leiomyoma.

The variably present collagen bundles may be somewhat akin to those seen in testicular fibrothecoma, but in the latter, these bundles are typically thicker and more diffuse, sometimes forming hyaline plaques, similar to those seen in the ovarian counterpart.[30] The pattern of immunostaining is also helpful in differentiating myoid gonadal stromal tumor from testicular fibrothecoma, as has been described previously.[30] Myoid gonadal stromal tumor shows consistent strong and diffusely positive immunostaining for S100 protein and SMA with focal or negative reactivity for inhibin. Testicular fibrothecoma, on the other hand, shows frequent patchy to diffuse inhibin and calretinin staining with variable, patchy S100 protein reactivity.[30] In addition, testicular fibrothecoma shows positive reactivity with SOX9, FOXL2, and SF-1 (C.S. Kao, T.M. Ulbright, and M.T. Idrees, unpublished observations), whereas myoid gonadal stromal tumor is positive for FOXL2 and SF-1 but negative for SOX9, supporting the hypothesis that these two are separate entities. SMA is commonly positive in testicular fibrothecoma and does not aid in the distinction from myoid gonadal stromal tumor.[30]

In our opinion, spindle cell tumors of the testis with sex cord differentiation appreciable on H&E- or reticulin-stained slides without distinct tubule or follicle formation should be diagnosed as "unclassified sex cord–stromal tumor," even with S100 protein and/or SMA positivity since these reactivities are nonspecific and may also be observed in other types of sex cord–stromal tumors.[5,7,9,30,31] We have excluded tumors with sex cord differentiation from our series. Careful light microscopic examination of standard H&E-stained

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Table 3
Clinicopathologic Summary of Testicular Myoid Gonadal Stromal Tumors

Reference	No. of Cases	Age, y	Laterality	Size, cm	Follow-up, mo	Disease Status
Evans[1]	1	4	Left	3.5	3	Alive and NED
Greco et al[2]	2	28, 48	Unknown	2, 3.5	12, 32	Both alive and NED
Weidner[3]	1	46	Right	2.5	12	Alive and NED
Renshaw et al[5]	1 (patient 4)	45	Unknown	2.1	60	Alive and NED
Du et al[4]	1	25	Right	1.5	12	Alive and NED
Kao and Ulbright (present study)	3	38, 43, 59	1 Left, 2 right	1.2, 1.3, 3.2	5, 31, 58	All alive and NED
Total	9	4-59 (mean, 37)	2 Left, 4 right, 3 unknown	1.2-3.5 (mean, 2.3)	3-60 (mean, 25; median, 12)	All alive and NED

NED, no evidence of disease.

Table 4
Immunohistochemical Findings in Myoid Gonadal Stromal Tumor and Potential Mimics[a]

Tumor	S100	SMA	Desmin	h-Caldesmon	Inhibin	Calretinin	SOX9	FOXL2	SF-1
Myoid gonadal stromal tumor	+ (diffuse, strong)	+ (diffuse, strong)	+/–	–	–/+ (focal)	–	–	+	+
Leiomyoma	–	+ (diffuse, strong)	+ (diffuse, strong)	+	–	–	–	–	–
Fibrothecoma	Variable	+	+ (focal)	Not available	+	Variable	+/–	+	+

–, negative; +, positive; +/–, positive or negative.
[a] Reticulin stain works best in differentiating unclassified sex cord–stromal tumor from others, where the former shows reticulin fibers surrounding nested arrangements of cells, but myoid gonadal stromal tumor and fibrothecoma show fibers around individual cells.

sections permits the identification of subtle sex cord elements in unclassified, spindle cell–predominant sex cord–stromal tumors. These usually stand out as darker, tight groupings of cells with rounder nuclei and indistinct, typically pale, often scant cytoplasm; they may be arranged in nests or short cords **Image 1F**. Such foci can be highlighted by a relative lack of reticulin fibers, contrasting with the surrounding pericellular stromal pattern (Image 1F, inset), and also by stronger reactivity for inhibin, although overall, the immunoprofile of these two entities may show significant overlap. Sometimes Sertoli cell, Leydig cell, and granulosa cell tumors may have a prominent component of spindle cells, but adequate sampling permits appreciation of more characteristic tumor features. A diagnosis of myoid gonadal stromal tumor should therefore be reserved for pure spindle cell tumors lacking sex cord differentiation and show, at the minimum, strong and diffuse positivity for both S100 protein and SMA.

A literature search for testicular tumors fulfilling our diagnostic criteria revealed six cases (Table 3).[1-5] Combining our cases with those previously reported (a total of nine) shows that testicular myoid gonadal stromal tumors are unilateral and small (100% <4 cm) and occur in a wide age range (4-59 years; mean, 37 years; median, 43 years) but mostly in young to middle-aged men. Occasional mitotic figures occur, but they lack features associated with malignant behavior established for tumors in the sex cord–stromal category.[32-34] Follow-up information for all nine patients (3-60 months; mean, 25 months; median, 12 months) shows that these tumors have behaved in a benign fashion. Hence, the biologic potential for small tumors (<4 cm) with low mitotic activity is extremely favorable. We cannot reliably assess prognostic features indicative of aggressive behavior at this stage given that all tumors fulfilling our diagnostic criteria have been benign.

In summary, we report the first series of myoid gonadal stromal tumor with detailed clinicopathologic findings, including new information on immunohistochemical properties, together with a review of previously reported cases and differential diagnosis. Furthermore, the new information on its immunophenotype provides support that this distinctive neoplasm originates from intertubular primitive mesenchymal cells that undergo myogenic differentiation rather than peritubular myoid cells. The experience, although limited, has been entirely benign and justifies a conservative approach in the management of patients with these tumors so long as the morphologic findings are within the spectrum of the cases we have herein summarized. Although one may argue that the distinction from other sex cord–stromal tumors of the testis is subtle, the combined morphologic, immunohistochemical, and ultrastructural findings are unique and clearly defined by Du et al,[4] warranting separation from other tumors. We believe our series of myoid gonadal stromal tumors will aid in the recognition of this rare entity and encourage further reports to expand our understanding of its behavior.

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