

AMR Seminar #73

Case – 1

Contributed by: Kumarasen Cooper, M.D.

History: Patient is 27-year old female who presents with incidental splenomegaly comprising 3 spleen masses, characterized on MRI to be likely littoral cell angiomias or SANT, less likely a malignant process.

Three masses of the spleen were incidental and found when the patient had a CT to evaluate ovarian cysts.

She reports no changes in her symptoms, still with a vague pressure in her abdomen 2-3 times per week. Otherwise, she feels well. No fatigue, no weight loss, no fevers, chills, night sweats. No have poor appetite over the past several years with early satiety but stable weight.

See abdominal radiological scan.

Pathology: Weight 858g. Cut surface revealed a 13 X 9cm mass with an irregular border and a heterogeneous cut surface with focal areas of fibrosis. The mass occupies approximately 80% of the splenic parenchyma.

See gross photographs: capsular and cut surface of spleen.

The mass lesion comprises multifocal scattered thin-walled small vessels lined with benign appearing endothelial lining cells.

Between these lobules within the splenic parenchyma are tufts of cells with ovoid or spindled morphology, which appear to be intra-vascular. These cells are uniform without atypia or mitotic activity.

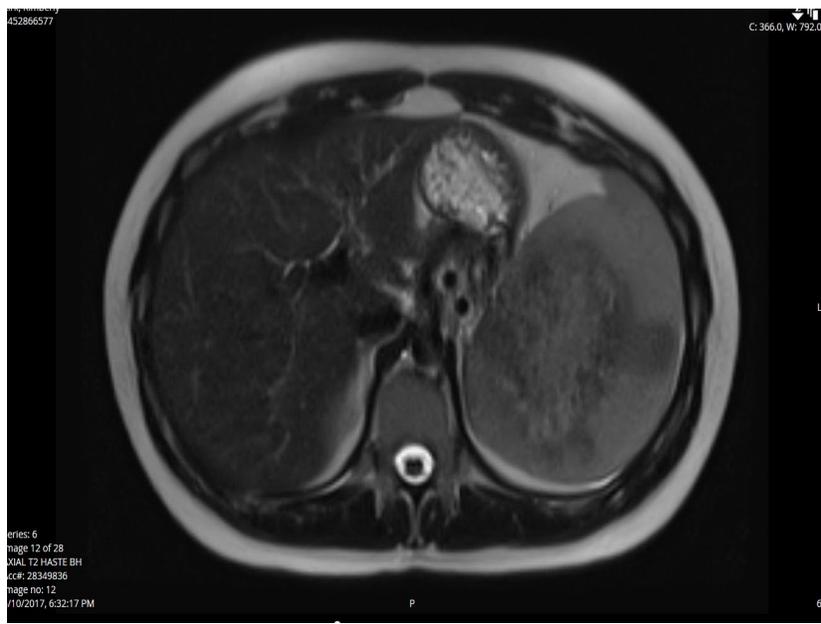
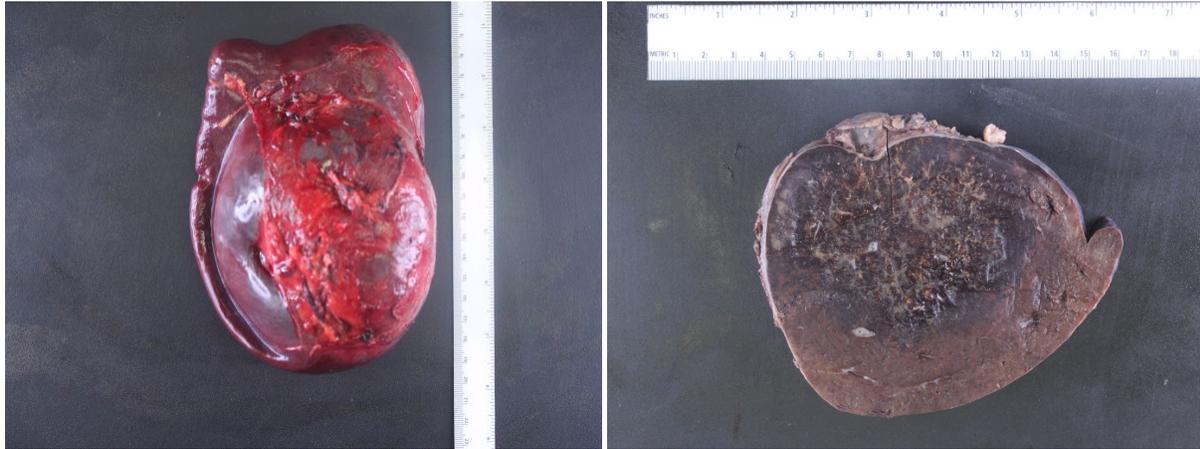
The tufts of cells are CD 31 and ERG positive (strong and diffuse). Negative for all else!

Gamna-Gandy bodies are also present in the intervening parenchyma.

Diagnosis: The mass lesion is a lobular hemangioma but the tufts of endothelial cells (which appear intravascular) are more complex.

Comment: The case was sent to Dr Chris Fletcher whose comment reads as follows: "The findings do not fit into any presently defined entity. While no overt features of malignancy are identified, the lesion would be best characterized as an ATYPICAL ENDOTHELIAL NEOPLASM, with an uncertain biologic potential. Close surveillance is recommended".

Has anybody seen anything like this?



AMR Seminar #72

Case – 2

Contributed by: Fredrik Petersson, M.D.

Clinical History and Gross Features: The patient is a 58 year old male who noted a painless lump in the neck. US showed several bilateral thyroid nodules; one dominant nodule was a 5 cm, heterogeneously hypoechoic solid largely replacing most of the left lobe and a 1.6 cm heterogeneously hypoechoic solid nodule in the isthmus and a 2.3 cm nodule in the right lobe, also heterogeneously hypoechoic and solid. No enlarged or sonographically suspicious cervical lymph nodes were seen. FNA was done and reported as PTC on the right side and suspicious for PTC on the left side. A total thyroidectomy + central neck dissection was performed. Cut sections of the left lobe showed a large, whitish rubbery tumour, measuring 5.0 x 3.0 x 2.8 cm, largely replacing the entire lobe (Fig. 1). (Cut sections of the right lobe showed a hard nodule measuring 1.9 x 1.5 x 1.0 cm, located in the superior pole and abutting the superior margin. Few other small whitish nodules were seen in the mid-pole.)

Histology: The submitted section is from the tumour in the left lobe. The tumour is unencapsulated and composed of nests of neoplastic cells with a predominantly follicular architecture interspersed within an abundant nodular fasciitis-/fibromatosis-like stromal background. The epithelial component consists of cuboidal or columnar cells with enlarged, crowded, oval, optically-clear nuclei with prominent nuclear grooves and occasional intranuclear inclusions. Tumour nests are separated by extensive stromal areas that contain spindled to stellate cells in a fibromyxoid background. In some areas, the stroma appears more cellular with parallel arrangements of myofibroblast-like cells, resembling fibromatosis. The stromal component comprises approximately 70-75% of the tumour volume.

After the histopathological diagnosis had been established, I went back to see the FNA-slides and there was some stromal tissue sampled occurring together with neoplastic epithelial cells (Fig 2).

Immunohistochemistry: B-catenin IHC showed mostly granular cytoplasmic expression in the stromal component; with no definite nuclear expression. The thyroid follicular cells exhibited membranous and granular cytoplasmic staining. There was variable, but significant expression of SMA with a nice myofibroblast-type tram-track cytoplasmic pattern.

Diagnosis and Comments: The tumour is a *papillary thyroid carcinoma with exuberant nodular fasciitis-/fibromatosis-like stroma*.

(LVI was present as well as extrathyroidal extension and positive margin. [The 1.9 cm tumour in the right lobe was a classical PTC and in addition several microcarcinomas were identified. 5/7 lymph nodes were involved by metastatic carcinoma - largest metastatic focus 0.4 cm and contained no stromal component.])

Papillary thyroid carcinoma with nodular fasciitis- or fibromatosis-like stroma was described for the first time by Ostrowski et al in 1989¹ (as "Myxomatous change in papillary carcinoma of thyroid") and by Chan et al² (as "Papillary thyroid carcinoma with exuberant nodular fasciitis-like stroma"). It is a very uncommon tumour (0.5% of all papillary thyroid carcinomas in the series by Chan et al and 0.17% in the series by Mizukami et al.³ In a recent report on two cases from two European institutions⁴, these two cases were the only ones they could identify in their archives, constituting 0.03% and 0.04% of all thyroid malignancies and of all PTCs, respectively.

According to the WHO book, tumours with nodular fasciitis- or fibromatosis-like stroma constitute two ends on a spectrum of one single nosological entity. (In our case some areas displayed a more fasciitis-like appearance while other areas were more fibromatosis-like.)

The great majority of the just under 30 cases that have been published have contained a clear predominance of the mesenchymal/stromal component over the epithelial component (usually >80% of the former and correspondingly <20% of the latter). The bulk of the tumour is thus represented by mesenchymal cells; fibroblasts/myofibroblasts. In three out of 14 studies I have gone through, there was reported an aberrant immunohistochemical expression of β -catenin in the nucleus and cytoplasm of the mesenchymal cells. In the study referred to above⁴, two cases were reported where the epithelial component carried a BRAF V600E mutation and the stromal component an activating CTNNB1 mutation in the mesenchymal component. (Based on these findings, the authors proposed the term "papillary thyroid carcinoma with desmoid-type fibromatosis" for such tumours.) The authors identified cytoplasmic and nuclear accumulation of β -catenin in their cases. We also performed IHC for β -catenin in our case and I must say that assessment for nuclear β -catenin accumulation is in my experience very challenging. This is partly due to the facts that the very slender myofibroblasts may have only their cytoplasm represented on the actual section and that the cytoplasm peripheral to the nucleus may acquire a shape that very closely mimics that of the elongated nucleus of a myofibroblast. This is conjunction with that any significant amount of true nuclear immunopositivity most often obscures or "overrides" the background tissue stain which adds to the difficulty. In addition, I have often encountered what I perceive to be overinterpretation of faint blushing of nuclear "stain/ immunopositivity" in a cell with strong and thus real cytoplasmic as nuclear accumulation, i.e. positivity. It would be interesting to hear the views of the members on this somewhat mundane, but far from irrelevant issue.

If there is any prognostic difference related to this type of PTC is hard to ascertain given the very limited number of cases and small series. What seems established though is that it is only the epithelial component that can metastasize. This was also true in our case. Whether the stromal component may recur locally or not is not very clear to me, i.e. does the nodular fasciitis-/ fibromatosis-like stroma have a significant potential for locally aggressive growth and/or local recurrence akin to bona fide fibromatosis.

The etiology/etiologies to the stromal component is not well studied. Based on the two cases mentioned above, activating CTNNB1 mutations appear to be one possibility. In addition, one previous report has demonstrated immunoreactivity of the stromal cells to transforming growth factor-beta, a cytokine known to induce scarring and activation of myofibroblasts.⁵ From a differential diagnostic point of view, especially based on FNA where a predominance of stromal is sampled the fibrous variant of Hashimoto thyroiditis and Riedel thyroiditis and low-grade mesenchymal tumours which may arise in the thyroid gland could be considered. Once the tumour is resected and the epithelial component can be assessed, the diagnosis should be straight forward.

Figures

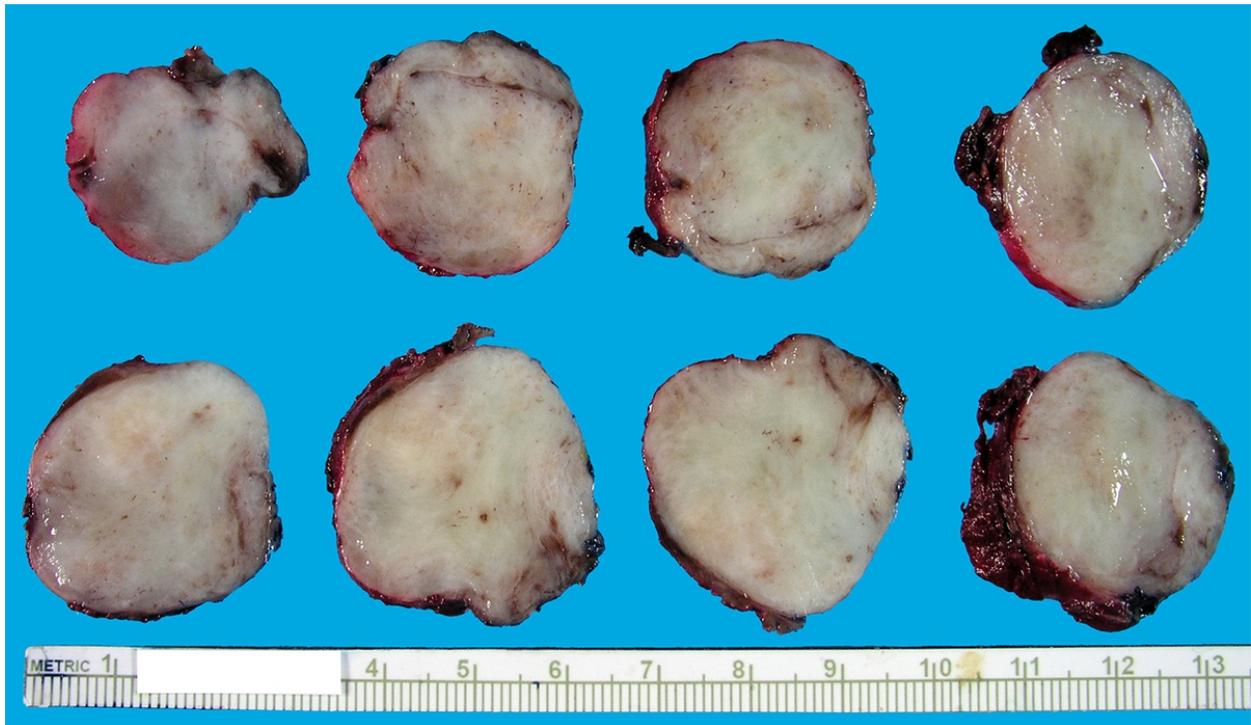


Figure 1. Cut sections of the PTC with nodular fasciitis-/fibromatosis-like stroma show a large, whitish rubbery tumour, measuring 5.0 x 3.0 x 2.8 cm, largely replacing the entire lobe.

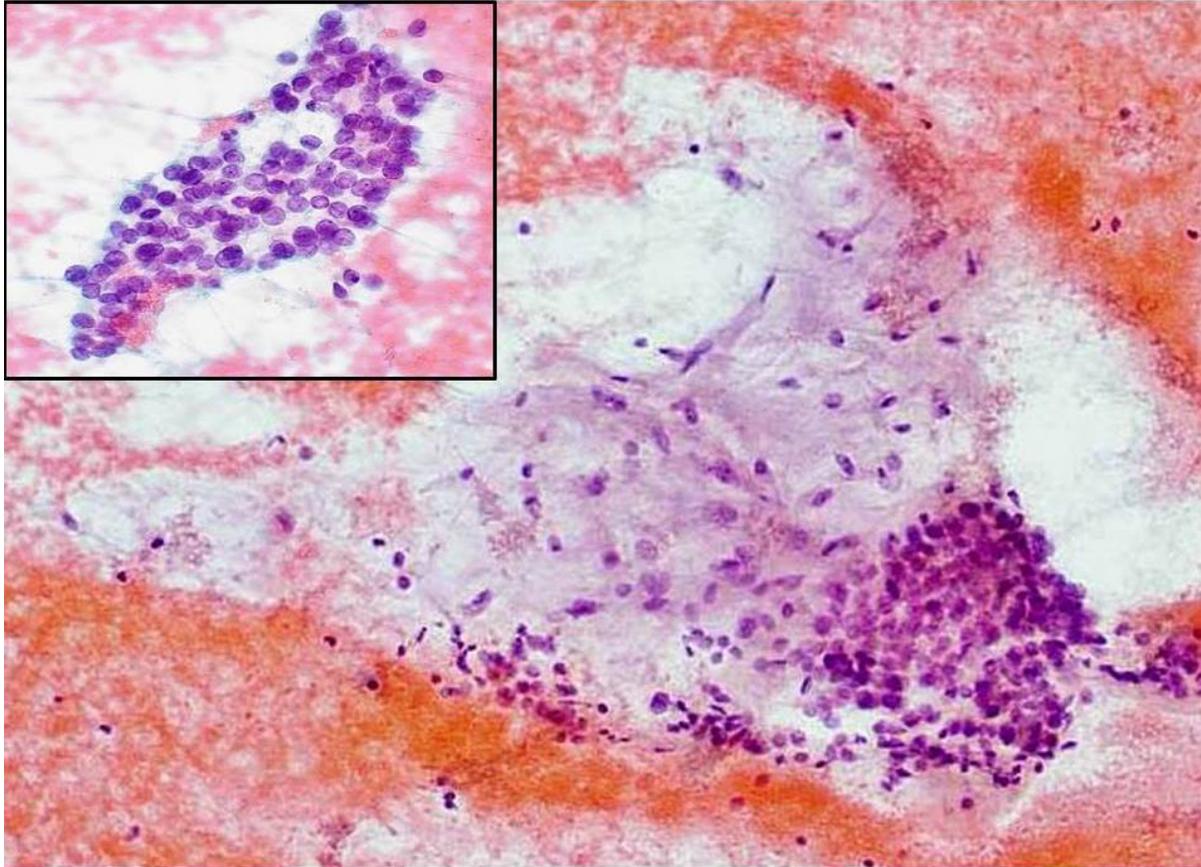


Figure 2. FNA from the PTC with nodular fasciitis-/fibromatosis-like stroma showing neoplastic epithelial cells occurring together with the stromal component.

References:

1. MA O, FL M, SL A: Myxomatous change in papillary carcinoma of thyroid. *Surg pathol* 1989, 2:249-56.
2. Chan JK, Carcangiu ML, Rosai J: Papillary carcinoma of thyroid with exuberant nodular fasciitis-like stroma. Report of three cases. *American journal of clinical pathology* 1991, 95:309-14.
3. Mizukami Y, Kurumaya H, Kitagawa T, Minato H, Nonomura A, Michigishi T, Noguchi M: Papillary carcinoma of the thyroid gland with fibromatosis-like stroma: a case report and review of the literature. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 1995, 8:366-70.
4. Rebecchini C, Nobile A, Piana S, Sarro R, Bisig B, Gerasimos SP, Saglietti C, Matter M, Marino L, Bongiovanni M: Papillary thyroid carcinoma with nodular fasciitis-like stroma and beta-catenin mutations should be renamed papillary thyroid carcinoma with desmoid-type fibromatosis. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2017, 30:236-45.
5. Toti P, Tanganelli P, Schurfeld K, Stumpo M, Barbagli L, Vatti R, Luzi P: Scarring in papillary carcinoma of the thyroid: report of two new cases with exuberant nodular fasciitis-like stroma. *Histopathology* 1999, 35:418-22.

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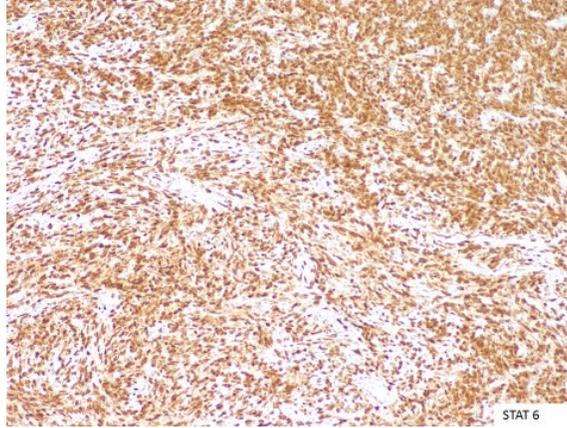
Case – 3

Contributed by: Murray Resnick, M.D.

Clinical history: This 14cm kidney tumor was resected from a 79 year old male. Grossly this was a well circumscribed firm to rubbery, tan/brown mass with central necrosis. The tumor was confined to the kidney and nearly replaced the entire parenchyma leaving a small rim of residual normal kidney seen in the figure below



Pathological Findings: The diagnosis of solitary fibrous tumor was made based on the characteristic morphologic features of a spindle tumor with alternating hypo- and hypocellular regions, a “patternless pattern” and “staghorn” vessels. The tumor cells stained strongly for STAT 6 (figure bellow), BCL-2 and CD99 and focally for CD34.



Based on the patients age (>55yr) tumor size of 14cm, mitotic count of 4 per 10 HPF, and tumor necrosis of greater than 10% the tumor has a high risk of metastasis, 73% risk of metastasis at 5 years (Table 1) (1).

Table 3 Modified four-variable risk stratification model for development of metastasis in solitary fibrous tumors

Risk factor	Score
Age	
< 55	0
≥ 55	1
Tumor size (cm)	
< 5	0
5 to < 10	1
10 to < 15	2
≥ 15	3
Mitotic count /10 high-power fields)	
0	0
1-3	1
≥ 4	2
Tumor necrosis	
< 10%	0
≥ 10%	1
Risk class	
Low	0-3
Intermediate	4-5
High	6-7

Diagnosis: Primary solitary fibrous tumor of the kidney.

Comment: Solitary fibrous tumors of the kidney are relatively rare with less than 50 cases reported (2-3). The differential diagnosis of renal SFT includes both benign and malignant spindle cell tumors including leiomyoma, leiomyosarcoma, schwannoma, synovial sarcoma, sarcomatoid renal cell carcinoma among other rarer entities. SFTs with aggressive clinical behavior (as seen here) have been described in up to 20% of all renal SFTs (4). The presence of fusions between *NAB2* and *STAT6* genes on chromosome 12q13 have been reported in the majority of SFTs and strong immunohistochemistry for STAT6 is considered a reliable surrogate marker for this fusion (5). Creytens (6) recently commented on the danger of confusing a retroperitoneal dedifferentiated liposarcoma, (which may be STAT6 positive (7)) with SFTs in the retroperitoneum or retroperitoneal organs. This issue would be especially relevant for needle biopsies. This is not a factor in this specific case based on the gross pathology and broader immunohistochemical profile.

References:

1. Demicco EG et al. Solitary fibrous tumor: A clinicopathologic study of 110 cases and proposed risk assesment mode. *Mod Pathol* 2012 25: 1298-306.
2. Kuroda N et al. Solitary fibrous tumor of the kidney with focus on clinical and pathological aspects. *Int J Exp Pathol* 2014 7: 2737-42.
3. Yang Y et al. Malignant solitary fibrous tumor of the kidney with lymph node and liver metastases. *Pathology* 2017 49:450-3.
4. Fine SW et al. Malignant solitary fibrous tumor of the kidney: report of a case and comprehensive review of the literature. *Arch Pathol Lab Med* 2006 130: 857-61.
5. Cheah AL et al. STAT6 rabbit monoclonal antibody is a robust diagnostic tool for the distinction of solitary fibrous tumor. *Pathology* 2014 46: 389-85.
6. Creytens D. Malignant solitary fibrous tumor of the kidney with lymph node and liver metastases: beware of STAT6 expression in dedifferentiated liposarcoma with a solitary fibrous tumor-like morphology. *Pathology* 2017 49:671.
7. Doyle LA et al. STAT6 is amplified in a subset of dedifferentiated liposarcoma. *Mod Pathol* 2014 27:1231-37.

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Case – 4

Contributed by: Ady Yosepovich, M.D.

Clinical History: A 64 YO male presented with 1 CM left breast palpable mass.

Pathologic findings: CNB – spindle cell lesion, excisional biopsy was performed.

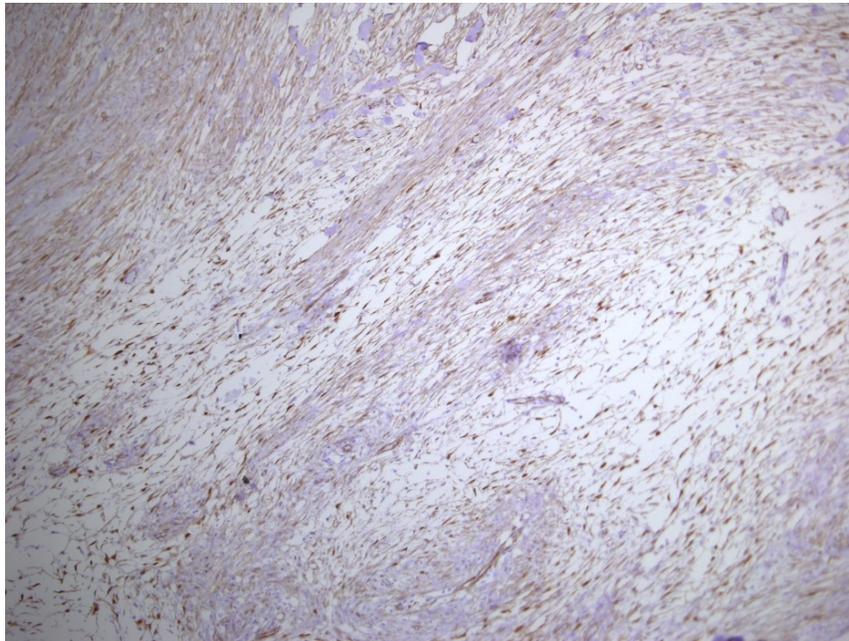
Histological evaluation demonstrated an irregular lesion which tended to infiltrate the surrounding tissue. The proliferation consists of elongated, slender, spindle-shaped cells of uniform appearance surrounded and separated from one another by abundant collagen. Keloid-like collagen fibers or extensive hyalinization is present.

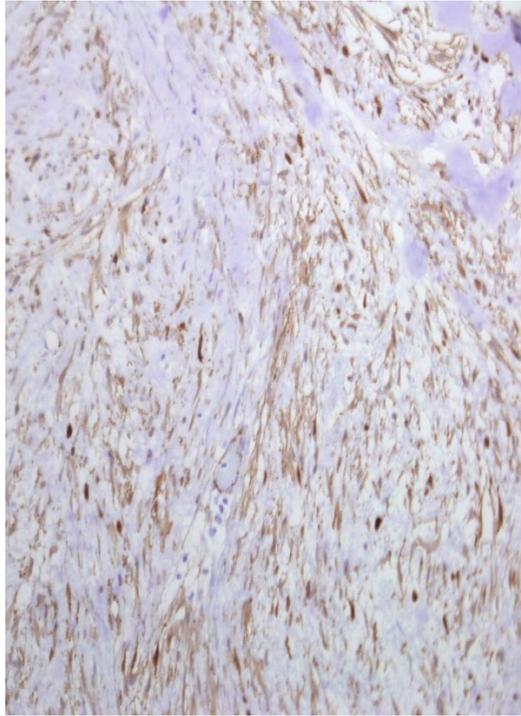
Normal breast tissue is not present on this slide but is present in other slides.

Keratin stains were negative.

Immunostain for Beta catenin was positive in nuclei of the proliferating cells.

Betta catenin stain:





Diagnosis: fibromatosis of the male breast

Comment: There are only few case reports of fibromatosis in the male breast, this is the first one that I saw (I do hope this is the correct diagnosis...) actually, looks like a scar but the nuclear positivity for beta catenin is convincing, no history of prior surgery or trauma.

The excision was not complete; the surgeons choose just to follow up.

Just wanted to share this, and to get your comments.

AMR Seminar #73

Case – 5

Contributed by: Barbara Gazić, M.D., Ph.D. (courtesy of Dr. G. Gasljevic and Dr. S. Gasparov)

Case History: A 49 year -old female presented with a slowly growing tumor in the left breast.

Pathologic findings: The tumor has a leaf-like appearance, created by projections of tumor stroma into epithelium-lined cystic spaces. Most of the stromal component is paucicellular to moderately cellular with spindle and stellate cells in an abundant myxoid matrix with very distinct C1Jrvilinear vessels and some scattered multivacuolated pseudo lipoblasts.

Final diagnosis: Malignant phyllodes tumor with myxofibrosarcoma-like heterologous differentiation.

Comment: Phyllodes tumors (PT) are rare fibroepithelial malignancies of the breast, accounting for less than 1% of malignant breast tumors. Extremely rarely heterologous sarcomatous differentiation can occur within the stromal component of PT in the form of a chondrosarcoma, osteosarcoma or liposarcoma. There are only few cases of PT with myxofibrosarcoma-like heterologous differentiation reported in the literature and most of them have been reported as myxofibrosarcoma or "malignant fibrous histiocytoma" of the breast.

References:

1. Dyer N.H., Bridger J.E., Taylor R.S. Cystosarcoma phylloides. Br. J. Surg.1966: 450-455.
2. Guerrero M.A., Ballard B.R., Grau A.M. Malignant phyllodes tumor of the breast: review of the literature and case report of stromal overgrowth. Surg. Oncol. 2003: 27-37
3. Hocevar M. Phoar Marinsek Z. Zidar A. Myxofibrosarcoma of the breast as an unusual variant of malignant fibrous histiocytoma: Report of a case. Surg Today. 2004:752-754
4. Nili F. Asadinejad E. Saffar H, Ghanadan A. Myxofibrosarcoma of the breast in a young pregnant woman: A case report and review of the literature. MEJC. 2017:57-62.

AMR Seminar #73

Case – 6

Contributed by: Ondrej Hes, M.D., Ph.D.

Clinical History: 67-year-old patient with prominent exophytic tumor in urinary bladder. Patient was followed for urothelial carcinoma of urinary bladder out of our institution. Because of local progression, he was submitted to our hospital. During routine work up, elevated PSA level was detected. Material is TUR.

Pathology: Tumor showed combined, mostly exophytic architectural growth pattern: pseudo-papillary, nested and cribriform. Voluminous tumor necrosis was not found. No sarcomatoid differentiation was noted.

The neoplastic cells showed CK7-/CK20-/GATA3- immunoprofile. Tumor was positive for PSA, PAP, and NKX3.1. We further examined TERT promoter mutation in our case, no mutation was disclosed.

Diagnosis: High-grade prostatic adenocarcinoma mimicking urothelial carcinoma

Comments: High-grade prostatic adenocarcinoma mimicking urothelial carcinoma (UC) was first described by Mai et al. in 2002, as an uncommon and rare type of adenocarcinoma of the prostate. Gordetsky and Epstein further described this entity in greater detail. These tumors are typically poorly differentiated with papillary structures containing central blood vessels, and demonstrate subtle gland-like formation resembling rosettes. The nuclei are usually pleomorphic, large, irregular and hyperchromatic, and the cells contain delicate pale cytoplasm.

Gordetsky in her series described pseudopapillary features in prostatic adenocarcinoma resembling UC. She further showed that the presence of pseudopapillary features in high-grade prostate adenocarcinoma represents a newly recognized morphology that overlaps with UC. This in turn can lead to diagnostic difficulties in distinguishing between a poorly-differentiated UC and a high-grade prostatic adenocarcinoma. This distinction is particularly important clinically because the treatment of these types of carcinomas requires different surgical and oncological therapeutic strategies, which rests on establishing a correct diagnosis in this setting.

In 2004, Pacchioni et al. described a case of large prostatic duct carcinoma showing a combination of both prostatic duct adenocarcinoma and high-grade urothelial carcinoma (UC). The authors concluded that this was a combined/mixed prostatic/urothelial carcinoma. However, it is possible to speculate, that their case was the same type of high grade prostatic carcinoma showed here.

We have paper accepted in Applied Immunohistochemistry and Molecular Morphology describing cohort of 10 such tumors. Tumor samples for our study were obtained mostly by transurethral resections (9/10 cases), and some cases indeed had uncertain clinical working diagnosis (urothelial versus prostatic origin), because of the tumoral mass in the urinary bladder. All tumors were also high-grade, mostly poorly differentiated, with solid and focally pseudopapillary growth, similar to the previously reported cases. They were positive for prostatic immunohistochemical markers (NKX3.1, PSA, and PAP), negative for urothelial immunostains. However the interpretation of PSA and PAP may not be straightforward, and may be quite challenging.

Differential diagnosis: 1) urothelial high-grade papillary urothelial carcinoma

Usually prostate adenocarcinomas have more uniform cytology, as opposed to the greater pleomorphism seen in UC. However, uncommonly prostate adenocarcinoma can show pleomorphic features overlapping with UC. The presence of micro-acinar or cribriform pattern suggesting glandular differentiation or presence of areas of well-differentiated prostatic carcinoma may aid to establish a diagnosis of prostatic adenocarcinoma. Immunohistochemically, a panel of prostatic markers such as NKX3.1, PSA, and PAP immunostains may further clarify the diagnosis. However, a panel including GATA3, CK7/CK20, p63 and high-molecular cytokeratin may be inconclusive and may create dilemmas regarding the final diagnosis, as they can be expressed in both prostatic adenocarcinoma (less often) and urothelial carcinoma. TERT promotor mutation is frequently noticed in high grade UCs and analysis can be useful diagnostic tool. None of the High-grade prostatic adenocarcinoma mimicking urothelial carcinoma cases from our above-mentioned series harbored TERT promotor mutation.

2) Metastasis

Depending on clinical and radiologic findings, further immunohistochemical stains may need to be utilized to exclude secondary metastasis.

References:

1. Mai KT, Collins JP, Veinot JP. Prostatic adenocarcinoma with urothelial (transitional cell) carcinoma features. *Appl Immunohistochem Mol Morphol*. 2002;10(3):231-6.
2. Gordetsky J, Epstein JI. Pseudopapillary features in prostatic adenocarcinoma mimicking urothelial carcinoma: a diagnostic pitfall. *Am J Surg Pathol*. 2014;38(7):941-5.
3. Wu XR. Urothelial tumorigenesis: a tale of divergent pathways. *Nat Rev Cancer*. 2005;5(9):713-25.
4. Zheng X, Zhuge J, Bezerra SM, Faraj SF, Munari E, Fallon JT, 3rd, et al. High frequency of TERT promoter mutation in small cell carcinoma of bladder, but not in small cell carcinoma of other origins. *J Hematol Oncol*. 2014;7:47.
5. Wu S, Huang P, Li C, Huang Y, Li X, Wang Y, et al. Telomerase reverse transcriptase gene promoter mutations help discern the origin of urogenital tumors: a genomic and molecular study. *Eur Urol*. 2014;65(2):274-7.
6. Pacchioni D, Casetta G, Piovano M, Fraire F, Volante M, Sapino A, et al. Prostatic duct carcinoma with combined prostatic duct adenocarcinoma and urothelial carcinoma features: report of a case. *Int J Surg Pathol*. 2004;12(3):293-7.

AMR Seminar #73

Case – 7

Contributed by: Kenneth Schoolmeester, M.D.

Clinical History: A 7-year-old girl presented with right-sided vulvar swelling four months in duration. Imaging identified an approximately 3.5 cm fibrous lesion with infiltrative features. The patient underwent resection of the lesion.

Microscopic Findings: Sections show a poorly defined and sparsely cellular fibrous process involving dermis and subcutis. The cells are spindle, uniformly cytologically bland and coarse between lobules of adipose tissue, blood vessels and nerves. Collagen fibers are present as well as parallel, streaming elastic fibers that are best identified by VVG stain.

Histochemical and Immunohistochemical Stain Results: VVG highlighted scattered elastic fibers. CD34 and ER were diffusely and strongly positive. PR, SMA, Desmin and S100p were negative.

Diagnosis: Childhood asymmetric labium majus enlargement.

Comment: This lesion is thought to be a physiologic response to hormonal stimuli of pre- and early puberty. A study in 2005 evaluated histologic, electron microscopic, cytogenetic and comparative age-matched autopsy findings in 14 cases and deemed the lesion non-neoplastic and a disproportionate response to hormonal surges. Other studies of clinically similar fibrous lesions of childhood registered as different names (prepubertal unilateral fibrous hyperplasia of the labium majus) also favored a non-neoplastic, hormonally driven etiology despite sometimes concerning clinical and imaging findings.

References:

1. Vargas SO et al. Childhood asymmetric labium majus enlargement: mimicking a neoplasm. Am J Surg Pathol. 2005;29(8):1007-16.
2. Altchek A et al. Prepubertal unilateral fibrous hyperplasia of the labium majus: report of eight cases and review of the literature. Obstet Gynecol. 2007;110(1):103-8.

AMR Seminar #73

Case – 8

Contributed by: Cyril Fisher, M.D.

Clinical History: An 83 year-old female felt that she had an abdominal mass. Imaging showed a 12 x 12 x 9.8 cm non-fatty heterogeneous anterior abdominal mass adherent to the transverse colon. The tumor was resected from the colonic mesentery with transverse colectomy. No other tumors were evident.

Pathologic features: Macroscopically this was a solid tan tumor within the mesocolon. Microscopy showed a multilobulated neoplasm focally infiltrating the colonic wall. The tumor was composed of hyper- and hypo cellular areas of whorled and fascicular distributions of cells with ovoid, even chromatin and indistinct cytoplasm with only minimal nuclear atypia, within fibromyxoid or hyaline stroma. The mitotic index was 4/10 HPF, and there was focal necrosis. The tumor was admixed with scattered variably-sized collagen rosettes, composed of acellular eosinophilic collagenous tissue with a surrounding cuff of rounded neoplastic cells.

With immunohistochemistry, the tumor cells were positive for desmin, smooth muscle actin and CD10, with scanty focal positivity for h-caldesmon. About 75% of tumor nuclei showed moderate to strong PgR and weak to moderate ER expression. MUC4, myogenin, CD117, DOG1, CD34, epithelial membrane antigen, AE1/AE3, S100 protein, HMB45, MelanA and CD99 were negative. *JAZF1-SUZ12* fusion transcripts were detected by RT-PCR.

Diagnosis: Endometrial stromal sarcoma with hyalinizing rosettes

Comment: Hyalinizing 'giant' rosettes, or nodules with central hyalinization, are rarely described in endometrial stromal sarcoma,^{1,2} and notably in endometrial stromal neoplasms with at least immunophenotypic smooth muscle differentiation as in this case.^{3,4} They can appear similar to the collagenous rosettes seen in some low-grade fibromyxoid sarcomas (LGFMS), characterized initially as hyalinizing spindle cell tumor with giant rosettes, but subsequently shown to be identical to LGFMS.^{5,6} Although usually less cellular and more spindled than endometrial stromal sarcoma, LGFMS can occasionally have increased cellularity, or have focal epithelioid morphology as in hybrid forms with the related sclerosing epithelioid fibrosarcoma. MUC4 is a highly sensitive immunohistochemical marker of LGFMS, and its absence effectively excludes this diagnosis⁷, as does a smooth muscle immunophenotype. The demonstration of the *JAZF1-SUZ12* fusion is of course diagnostic of endometrial stromal sarcoma. Endometrial stromal sarcoma in this location could arise from endometriosis, or as metastatic disease. It emerged that the patient had a hysterectomy 40 years previously for 'benign pathology', material from which was not available for review. Conceivably, this is a late-developing solitary metastasis.

References:

1. Dundr P, Fischerova D, Povysil C, et al. Myxoid mixed low-grade endometrial stromal sarcoma and smooth muscle tumor of the uterus. Case report. *Cesk Patol.* 2012;48:103-106.
2. Cady FM, Kuhn E, Holt JB. Endometrial stromal sarcoma with hyalinizing giant rosettes and separate leiomyoma with palisading nuclei in the same uterus. *Int J Surg Pathol.* 2006;14:326-327.
3. Evans HL. Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. *Cancer.* 1982;50:2170-2182.
4. Oliva E, Clement PB, Young RH, Scully RE. Mixed endometrial stromal and smooth muscle tumors of the uterus: a clinicopathologic study of 15 cases. *Am J Surg Pathol.* 1998;22:997-1005.

5. Folpe AL, Lane KL, Paull G, Weiss SW. Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes: a clinicopathologic study of 73 cases supporting their identity and assessing the impact of high-grade areas. *Am J Surg Pathol* 2000; 24:1353-1360.
6. Reid R, de Silva MVC, Paterson L, Ryan E, Fisher C. Low grade fibromyxoid sarcoma and hyalinizing spindle cell tumour with giant rosettes share a common t(7;16)(q34:p11) translocation. *Am J Surg Pathol* 2003; 27: 1229-1236.
7. Doyle LA, Moller E, Dal Cin P, Fletcher CD, Mertens F, Hornick JL. MUC4 is a highly sensitive and specific marker for low-grade fibromyxoid sarcoma. *Am J Surg Pathol*. 2011;35:733-741.

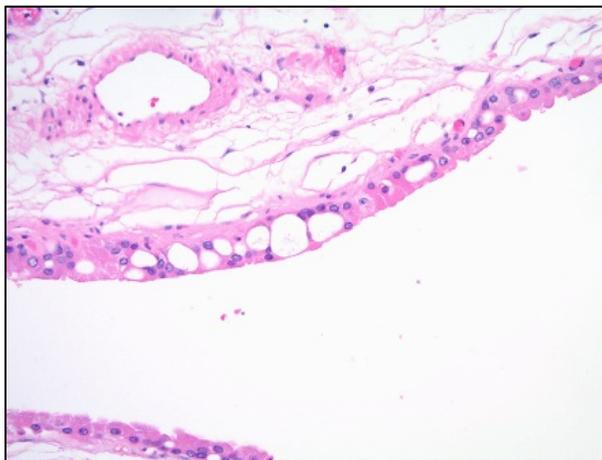
AMR Seminar #73

Case – 9

Contributed by: Jesse K. McKenney, M.D.

Clinical History: The patient is a 65-year-old man with a history of end stage kidney disease on dialysis, who presented with a cystic renal mass by imaging surveillance and underwent nephrectomy.

Histologic findings: Histologically, the kidney showed a type 1 papillary renal cell carcinoma (not shown), numerous cortical cysts, and the multicystic mass lesion represented by the enclosed slide. This cystic mass lesion was characterized by numerous back-to-back cysts of varying caliber lined by atypical epithelial cells with prominent eosinophilic cytoplasm. In rare foci, the lining cells had cytoplasmic vacuolization creating a sieve-like pattern (image below).



Diagnosis: "Acquired cystic disease-associated renal cell carcinoma-like cyst"

Comment: This patient had a clinical diagnosis of acquired cystic kidney disease secondary to dialysis. The current cystic lesion had histologic features of what has been described in the literature under the term "acquired cystic disease-associated renal cell carcinoma-like cyst". While this likely represents a continuum, it has been suggested that at least some solid nodular growth within the cyst is required for diagnosis as a renal cell carcinoma of the "acquired cystic disease-associated subtype". In our experience, that distinction can be somewhat subjective in a subset of cases. These cysts have significant histologic overlap with the tubulocystic variant of renal cell carcinoma, but those should lack the background acquired cystic changes and the sieve-like vacuolization that was present at least focally in this case.

References:

1. Tickoo SK, Gopalan A, Tu JJ, et al. Spectrum of epithelial neoplasms in end-stage kidney disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic renal neoplasia. *Am J Surg Pathol* 2006;30(2):141-53
2. Przybycin CG, Harper HL, Reynolds et al. Acquired cystic disease-associated renal cell carcinoma: a multi-institutional study of 40 cases with clinical follow-up. *Am J Surg Pathol* 2018; 42(9):1156-1165.
3. Sun Y, Argani P, Tickoo SK, Epstein JI. Acquired cystic disease-associated renal cell carcinoma-like cysts. *Am J Surg Pathol* 2018 (Epub ahead of print)

AMR Seminar #73

Case – 10

Contributed by : Dr. J. Forteza Vila (Valencia)

Clinical history : A 52-year-old man with weight loss (3.5 kg), mesenteric and retroperitoneal adenopathies.

He was admitted in hospital for fever and neutropenia with autoimmune hemolytic anemia.

In a bone marrow smear, there is an absence of a mature myeloid series and atypical infiltration of lymphoid forms, although mature in appearance.

In the Flow Cytometry of the bone marrow aspirate, the following data was obtained:

- erythroid series (1%),
- monocyte series (2%),
- lymphoid series (15.60%),
- myeloid series (68.1%) and
- blasts CD11b - / HLA-DR + / CD34 + / CD117 + (0.1%).

Possible viremia for B119 parvovirus. Bacteremia, distributed shock and hemophagocytic syndrome.

The patient, being in the ICU, stabilizes, remits neutropenia.

The patient undergoes a septic shock with hemolytic anemia and antiparvovirus antibodies, but it evolves well and sells from the ICU. In the last days of ICU, bone marrow biopsy and lymph node biopsy were carried out.

Pathology:

Bone marrow

Aplastic with neutropenia and hemophagocytosis.

Nuclear and cytoplasmic vacuoles compatible with parvovirus infection.

The patient has a lymphoid proliferation that infiltrates superficially the bone marrow, which shows the hemophagocytic syndrome.

Lymph nodes

Polymorphic lymphoid proliferation, large lymphoid cells, atypia and alterations in modulation.

Evolution : In the course of the evolution, and when the patient left the ICU, he remitted the haemophagocytic syndrome, he remitted the neutropenia, as well as the clinical manifestations of the lymphoproliferative syndrome.

Diagnosis : Bone marrow aplasia, hemophagocytosis and lymphoproliferative syndrome.

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Case – 11

Contributed by: Markku Miettinen, M.D.

Clinical History: 56-year-old man with a chest wall mass and multiple bone fractures, attributed to oncogenic osteomalacia. A 6 cm mass from removed from right chest wall. The mass involved a rib and extended into soft tissue. Grossly it was cystic and hemorrhagic.

Diagnosis: Phosphaturic mesenchymal tumor

Discussion: This is an unusual, clinically very distinctive tumor. Tumor cells produce fibroblast growth factor 23, which promotes phosphate excretion. Tumors can be very small and difficult to found and they can involve either soft tissue or bone. The current tumor appears to be of rib bone origin, with a soft tissue component. Small tumors can be detected by special imaging techniques, such as octreotide scanning.

Histologically the tumors vary, but often contain hemangiopericytoma-like vascular element, small epithelioid cells remotely reminiscent of glomus tumor cells, and often focal cartilaginous differentiation, sometimes with calcification. The current case seems to be most consistent with the mixed connective tissue type of phosphaturic mesenchymal tumor. Mitotic activity and atypia are low. Many of these tumors contain FGF1- or FGFR1-involving gene fusions. Some tumors have recurred locally, but only few have metastasized.

Immunohistochemistry is non-specific. The current case had focal S100 expression in the cartilage-like areas, but was negative for CD34, desmin, HMB45, keratins AE1/AE3, and SMA. However, FGF23 expression has been thought of a disease marker, but this has not been widely validated.

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Case – 12

Contributed by: Saul Suster, M.D.

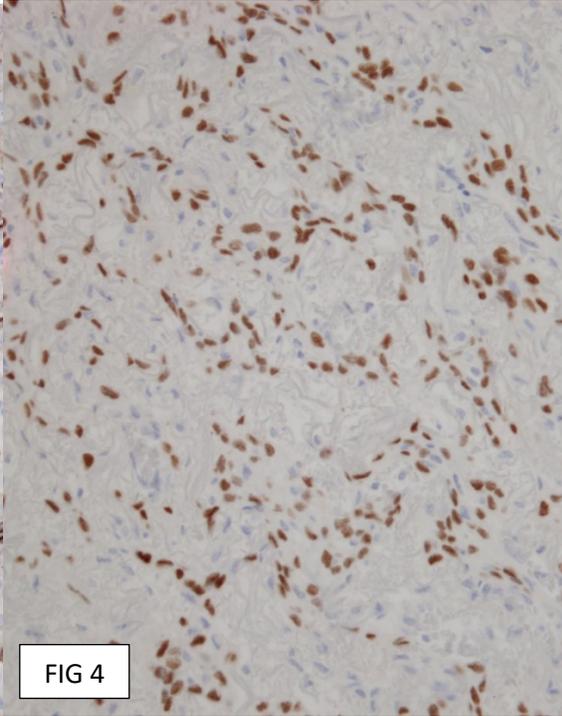
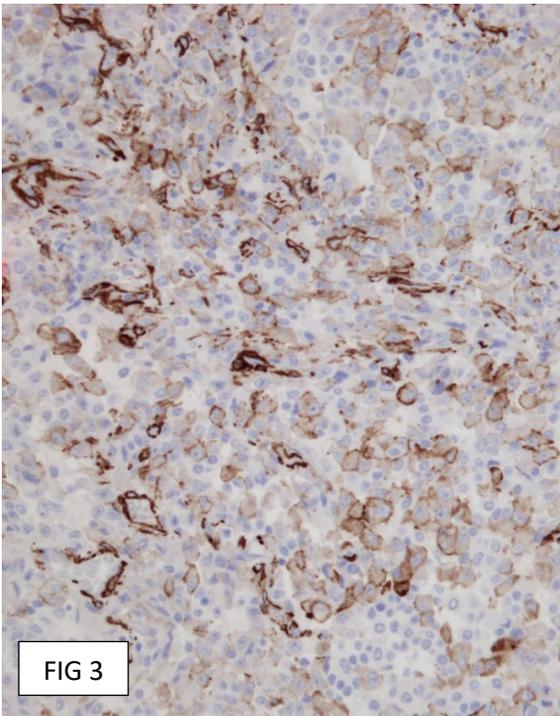
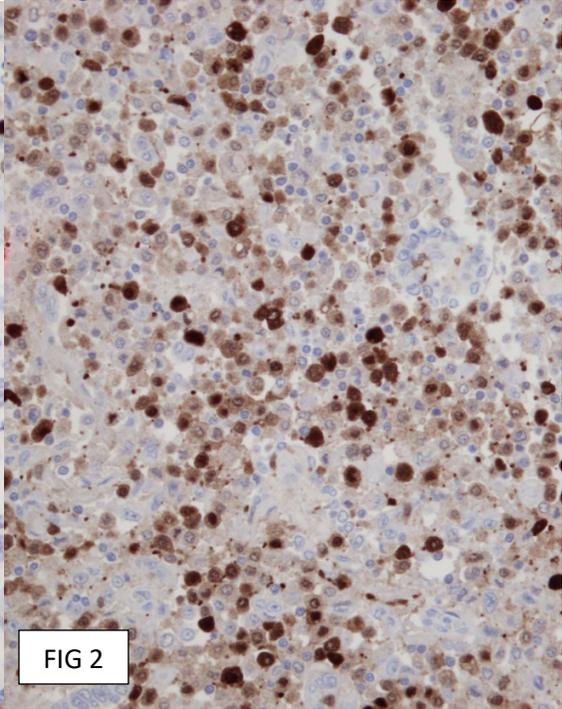
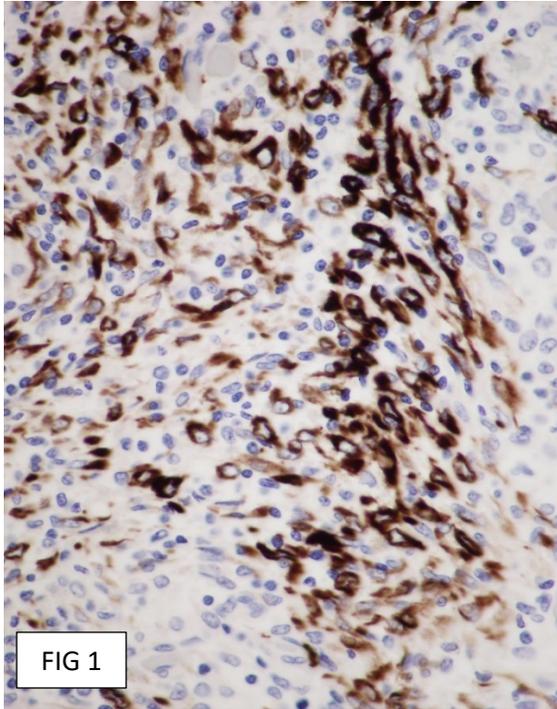
Case history: A 74 year old woman with a past history of smoking (quit 10 years ago) was seen for hemoptysis. She had no other significant history or evidence of tumor elsewhere. CT scans showed a 7 cm mass in his right upper lobe of lung. A transbronchial biopsy was done and diagnosed as a spindle cell carcinoma, consistent with sarcomatoid squamous cell carcinoma. A lobectomy with resection of the mass was undertaken. On cut section, a large mass measuring 8 cm. in greatest diameter composed of homogeneous, rubbery tan tissue was seen. The mass was 0.2 cm. from the pleural surface and 0.7 cm. from the bronchial resection margin.

Pathological Findings: the histology showed sheets of tumor cells with round to oval nuclei and abundant eosinophilic cytoplasm admixed with scattered inflammatory elements. Entrapped respiratory elements are also present at the periphery of the tumor. Focal nuclear pleomorphism with prominent nucleoli were also seen. Scattered mitotic figures, including abnormal mitoses were present. Immunohistochemical stains were positive for CK7 (Fig. 1) and showed convincing nuclear positivity for S-100 protein in the tumor cells (Fig. 2). The tumor cells also showed positive staining for caldesmon (Fig. 3), calponin and p63 (Fig. 4). Stains for CD10, CD21, CD35, TTF1, desmin and CD68 were negative. MIB-1 showed increase in proliferation index (>20% nuclear positivity).

Diagnosis: Myoepithelial carcinoma of lung.

Comment: This is the second case I see within a year. The case was submitted from a community hospital where a diagnosis of pleomorphic carcinoma with associated spindle cell component was being considered. Pleomorphic or spindle cell carcinomas of the lung tend to show more significant nuclear pleomorphism, extensive necrosis and high mitotic activity, which led to further investigation in this particular case. The immunophenotype is more in-keeping with a myoepithelial carcinoma than a high-grade pleomorphic carcinoma.

References: Rosen LE et al. Myoepithelial carcinoma of the lung: a review. Appl Immunohistochem Mol Morphol 23:397-401, 2015.



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Case – 13

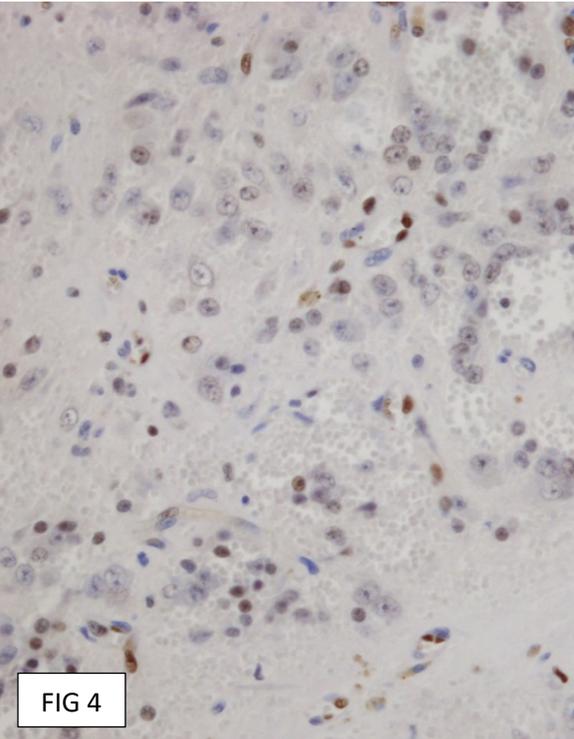
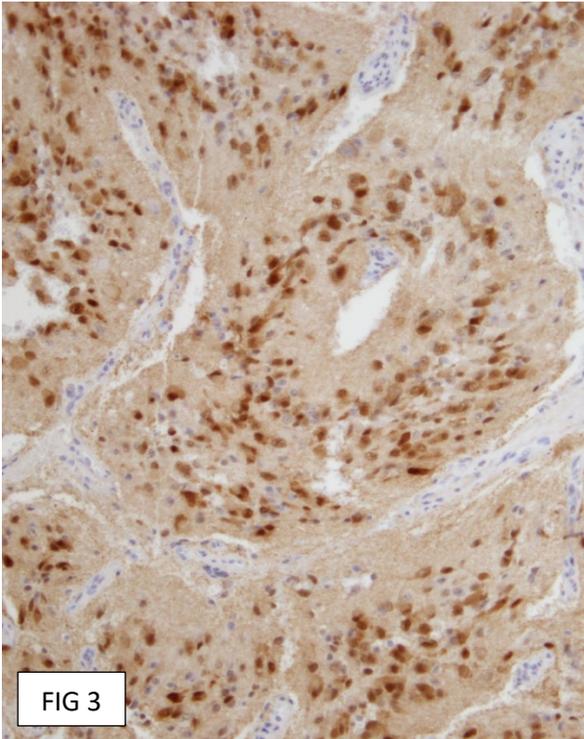
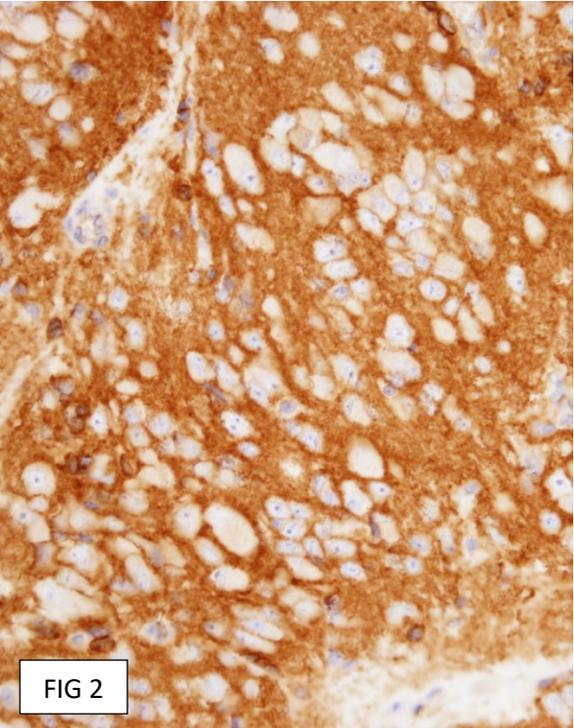
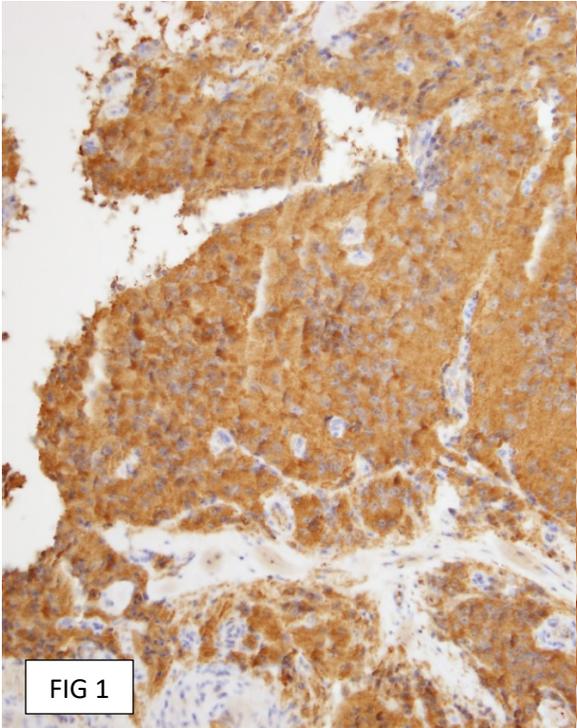
Contributed by: Saul Suster, M.D.

Clinical History: A 27 year old man with a history of treated Ewing's sarcoma of the femur was seen for a large intranasal mass. The mass (enclosed slides) was biopsied. At the time (9 years ago) the biopsy was interpreted as metastatic Ewing sarcoma. The tumor cells showed positive staining for NSE and synaptophysin. CD99 was equivocal and stained mostly the intercellular matrix, and FLI-1 was negative. A FISH assay showed split signals for EWSR1 in 40% of the cells. Based on the results of FISH, a diagnosis of metastatic Ewing sarcoma was favored.

Pathology: I came across this case by accident looking for small blue cell tumor of the nasopharynx and was intrigued by the histology, which is strikingly reminiscent of a differentiating neuroblastoma. I repeated the stains; NSE was strongly positive in all the tumor cells (Fig. 1); CD99 stained the intercellular matrix but not the tumor cell membranes (Fig. 2), and synaptophysin and CD56 showed an identical pattern of staining as CD99; Neu-N showed nuclear staining of the tumor cells (Fig. 3); and FLI-1 (Fig. 4) was negative in the tumor cells (only stained small nuclei of endothelial cells). Other stains including desmin, myogenin, keratin, S100, chromogranin and GFAP were negative.

Diagnosis: Ewing sarcoma vs. olfactory neuroblastoma.

Comments: I sent the case to Bruce Wenig for his opinion and he indicated he did not believe this was a metastasis from Ewing sarcoma/PNET, irrespective of the FISH results. Based on the lobular growth pattern he favors an olfactory neuroblastoma. He suggested reviewing the original slides of the Ewing tumor which we have been unable to locate so far. The histology really looks like a neuroblastoma to me, right down to the neuropil and scattered cells that seem to be displaying ganglionic differentiation. Has anyone seen a case like this before? Could this be olfactory neuroblastoma (lightning *can* strike twice!) with an unexpected EWSR1 translocation? We're discovering more and more non-Ewing tumors that can harbor this translocation; so, obviously EWRS1 does not represent a molecular "signature" for any particular entity and it is evidently not restricted to Ewing sarcoma. I would welcome any comments regarding how you would approach this case.



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Case – 14

Contributed by: Jason L. Hornick, M.D., Ph.D.

Clinical History: A 62-year-old man presented with small bowel obstruction and was found to have a large, circumferential mass in the ileum, which was resected.

Pathologic findings: The tumor involves the full-thickness of the bowel wall and is dominated by cells with rhabdoid cytomorphology; there is also an area of the tumor with a fascicular spindle cell appearance. Scattered pleomorphic and multinucleated cells are seen. Several lymph nodes contained metastatic tumor. By immunohistochemistry, a small subset of cells is positive for keratin 8 (CAM5.2); other keratins (and a large panel of many other markers) are negative. The tumor cells show loss of nuclear staining for SMARCA4 (BRG1). Expression of mismatch repair (MMR) proteins is retained.

Diagnosis: Undifferentiated carcinoma with rhabdoid and sarcomatoid features.

Comments: Undifferentiated (and rhabdoid) carcinomas have been described at a wide range of anatomic sites including the gastrointestinal tract; a subset of such tumors shows loss of staining for various SWI/SNF complex members, including SMARCB1 (INI1), SMARCA4 (BRG1), and others. Without a conventional (adeno) carcinoma component or mismatch repair deficiency, it is difficult to confirm that such tumors are indeed carcinomas (especially without much keratin expression; perhaps some are sarcomas?). This sarcoma versus carcinoma debate for SMARCA4-deficient poorly differentiated (or undifferentiated) malignant neoplasms rages in the thoracic pathology community.

References:

Agaimy A, Daum O, Märkl B, et al. SWI/SNF Complex-deficient Undifferentiated/Rhabdoid Carcinomas of the Gastrointestinal Tract: A Series of 13 Cases Highlighting Mutually Exclusive Loss of SMARCA4 and SMARCA2 and Frequent Co-inactivation of SMARCB1 and SMARCA2. *Am J Surg Pathol.* 2016 Apr;40(4):544-53.

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Case – 15

Contributed by: Kyle Perry, M.D.

Clinical history: This patient presented to the emergency room with gross hematuria for three days. A CT scan showed findings suggestive of a possible blood clot within the bladder. He underwent cystoscopy which revealed a sessile solid tumor on the posterior bladder wall extending to the dome of the bladder. A transurethral resection was performed.

Pathologic findings: Areas of the resected tumor demonstrated findings consistent with a high grade papillary urothelial carcinoma (Figure 1A). However, substantial portions of the tumor contained background myxoid material. The neoplastic cells were relatively small and somewhat discohesive (Figure 1B). In some areas of the tumor, the neoplastic cells formed a microcystic architecture (Figure 1C), while others contained cells which formed a vaguely cord-like arrangement (Figure 1D). Both the conventional and myxoid components of the tumor were positive for AE1/AE3 cytokeratin stains. Definitive muscularis propria involvement was not seen in the material available for examination.

Diagnosis: Invasive urothelial carcinoma with chordoid features.

Comment: When working up this case, I was trying to figure out the appropriate subclassification for this tumor. Although the cells exhibited some of the discohesion associated with plasmacytoid urothelial carcinoma, the myxoid matrix and lack of signet ring cells would be unusual for that designation. I showed this to a colleague at Henry Ford (Dr. Sean Williamson) who thought this tumor nicely fit the description of invasive urothelial carcinoma with chordoid features, as reported by Dr. Roni Cox and Dr. Jesse McKenney. (1) In this publication, the authors described a series of invasive urothelial carcinomas with cellular cording and an associated myxoid stromal matrix, resembling extraskeletal myxoid chondrosarcoma. In the same year, Dr. Tavora and Dr. Epstein described a series of urothelial carcinoma with abundant myxoid stroma which also shares features with this present case.(2)

The differential diagnosis for this particular subtype would include invasive adenocarcinoma of the bladder with extensive mucin deposition. Similarly, urachal adenocarcinoma or cystitis glandularis with extensive mucin production could also be considered. This case, however, does not exhibit areas of associated glandular differentiation seen in these neoplasms. Nephrogenic adenoma can exhibit fibrous and myxoid features. If needed a negative Pax-8 stain could help exclude this as a possibility.

Another peculiar entity which should also be excluded is myxoid cystitis with chordoid lymphocytes. In this lesion, inflammatory lymphocytes aggregate in a cord-like manner in the background of myxoid stroma, potentially mimicking a urothelial carcinoma with myxoid or chordoid features.(3) Of course, a positive AE1/AE3 stain could help exclude this consideration.

Identification of this subtype of urothelial carcinoma can be of particular value to the patient, as urothelial carcinoma with chordoid features can often present with high stage disease. Although muscularis propria invasion was not explicitly identified in this specimen, we noted that unsampled involvement cannot be entirely excluded given a substantial portion of this subtype is associated with advanced stage.

At present, the patient is awaiting further work-up.

Figure 1A-D

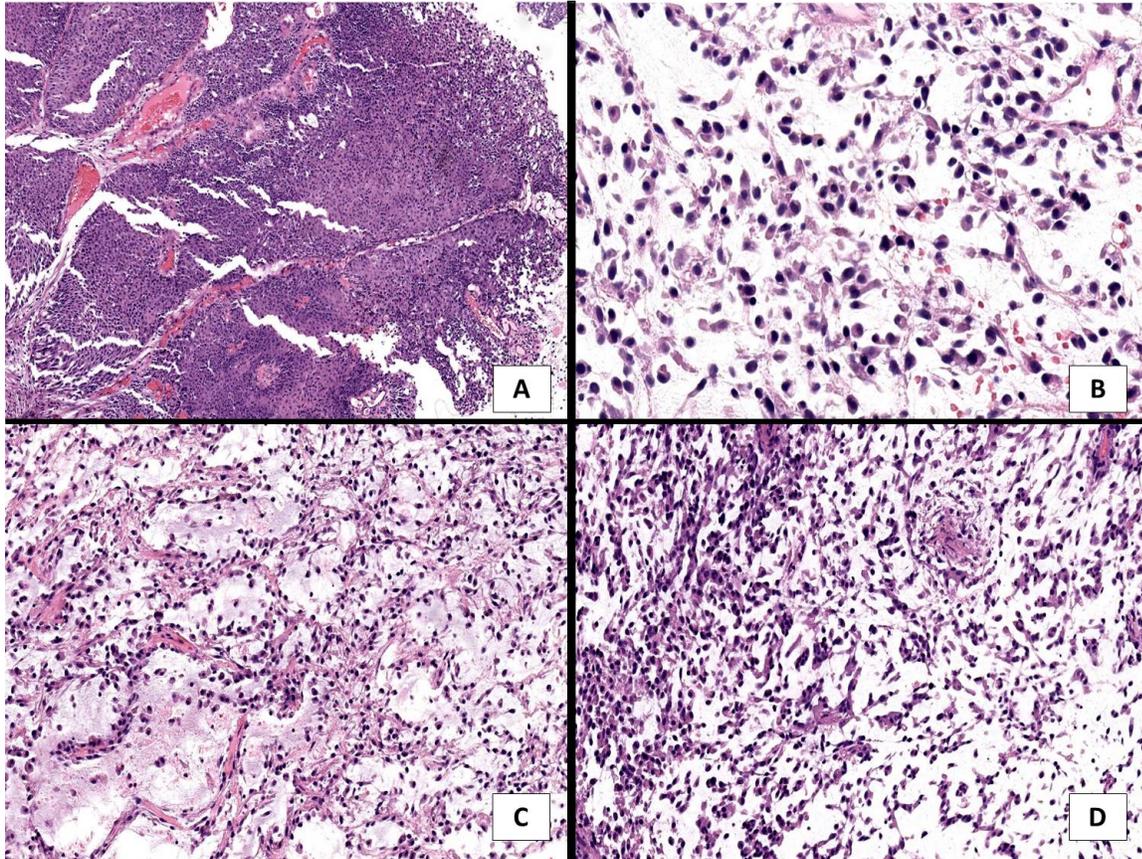


Fig 1. Morphologic features of invasive urothelial carcinoma with chordoid features. A. Areas of conventional high grade papillary urothelial carcinoma. B. Other areas of tumor exhibit small discohesive tumor cells with abundant background myxoid matrix. C. The cells are focally arranged in a microcystic architecture. D. In other portions, the cells show a cord-like arrangement, reminiscent of extraskeletal myxoid chondrosarcoma.

References:

1. Cox RM, Schneider AG, Sangoi AR, Clingan WJ, Gokden N, McKenney JK. Invasive urothelial carcinoma with chordoid features: a report of 12 distinct cases characterized by prominent myxoid stroma and cordlike epithelial architecture. *The American journal of surgical pathology*. 2009;33(8):1213-9.
2. Tavora F, Epstein JI. Urothelial carcinoma with abundant myxoid stroma. *Human pathology*. 2009;40(10):1391-8.
3. Hameed O. Myxoid cystitis with "chordoid" lymphocytes: another mimic of invasive urothelial carcinoma. *The American journal of surgical pathology*. 2010;34(7):1061-5.