

## **COMMENTS FOR AMR SEMINAR #73**

### **CASE NO. 1 – CONTRIBUTED BY: Kumarasen Cooper, M.D.**

**Abbas Agaimy** – Spectacular case Kum, never seen something like this before. Those intravascular lesions show some neuroectodermal-like subtle features and cytoplasmic material. This might be some of those odd translocation cases. I would speculate the intravascular component likely the hen and the capillary proliferations the egg! Thanks Kum for contributing this case which may never see again.

**Gerald Berry** – I don't think I have seen that kind of vascular tufting before. Vague resemblance to endothelial proliferations in plexiform lesions in PAH although lacking the inflammatory cells. I think the uncertain malignant potential is wise!

**Ira Bleiweiss** – Hemangioma with weird endothelial cells (tufts, as you say). Not sure what else to make of it, but I suspect benign and never to be heard from again.

**Alberto Cavazza** – Fascinating case, never seen before.

**Göran Elmberger** – Challenging case. Peculiar endothelial proliferations. Unfortunately, nothing to add.

**Franco Fedeli** – It is a really exceptional case. It seems to me related to SANT with intravascular tufts of cells.

**Maria Pia Foschini** – The mass lesion is a lobular hemangioma with necrosis and vascular thrombosis, but the tufts of endothelial cells are more complex. Given the dimensions of the mass, it could be considered as non-malignant. We suggest wait and see.

**Masaharu Fukunaga** – Thank you very much for the interesting case, Kum. The spindle cell proliferation is very distinctive, but I have never seen it before. Gamma-Gandy bodies are also new to me.

**Thomas Krausz** – I agree that part of the tumor is a benign vasoformative tumor (hemangioma). The tufted, not exactly glomeruloid, intravascular endothelial nodules are morphologically bland, focally palisaded with pseudo rosettes and without mitotic activity. There is no myxohyaline matrix. Like Kum and Chris, I cannot classify it, but favor benign. Molecular study might reveal the soul...

**Jesse McKenney** – This is why I dread someone at my door saying: "can I show you a vascular lesion". It has very unusual features somewhat reminiscent (but not quite prototypical) of papillary intralymphatic angioendothelioma or retiform hemangioendothelioma.

**Thomas Mentzel** – To be honest I haven't seen this kind of an intravascular, tuft-like growth of spindled endothelial cells within a given case of large haemangioma. Probably it represents a similar phenomenon as the well-known intravascular papillary endothelial hyperplasia. Despite the size of the lesion I see no convincing features of malignancy.

**Markku Miettinen** – Atypical vascular neoplasm. The intravascular cellular proliferation is reminiscent of a Dabska-type vascular change (papillary intralymphatic angioendothelioma). There are mixed angioma components, hemangioma and lymphangioma-like. Agree on somewhat uncertain biologic potential although favoring an indolent, non-malignant process.

**Kyle Perry** – Interesting. Some of the spindled cells seemed to have features similar to one of the composite hemangioendothelioma cases I saw (Mod Pathol. 2017 Nov;30(11):1589-1602.-Figure 1b and Figure 1c). However, my understanding is that the cells in this case were negative for synaptophysin, so, probably not the exact same process. Still I think composite hemangioendothelioma could be considered.

**Fredrik Petersson** – I have not seen anything like this before. One easy part (1; the hemangioma) one impossible part (2; the endothelial nodules). Considerations for 2 were myoid nodules, glomoid bodies, and carcinoid metastases. Looks cytologically bland. Some of the hemangiomatous areas appear thrombosed with fibrin. Could this be a thrombosis-related secondary endothelial proliferation induced by cytokines/growth factor related to a thrombotic process? On the other hand, why is it not seen more frequently, many large benign vascular lesions are partly thrombosed. The case should be published! Intriguing.

**Brian Rubin** – I've seen these tufts before in the spleen but like you, I'm not sure what to call them. I saw them in a case of a patient with angiomatosis involving multiple tissues and organs, but I only saw the tufts in the spleen. They remind me a bit of the tufts seen in Kaposiform hemangioendothelioma.

**Saul Suster** - Very unusual case; the intravascular tufts are identical to those seen in Dabska's tumor (papillary intralymphatic angioendothelioma). Why not a Dabska tumor of the spleen?

**Paul Wakely** – Wow, what a case Kum!! Some weird sort of glomeruloid angiomatosis? Never encountered this before.

**Ady Yosepovich** – Thank you for sharing this unusual case, I thought on the first look about meningothelial nodules – but immunostains did not fit.

#### **CASE NO. 2 – CONTRIBUTED BY: Fredrik Petersson, M.D.**

**Abbas Agaimy** – Pretty Case of PTC with exuberant NF-like/fibromatosis-like stroma. thanks Fred.

**Gerald Berry** – PTC with NF-like stroma. Beautiful case! I have been looking for one of these for many years now. Lovely example.

**Justin Bishop** – Very nice case. An angioinvasive well-differentiated carcinoma best classified as PTC based on architectural and nuclear features, dominated by a paucicellular population of bland fibroblasts that is far too extensive to simply be an FNA-related scar. This is the first time I've seen a convincing example of this exceedingly rare variant. Thank you for sharing.

**Ira Bleiweiss** – Agree. Wow. Never seen such a stroma in papillary thyroid ca.

**Alberto Cavazza** – Nice example of an unusual variant of papillary thyroid carcinoma. I agree with your comments on  $\beta$ -catenin immunostain.

**Kum Cooper** – This a great case Fred. Thank you for sharing. I understand your difficulty with assessing beta-catenin nuclear staining. Usually in the core biopsies from fibromatosis we see very focal nuclear staining and along with the morphology able to make a diagnosis.

**Göran ElMBERGER** – Papillary thyroid carcinoma with fasciitis-like stroma/fibromatosis-like stroma seems to be a rare and challenging tumor. Happy now to have seen one! Suggested independent driver mutations in epithelial and mesenchymal component very interesting if true. A true carcinosarcoma?? I could assume a nightmare in FNA practice where these kinds of tumors usually first show up. A

differential of fibroproliferative diseases like fibrous thyroiditis and other tumors of mesenchymal derivation is very challenging...

**Franco Fedeli** – I have never seen this type of variant of papillary carcinoma of the thyroid. The cells of the papillary carcinoma have a tall appearance that usually shows the strongest association with BRAF p V600 E mutation.

**Maria Pia Foschini** – The tumor is a papillary thyroid carcinoma with exuberant nodular fasciitis/fibromatosis-like stroma.

**Masaharu Fukunaga** – Thank you very much for the interesting case and detail discussion, Fredrik. It is a great case and educational.

**Thomas Krausz** – Agree with diagnosis. The couple of cases I have seen before were less collagenous, more nodular fasciitis-like.

**Jesse McKenney** – Great case!!! I had not seen one of these on a slide.

**Thomas Mentzel** – Many thanks for sharing this rare and unusual case!

**Markku Miettinen** – Agree on papillary carcinoma with nodular fasciitis like stroma. Indeed, mucinous cleavage spaces, as expected in nodular fasciitis, are seen in the stroma.

**Kyle Perry** – Thanks for sharing this case. I completely agree with your experience regarding the beta catenin stain. I am now just sequencing CTNNB1 in situations where I need better clarity.

**Brian Rubin** – Very interesting case. I don't have the opportunity to look at a lot of thyroid neoplasms, but I was thinking it might be some sort of adenocarcinoma ex myoepithelioma-type diagnosis. I looked at the case again after reading your diagnosis and the cytological features of the carcinomatous component are those of papillary carcinoma.

**Saul Suster** – Very nice example of this rare tumor. Current thought is that the spindle proliferation in the stroma represents fibromatosis rather than nodular fasciitis, an important distinction to make because if it is fibromatosis then the chances for local recurrence of the stromal component are significant.

**Paul Wakely** – Thank you Fredrik. My long wait is finally over to have an example of this variant in my personal collection.

### **CASE NO. 3 – CONTRIBUTED BY: Murray Resnick, M.D.**

**Abbas Agaimy** – Primary renal SFT, it shows mitotic activity, Dr. Argani presented at USCAP BCOR expression in these renal cases as pitfall with BCOR-rearranged renal sarcomas. Nice case, thanks.

**Gerald Berry** – Agree with the diagnosis of SFT of the kidney. The untoward prognostic findings are alarming.

**Ira Bleiweiss** – Agree. Convincing SFT of kidney.

**Alberto Cavazza** – Nice example of SFT in an unusual location.

**Kum Cooper** – Thanks Murray. You have covered all the recent updates in SFT nicely.

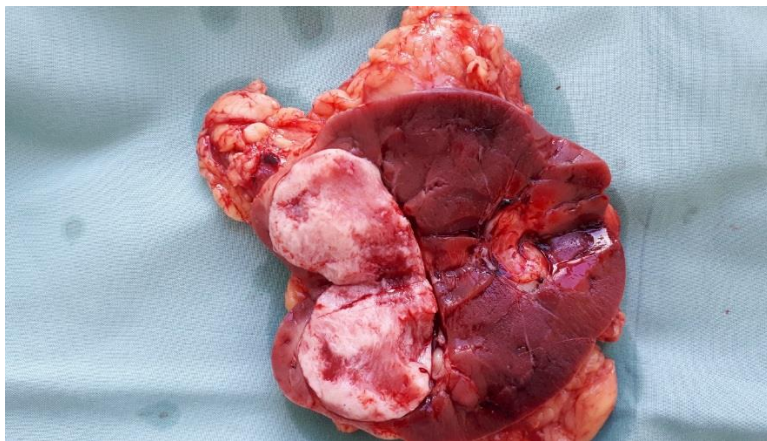
**Göran Elmberger** – I often see this tumor in the lung and pleura but never in the kidney. Certainly makes diagnosis more challenging... Our favorite man from Istanbul syndrome... Demicco's risk-assessment score seems practical.

**Franco Fedeli** – SFT of the kidney. The morphology of this tumor is typical.

**Maria Pia Foschini** – Primary solitary fibrous tumor of the kidney.

**Masaharu Fukunaga** – I agree. A very beautiful case of SFT. Thank you, Murray.

**Ondřej Hes** – Nice coincidence for me. We got similar case 2 weeks ago. Primary renal lesion, clinical working diagnosis was renal cell carcinoma. In our case, no necroses were seen. Gross photo from our recent case:



**Thomas Krausz** – Very nice example.

**Jesse McKenney** – Nice example of SFT.

**Thomas Mentzel** – A nice example of a malignant SFT arising in an unusual anatomic location.

**Markku Miettinen** – Agree on solitary fibrous tumor.

**Kyle Perry** – Thanks. I agree that the pitfall with dedifferentiated liposarcoma is important to be aware of... Overall STAT6 has seemed to hold up pretty well with respect to its specificity.

**Fredrik Petersson** – Great case. Good piece of information to learn that some dedifferentiated LS can be STAT6 amplified! Thanks.

**Brian Rubin** – I don't think I've ever seen SFT of the kidney but there is no doubt about the diagnosis. Great case.

**CASE NO. 4 - CONTRIBUTED BY: Ady Yosepovich, M.D.**

**Abbas Agaimy** – Male breast fibromatosis, distinctively rare presentation, thanks.

**Gerald Berry** – I think the beta-catenin stain is positive, so fibromatosis is reasonable. Given the small size and ease of follow-up, I think close surveillance rather than re-excision is reasonable.

**Justin Bishop** – I also wondered if this was a scar and whether I missed the lesion on the recut I received... thanks for sharing your convincing beta-catenin immunostain.

**Ira Bleiweiss** – Agree. Fibromatosis of male breast. Nice finger-like projections. I've only seen one previous case in a male which interestingly also had keloid-like areas that you point out. In my case, they were even more prominent and packed of spindle cells in between them, mimicking myofibroblastoma. By the way, I presented that case at the memorable AMR meeting in Tel Aviv in 2013.

**Alberto Cavazza** – My fear was a fibromatosis-like carcinoma, but at the end I agree with you.

**Kum Cooper** – Nice example Ady. Agree with your interpretation. Recently I saw a breast biopsy with spindle cells and nuclear beta-catenin positive. Resection showed a phyllodes tumor (the stroma of which may show nuclear beta-catenin immunoreactivity which I learned the difficult way!).

**Göran Elmberger** – Interesting rare case where I would agree on diagnosis. Nuclear beta catenin is very supportive given the difficult differential diagnosis of spindle cell fibromatosis-like sarcomatoid carcinoma. In the latter up to 15 % are said to be cytokeratin negative...

**Franco Fedeli** – In this case, the important differential diagnosis is with fibromatosis-like metaplastic carcinoma of the breast. In these tumors the atypia can be mild or absent and the cells are invariably p63 positive.

**Maria Pia Foschini** – Fibroepithelial lesion with chronic inflammation. We don't agree with the given diagnosis of fibromatosis.

**Masaharu Fukunaga** – I agree. I saw a few cases of fibromatosis of the breast. It seems to be Keloid. Thank you very much, Ady.

**Thomas Krausz** – I did not realize until now that fibromatosis can have focal keloidal features; however, Zreik and Fritchie observed these in 16% of their series (Am J Clin Pathol 2016; 145332-340).

**Jesse McKenney** – Mutational testing would be interesting in this case.

**Thomas Mentzel** – Many thanks. Was there a previous biopsy? I've found foreign body material and a histiocyte-rich granulomatous inflammation in my slide.

**Markku Miettinen** – Not a typical desmoid but may be one in the light of nuclear beta-catenin positivity.

**Fredrik Petersson** – Fibromatosis OK for me. Nuclear beta catenin always difficult to ascertain. Some myxoid areas. Centrally on my section aggregated MNGs and some foreign material in spaces. Previous injection?

**Brian Rubin** – Like you, I wondered about a scar or similar due to trauma because of all of the intra-lesional inflammation. However, the lesion does infiltrate at the edge and there does appear to be nuclear immunoreactivity for B-catenin, so I would have also called it extra-abdominal desmoid fibromatosis too. The keloidal hyalinization seen in the case would be consistent with scar, desmoid, or fasciitis.

**Saul Suster** - I think this is quite convincing for fibromatosis morphologically.

**Paul Wakely** – Agree. Definitely an example of desmoid-type fibromatosis.

**CASE NO. 5 – CONTRIBUTED BY: Barbara Gazić, M.D., Ph.D.**

**Abbas Agaimy** – Nice example of relatively paucicellular malignant phyllodes with MDS-like features, pitfall on core biopsy, thanks.

**Gerald Berry** – I agree with malignant PT.

**Justin Bishop** – Interesting! I hadn't previously considered myxofibrosarcoma to be a form of "heterologous" differentiation like the more common osteosarcoma, chondrosarcoma, rhabdomyosarcoma, etc. Thanks for sharing this interesting case.

**Ira Bleiweiss** – I agree that this should be classified as a rare variant of malignant phyllodes tumor. Despite the lack of usual stromal cellularity, it does have focal subepithelial condensation, favoring phyllodes. Primary MFH or myxofibrosarcoma are diagnoses of exclusion and should only be diagnosed when there is a total lack of epithelial component.

**Alberto Cavazza** – I thought of a malignant phyllodes tumor with liposarcomatous differentiation, but I am not an expert and in retrospect I clearly misinterpreted the lipoblast-like cells of myxofibrosarcoma. Great case!

**Kum Cooper** – Beautiful example with myxofibrosarcoma. Thank you for sharing this case. A recent paper has shown no MDM2 amplification in liposarcomatous differentiation.

**Göran Elmberger** – Interesting and challenging case. To me diagnosis seems reasonable. Why myxofibrosarcoma-like rather than with heterologous myxofibrosarcoma?

**Franco Fedeli** – Malignant phyllodes with myxofibrosarcoma-like heterologous differentiation. In this case the malignancy is diagnosed not by increased mitotic activity but by fibromyxosarcoma that usually has nuclear atypia but very few mitosis

**Maria Pia Foschini** – Phyllodes tumor with myxoid stroma. We suggest wide surgical excision.

**Masaharu Fukunaga** – A very beautiful case of malignant phyllodes tumor with myxofibrosarcoma-like differentiation. Thank you, Barbara.

**Thomas Krausz** – I agree with the histologic description however, I am not convinced about malignancy as I could not find significant mitotic activity, there is no stromal overgrowth and stromal giant cells with broad morphologic spectrum may occur not only in phyllodes tumor but also in fibroadenoma.

**Jesse McKenney** – Unusual phyllodes.

**Thomas Mentzel** – Given that malignant phyllodes tumour has a sarcomatous usually fibrosarcomatous mesenchymal component, I would suggest calling the lesion malignant phyllodes tumour with a myxofibrosarcomatous mesenchymal component. The term heterologous differentiation is reserved for cases showing features of liposarcoma, osteosarcoma, chondrosarcoma or rhabdomyosarcoma in my opinion.

**Markku Miettinen** – Agree on phyllodes tumor but not sure on malignancy based on the submitted material. Very low mitotic activity. Borders are not seen. No sarcomatous overgrowth. However, cannot rule out low-grade features, based on moderate to severe atypia.

**Kyle Perry** – Very interesting case. My residents enjoyed seeing it.

**Fredrik Petersson** – Unusual malignant phyllodes tumor! High-grade nuclear atypia in the myxoid stromal component, but low to moderate cellularity and scarcity of mitotic figures. Would have been interesting to see the Ki-67 proliferation IHC.

**Brian Rubin** – Uncanny how much it looks like myxofibrosarcoma but agree that malignant phyllodes tumor with myxofibrosarcoma-like heterologous differentiation makes more sense.

**Saul Suster** – Agree with the diagnosis.

**Paul Wakely** – The stroma is a 'spitting image' of soft tissue high-grade myxofibrosarcoma.

**Ady Yosepovich** – I thought that the epithelial component is atypical too- papillary DCIS? I do not think there is heterologous elements – just malignant phyllodes tumor.

**CASE NO. 6 – CONTRIBUTED BY: Ondrej Hes, M.D., Ph.D.**

**Abbas Agaimy** – Nice case Ondra, why are such lesions almost always high-grade, ductal like and sometimes villous? I know a couple of cases initially mistaken for adenomas rectal type, papillary carcinoma etc. until lung mets came. Thanks, Ondra.

**Gerald Berry** - The intrinsic value of immunostains in this location! A nice case.

**Ira Bleiweiss** – Agree and what a mimic it is.

**Alberto Cavazza** – Very educational comments on a not so unusual problem. From time to time this is a mistake is seen, also from experienced pathologists.

**Kum Cooper** – Thank you for sharing this case Ondra. I have not seen this pattern before in prostate carcinoma.

**Göran Elmberger** – Great case. Hard to differentiate from prostatic ductal adenocarcinoma?

**Franco Fedeli** – I agree with the possibility of prostatic duct adenocarcinoma. In some areas the papillary fronds are lined by pseudostratified columnar epithelium.

**Maria Pia Foschini** – High grade prostatic cancer.

**Masaharu Fukunaga** – It is a pitfall for diagnosis. Thank you. Very interesting case and great discussion, Ondrej.

**Thomas Krausz** – Highly educational case with excellent discussion.

**Jesse McKenney** – I'm very thankful for the emergence of NKX3.1.

**Thomas Mentzel** – Given the anatomic location a true diagnostic pitfall!

**Markku Miettinen** – Agree on metastatic prostate carcinoma.

**Kyle Perry** – Thanks for sharing the case Ondrej. It's a good reminder to stain poorly differentiated carcinomas of the bladder to confirm primary.

**Fredrik Petersson** – Great educational case!

**Brian Rubin** – Interesting case. Fooled me.

**CASE NO. 7 CONTRIBUTED BY: Kenneth Schoolmeester, M.D.**

**Abbas Agaimy** – Pediatric asymmetric labium enlargement, clinical info is useful for diagnosis, nice slide thanks Dr. Schoolmeester and welcome.

**Gerald Berry** – First example that I have seen. The explanation of “disproportionate hormonal response” seems a little odd to me as the child is only 7 years old! No features of RMS or other malignancies.

**Justin Bishop** – Very subtle histologic changes.

**Alberto Cavazza** – I ignored the entity, thanks for sharing.

**Kum Cooper** – Thanks Kenneth. So, is this different from the juvenile vulvar fibroma described by Chris Fletcher?

**Göran Elmberger** – Interesting lesion. New to me. Peculiar mucoid degeneration of nerves...

**Franco Fedeli** – Childhood asymmetrical labium major enlargement. A lesion bound to hormonal stimuli.

**Maria Pia Foschini** – Malformative lesion.

**Masaharu Fukunaga** – I have never seen childhood asymmetric labium major enlargement. Thank you very much for sharing with us and for wonderful discussion. It seems to be difficult to point out a proliferation of collagen fiber.

**Thomas Krausz** – Agree with diagnosis. I have seen a few cases before. Without proper clinical history it could cause diagnostic difficulty.

**Jesse McKenney** – Agree...I regard this as a non-neoplastic, hormonally related vulvar enlargement.

**Thomas Mentzel** – Given the morphological and immunohistochemical features I was thinking on a prepubertal vulvar fibroma (Am J Surg Pathol 2004; 28: 1601-1608), that may recur.

**Markku Miettinen** – No neoplasia, agree on physiological change.

**Fredrik Petersson** – Never heard of this. Thank you for enlightening me.

**Brian Rubin** – Interesting case – never heard of it before. Reminded me of a vulvovaginal stromal polyp that isn't very cellular.

**Saul Suster** – Nice case! Welcome, Ken, to the Club!

**CASE NO 8. – CONTRIBUTED BY: Cyril Fisher, M.D.**

**Abbas Agaimy** – Very nice example of ESS with hyalinizing rosettes occurring at extra genital site (endometriosis?). The cytology is typical, but the LGFMS-like rosettes are misleading, thanks Cyril for sharing this beautiful slide.



**Gerald Berry** – Agree. Unusual case.

**Justin Bishop** – Nice rosettes! I was not aware that ESS could show this impressive feature, thanks for sharing.

**Ira Bleiweiss** – Agree. Can't recall ever seeing this before.

**Alberto Cavazza** – Very educational case. Many years ago, I saw an almost identical case in the lung (with giant rosettes), and it turned out to be a metastatic uterine low-grade endometrial stromal sarcoma (I suspect a similar case was published on AJSP 1998;22:1431-1433). I did not recognize the previous case, but I did not learn from my mistake because I did not recognize also yours!

**Kum Cooper** – Thank you Cyril for this educational and instructive case. I was glad to note that you did the MUC4 and your discussion centered around LGFMS since that was my first differential! I think the millennials would call this a "sick" case!

**Göran Elmberger** – Great case and difficult case. I pulled a list of collagen rosettes from Google and an interesting group of lesions showed up one of them being sclerosing perineurioma that was in my differential from first morphological impression. Also there seems to be an interesting precursor-lesion like hyperproliferation going on in submucosa and muscularis propria that made me think of a primary lesion of neurogenic differentiation here. JAZF1-SUZ12 on the other hand seem not to be widely described outside ES but I don't know how extensive research on this topic has been done... Admittedly if lesion occurred in uterus, I would have no problems accepting it as ES. Would be nice to locate uterus! Any other lesions around?

**Franco Fedeli** – Endometrial stromal sarcoma. Hyalinizing rosettes are occasionally present in some cases of low grade fibromyxoid sarcoma.

**Maria Pia Foschini** – Endometrial stromal sarcoma with hyalinizing rosettes. The absence of features such as necrosis, mitosis and atypia are consistent with a low-grade lesion.

**Thomas Krausz** – What a picturesque, highly educational case. Thank you very much for submitting it.

**Jesse McKenney** – Great "starburst" pattern!

**Thomas Mentzel** – Many thanks for sharing this wonderful case!

**Markku Miettinen** – Even if this looks like a low grade fibromyxoid sarcoma (LGFMS) with hyaline rosettes, the JAZF1-SUZ12 fusion, ER-positivity and negative MUC4 indeed support endometrial stromal sarcoma. Without fusion, studies might have gone as a LGFMS.

**Kyle Perry** – When I first saw the case, I thought this was going to be an odd presentation of hyalinizing spindle cell tumor with giant rosettes. I will certainly keep ESS in the differential diagnosis (will also show our gyn pathologists).

**Fredrik Petersson** – We have seen a very similar case (endometrial stromal tumor with a muscle phenotype and collagenous rosettes) in a 54 y/o female with a large pelvic mass and previous hysterectomy (performed in a different country). Great succinct discussion. Thanks.

**Brian Rubin** – Awesome case with fantastic rosettes. As you stated, that kind of rosette is really rare, so the differential diagnosis is small and it's relatively straightforward to work your way through it using IHC and diagnostic molecular alterations.

**Saul Suster** – Had never seen this before in ESS, thank you for sharing it. Endometrial stromal sarcoma at metastatic sites can be a great mimicker and can be difficult to diagnose in the absence of a history.

**CASE NO 9. – CONTRIBUTED BY: Jesse K. McKenney, M.D.**

**Abbas Agaimy** – ACD-associated RCC-like renal cyst..., nice example with tubulocystic-like pattern. The name is really difficult and long and you have to be sure that the clinician heard you to the end, thanks Jesse for the great case.

**Gerald Berry** – Welcome Jesse! Nice example of acquired cystic disease-associated renal cell carcinoma-like cyst.

**Justin Bishop** – I thought I nailed it with tubulocystic RCC, but I wasn't paying attention to the background kidney.

**Alberto Cavazza** – Very nice and stimulating case. I thought this was a tubulocystic renal cell carcinoma.

**Kum Cooper** – Thank you for sharing this newly described entity. There are also benign entrapped tubules indicating that this is benign. I suppose this is in some way similar to the "atrophic kidney-like" lesion you described in AJSP December 2018, except the clinical setting is different.

**Göran Elmberger** – I would have some problems distinguishing this lesion from acquired cystic disease-associated RCC multicystic type given nuclear atypia and microfenestration a hallmark also of this cancer. Perhaps reasonable as you suggest considering a continuum of lesions. Would a FISH study help?

**Franco Fedeli** – In end stage kidney disease can occur many types of kidney tumor.

**Maria Pia Foschini** – Benign cystic tumor of the kidney.

**Ondřej Hes** – Thank you Jesse to send this case. VERY nice. For me it is sometimes difficult to make the diagnosis of acquired cystic disease associated RCC. Based on the definition, nearly all patterns are allowed 😊, also cytologic features are not precisely defined. We have only the anamnesis and presence of oxalate crystals left 😊.

**Thomas Krausz** – Historically I would have called it cystic renal cell carcinoma. The lining is quite atypical. Is this conceptually an intraepithelial (in situ) carcinoma?

**Thomas Mentzel** – Was there any connection of the cystic lesion with the mentioned renal cell carcinoma?

**Kyle Perry** – Thanks Jesse. We have had a few of these cases come up in the past year. As you noted, distinguishing between these two entities can be challenging and I appreciated the recent AJSP publication.

**Fredrik Petersson** – Amazing piece of nomenclature! We have seen these types of cysts several times but signed them out descriptively. Of note, tubulocystic RCC may mimic cystic renal disease (Iakovleva G et al. Histopathology. 2015 May;66(6):892-4).

**Brian Rubin** – Didn't know about this so I was glad to learn about it.

**Saul Suster** – Great case! Thanks for sharing – I was not aware of this. Welcome Jesse to the Club!

**CASE NO. 10 – CONTRIBUTED BY: Dr. J. Forteza Vila**

**Abbas Agaimy** – Admittedly one of my many weaknesses, but very well illustrated and discussed diagnosis, thanks.

**Gerald Berry** – The hemophagocytosis is very impressive in this case. Usually I have to struggle to be convinced of it.

**Alberto Cavazza** – I suspect this may be a reactive lymphoid proliferation to virus, but my hematopathological experience is too limited for this case.

**Kum Cooper** – Thank you for sharing this interesting case. I also wondered about Kikuchi's momentarily!

**Göran Elmberger** – Blind spot. Pass.

**Franco Fedeli** – My first suspect in this lymph node is a lymphoid process compatible with high grade lymphoma.

**Maria Pia Foschini** – No specific comments, difficult case.

**Thomas Krausz** – Not being a "modern era" hematopathologist, on the H&E I could not decide whether this was a myeloid or lymphoid malignancy.

**Jesse McKenney** - Hemepath consult for me...

**Fredrik Petersson** – I am unclear about this case.

**Brian Rubin** – I wasn't sure what to make of this. I suspected infection but couldn't find organisms.

**CASE NO. 11 – CONTRIBUTED BY: Markku Miettinen, M.D.**

**Abbas Agaimy** – Great case of PMT, looks much odd and misleading if symptoms not known, we recently described consistent expression of SATB2 in addition to the known SSTR2A, etc. markers which might help in combination but still the serology is most relevant. Thanks Markku.

**Gerald Berry** – Agree with the diagnosis of phosphaturic mesenchymal tumor.

**Justin Bishop** – Very interesting microcystic pattern, and without any calcifications that I could see. Without the history, would've been quite difficult! Thank you for submitting.

**Ira Bleiweiss** – Interesting. I had no idea what this was.

**Alberto Cavazza** – Very instructive and unusual case, thanks for sharing.

**Kum Cooper** – Thanks Markku for this case of PMT. Without the grungy cartilage-like matrix it was difficult to recognize, although the history was helpful! But the case does highlight the nice mesenchymal component which is usually overcrowded by the matrix.

**Göran Elmberger** – Great case. Smudgy matrix bluish... pseudoalveolar formations. Aneurysmal bone cyst like reaction focally. As you say the clinical situation is the most important clue but non-phosphaturic variants are described. Recently saw a pulmonary metastasis from a non-phosphaturic primary in iliac bone in young woman. Tricky case and I had to get some help from British laboratory to perform fibroblast factor 23 IHC to prove the diagnosis.

**Franco Fedeli** – Phosphaturic mesenchymal tumor. In my experience the tumors that I saw were characterized by a hypocellular to moderate cellular proliferation of bland cells. In this case the tumor is extremely cellular.

**Maria Pia Foschini** – Phosphaturic mesenchymal tumor. Given the absence of osteoblast-like cells and foam cells the lesion should be considered as quite unusual.

**Thomas Krausz** – Agree with diagnosis, though without the clinical context I would have struggled with the diagnosis. The morphologic spectrum of phosphaturic mesenchymal tumor is quite broad.

**Jesse McKenney** – By H&E alone without history, I was considering myopericytoma/glomus family, myoepithelioma, or other salivary gland-like/adnexal tumor.

**Thomas Mentzel** – Irrespective of the clinical findings the given slide is very difficult. The few examples of phosphaturic mesenchymal tumour I've seen contained also bland fibroblast-like cells and an unusual basophilic material was seen in the stroma (which is absent on the given slide).

**Michal Michal** – It must be a very rare pattern of PMT. I have not seen such interesting angioma-like pattern in any of nearly 40 cases of PMTs in our files.

**Fredrik Petersson** – Challenging morphology. There are no cartilaginous-like areas on my section. No "grungy" calcification of the matrix or osteoclast-type giant cells. There is fat, and in the few cases that I have seen there has been a lipomatous component. Was this tumor FGF-23 positive? Elevated serum levels? Abbas AJSP paper from 2017 shows nicely how wide the morphological spectrum of PMT is. Now also with epithelial elements (recently published large series from China; 22 cases *in the jaws!*) Wu H et al. Mod Pathol. 2019 Feb;32(2):189-204 (Thanks Michal!).

**Brian Rubin** – Very nice case. I'm always struck by how vascular these tumors are, often simulating a weird spindle cell hemangioma or similar.

**Saul Suster** – Great case! I would have never thought of PMT on the H&E; I've never seen this unusual microcystic growth pattern in the cases I've had so far.

#### **CASE NO. 12 – CONTRIBUTED BY: Saul Suster, M.D.**

**Abbas Agaimy** – Good but difficult example of myoepithelial lung carcinoma. Some might have been misnamed poorly differentiated SCC or pleomorphic carcinoma as stated in the discussion. IHC is convincing and histology covers most of myoepithelial patterns in the same slide. Thanks Saul for sharing this teaching case.

**Gerald Berry** – The morphology and immunostaining support myoepithelial differentiation.

**Justin Bishop** – Wow. I'm not sure I would've considered myoepithelial carcinoma in this location, although in retrospect it certainly fits. I wonder if thoracic myoepithelial carcinomas are more soft tissue-type, or derived from the seromucinous glands of the airways, or both.

**Ira Bleiweiss** – Agree. Sounds right based on IHC.

**Alberto Cavazza** – Very stimulating case. I thought at a sarcomatoid carcinoma with squamous differentiation and vascular invasion, but I think the stains demonstrate you are absolutely right. To me, in such a case, the limit between sarcomatoid carcinoma with myoepithelial differentiation and myoepithelial carcinoma is quite blurred: probably I would prefer the former definition, acknowledging that myoepithelial is one of the possible (and probably less frequent) lines of differentiation a sarcomatoid carcinoma may have, but I think the choice is quite subjective.

**Kum Cooper** – Thank you Saul for sharing this educational case with us. Goran also showed us a case in recent years. In the lung myoepithelial carcinoma does not readily come to mind. In fact, I also wondered about rhabdoid morphology and thought of the SMARC-deficient thoracic carcinomas. This case looks morphologically high grade too. Was this case rearranged with EWSR-1?

**Göran Elmberger** – Great case. I guess the most problematic thing is to include SGT tumors in the differential diagnosis when dealing with lung tumors. If the same tumor occurred in salivary gland it would not be a very difficult diagnosis. Situation reminds me of the situation in breast and classification of metaplastic carcinomas and perhaps skin.

**Franco Fedeli** – Great case Saul. In one part of the tumor there is a component reminiscent of mixed tumor of salivary glands with myoepithelial differentiation

**Maria Pia Foschini** – Myoepithelial carcinoma of lung. Immunohistochemistry is consistent with diagnosis.

**Thomas Krausz** – Agree with diagnosis. The immuno-profile is convincing.

**Jesse McKenney** – I'm glad I didn't get the original biopsy.

**Thomas Mentzel** – Another difficult case on H&E, many thanks! Did you perform INI1 staining? A significant number of myoepithelial carcinomas show loss of INI1 expression.

**Markku Miettinen** – Agree. Sarcomatoid carcinoma which by markers looks like a myoepithelial carcinoma.

**Kyle Perry** – Thanks Saul. I will certainly keep this entity in mind when encountering a tumor with only scattered mitotic figures.

**Fredrik Petersson** – Infiltrative epithelioid and spindle cell neoplasm with atypia. IHC profile convincing and shows that expression patterns in myoepithelial neoplasms are commonly heterogenous. I note that the IHC panel contains follicular dendritic cell markers; the admixture of lymphocytes is focally very significant. Hence FDC-sarcoma very relevant differential on H&E.

**Brian Rubin** – Agree with diagnosis of myoepithelial carcinoma.

**Paul Wakely** – The 'plasticity' of those myoepithelial cells continues to fascinate this observer.

**Ady Yosepovich** – Thank you for sharing this unusual case – SOX10 is positive in breast myoepithelial carcinoma, is could be interesting to try it in this tumor too.

**CASE NO. 13 – CONTRIBUTED BY: Saul Suster, M.D.**

**Abbas Agaimy** – Very unusual case for both DDx. Spontaneously I would call it olfactory neuroblastoma although admittedly somewhat different and it really recapitulates the pediatric neuroblastoma that underwent maturation more than the classical grade 1 ONB. Never see maturation of Ewing into any other tumor although not totally excluded being of some possible neuroectodermal origin. Unusual as well and again more akin to conventional neuroblastoma are the very large nuclei of ganglion cells and the abrupt transition to a minor focus of neuroblastic elements. This case is a good candidate for RNA fusion testing in the light of the Ewing history of the patient. Thanks Saul for sharing this spectacular and tough case.

**Gerald Berry** – I agree with you and Bruce and would favor olfactory neuroblastoma. I guess I am of the vintage that morphology holds primacy and I try not to be swayed solely by molecular patterns!

**Justin Bishop** – What an interesting case. It really looks very little like either Ewing sarcoma or olfactory neuroblastoma. I've occasionally seen olfactory neuroblastomas with ganglion cells before, but never this extensive. The tumor cell morphology is quite unusual, as is the arrangement of the gliofibrillary stroma. The described staining pattern is also atypical for ONB. Lastly, ONB has never been reported positive for *EWSR1* rearrangements. I notice that cases of Ewing sarcoma with neuroblastoma-like differentiation, particularly following treatment, have been reported. I wonder if that could explain all the findings in this case. It would be interesting to know what the *EWSR1* fusion partner was in this case, and obviously seeing the original tumor would be fascinating.

**Ira Bleiweiss** – In my humble non-expert opinion, this looks more like olfactory neuroblastoma.

**Alberto Cavazza** – This looks like olfactory neuroblastoma (with ganglionic differentiation) also to me. I agree that to review the previous bone sarcoma would be interesting: if the diagnosis of Ewing is confirmed, maybe the possibility of a syndromic predisposition could be suggested in this young patient?

**Kum Cooper** – Thanks Saul for sharing this case. One wonders what we all have stored in the "paraffin bank"! I agree that this is an olfactory neuroblastoma. I am also wondering whether the FISH signals are true or represent fragmentation of the chromosome that can give false signals (See paper by Cristina Antonescu in *Genes, Chromosomes, Cancer* 2016). I have learned not to entirely trust molecular as the gold standard especially if the morphology does not fit!

**Göran Elmberger** – Highly interesting and difficult case. At low power, my first impression was ONB but on higher magnification it does not fit with any of those I have previously seen. I would favor a "matured" differentiating metastasis of Ewing sarcoma similar to what we see in pulmonary metastases from germ cell tumors of the testis. In that case we use ip12 as marker of GCT as proof and in this case *EWSR1* does the same job. This phenomenon has been described in literature with neuronal maturation including ganglioneuroblastoma-like differentiation with expression of neuronal markers. I do recognize Saul's argument of our limited knowledge of *EWSR1* and other mutational fingerprints outside the box is very limited and that sometimes (but rarely) lightning strikes twice... Of course, here it is very difficult to be sure and an open watchful waiting and attempt at local radical treatment should be recommended.

**Franco Fedeli** – I think that in this case morphology beats genetic-molecular findings.

**Maria Pia Foschini** – Olfactory neuroblastoma.

**Ondřej Hes** – Although I am a soft tissue ignorant, Ewing sarcoma would not be in my differential diagnosis. I have one general comment: we face this in GU pathology, and I see it across the organs... We test tumors for particular mutations, translocations, gene abnormalities, because we expect particular changes from the morphology. If we (and I have such experience from kidney tumors) test blindly tumors (regardless morphology), from time to time very unusual results can be seen. Not always, just from time to time. I expressed this opinion during my lecture in last USCAP. In renal tumors, we are facing a crisis of dogmas ☺ I think it is not too far from reality ☺.

**Thomas Krausz** – I agree, on H&E this looks like differentiating neuroblastoma rather than metastatic Ewing sarcoma. Sometimes, when molecular result does not match the H&E, I ask to double check the molecular data...

**Jesse McKenney** – Looks like olfactory neuroblastoma to me.

**Thomas Mentzel** – Many thanks for the excellent discussion! For me the lesion doesn't look like Ewing sarcoma and it would be great to review the previous case. We found as well EWS translocation in non-Ewing sarcomas; i.e., cases of rhabdomyosarcoma.

**Markku Miettinen** – Histologically it looks like ganglioneuroblastoma.

**Michal Michal** – It looks like ganglioneuroblastoma. I have never seen a case like this in this location.

**Kyle Perry** – I also favor neuroblastoma. It would be interesting to sequence the EWSR1 to see what the partner is...

**Fredrik Petersson** – I agree that this is a new primary neural tumor and as you say with ganglionic differentiation set in a distinct neuropil-type matrix. There are smaller cells, and they appear also to be positive for Neu-N. What about an ONB with ganglioneuroblastic differentiation? (Squillaci S. Olfactory neuroblastoma with focal ganglioneuroblastic differentiation: a case report with literature review. *Pathologica*. 2014 Jun;106(2):61-6).

**Brian Rubin** – It would be interesting to obtain the original "Ewing" sarcoma. It makes more sense that the original was a mesenchymoma or neuroblastoma. I'm happy to do NGS-based gene fusion analysis on the current case to see if it indeed has an *EWSR1* gene region rearrangement and determine the fusion partner.

**Saul Suster** – My case. Brian, I will be happy to take you up in your offer to sequence this tumor – will start looking for the block. Unfortunately, we do not have the original bone tumor.

**Paul Wakely** – Before reading your notes on this case Saul, I thought this was an ONB with florid ganglionic differentiation. However, if those cells really are ganglion cell precursors, I am bothered by the fact that your GFAP stain is negative.

**Ady Yosepovich** – My first impression was paraganglioma – there is an unusual nested pattern...

**CASE NO 14. – CONTRIBUTED BY: Jason L. Hornick, M.D., Ph.D.**

**Abbas Agaimy** – Rare case of SMARCA4-deficient undifferentiated rhabdoid carcinoma in the small bowel presenting with acute abdomen. During preparation of our cited series, I found out that one patient (also with SMARCA4 loss) had NSCLC, therefore excluded from the series. Since then, I have collected some 9 cases of undifferentiated large cell carcinomas from lung presenting with acute abdomen with small bowel mets (a MS is in preparation). These cases are indistinguishable from the primary rhabdoid GI tumors and all were transmural rhabdoid and keratin-poor frequently. I therefore now always recommend chest imaging and history regarding NSCLC, most were synchronous to the diagnosis of the lung carcinoma and others metachronous. Interestingly some had concordant histology where dedifferentiation occurred in the mets only (same phenomenon was reported earlier by Dr. Samir Amr in the Annals as malignant rhabdoid tumor of the ileum following lung adenocarcinoma). Would be very interested to know if this patient really has no occult or previous NSCLC. Thanks Jason for a great case.

**Justin Bishop** – The SMARCA4 story is also creeping into the sinonasal tract, where there is now a form of SMARCA4-deficient sinonasal carcinomas that appear similar to the much more common SMARCB1-deficient tumors. We're following the lung and GI experiences closely!

**Ira Bleiweiss** – Agree. Very rhabdoid indeed.

**Alberto Cavazza** – Very nice case, I have no comments.

**Kum Cooper** – Thanks Jason for this great example. Yes, the sarcoma vs carcinoma debate is baffling. Does claudin-4 not do it? (as per your paper in Mod Pathol).

**Göran Elmberger** – Malignant rhabdoid tumor. Partial positivity for CK 8, mucosal infiltration/ulceration and lymph node metastasis is at least not incompatible with a sarcomatoid carcinoma even if we all await result of debate. Perhaps a drift towards a more molecular driven tumor classification swiftomas...

**Franco Fedeli** – Undifferentiated carcinoma with rhabdoid and sarcomatoid feature. Do these tumors have a neuroendocrine differentiation?

**Maria Pia Foschini** – Undifferentiated carcinoma with sarcomatoid features.

**Thomas Krausz** – I agree, that in this particular case it is difficult to be certain whether this is a carcinoma or sarcoma.

**Jesse McKenney** – Great case!

**Thomas Mentzel** – I do agree completely about the problematic issue in differentiating undifferentiated sarcomatous carcinoma with rhabdoid features from an undifferentiated sarcoma with aberrant cytokeratin expression.

**Markku Miettinen** – Malignant sarcomatoid neoplasm with BRG1/SMARCA4 loss, by studies.

**Fredrik Petersson** – Good case. Light microscopical similarities to the "large cell variant of small cell hypercalcemic ovarian carcinoma/malignant rhabdoid tumor of the ovary", which has biallelic inactivation of SMARCA4. Increasing group of tumors with SWI/SNF complex gene aberrations. The terminological debate of "carcinoma" versus "sarcoma" is scholasticism, not biology.



**Brian Rubin** – The debate about whether these lesions are carcinoma or sarcoma is interesting. It seems like all poorly differentiated lesions end up with a differentiation pattern that is more sarcoma-like than carcinoma-like (aka epithelial to mesenchymal transition – what heresy!). The process seems to be more prominent in lesions that lose INI1, SMARCA4, or other members of the BRG complex.

**Ady Yosepovich** – My first impression was metastatic melanoma, would have done some stains for this...

**CASE NO. 15 – CONTRIBUTED BY: Kyle Perry, M.D.**

**Abbas Agaimy** – Urothelial carcinoma with chordoid pattern, very rare and challenging diagnosis versus so-called myxoid/chordoid cystitis. Thanks Kyle.

**Ira Bleiweiss** – Agree. Very myxoid indeed.

**Alberto Cavazza** – I thought a plasmacytoid variant of urothelial carcinoma, but in retrospect I am convinced you are perfectly right. Very nice example of an unusual variant.

**Kum Cooper** – Thanks Kyle for this interesting case. Never seen before but happy to have an H&E slide of this example.

**Göran Elmberger** – Interesting pattern. Name seems appropriate. Good to know in differential diagnosis of UC.

**Franco Fedeli** – Urothelial carcinoma with chordoid features. The differential diagnosis with plasmacytoid urothelial carcinoma is impossible

**Maria Pia Foschini** – Invasive urothelial carcinoma with myxoid features.

**Ondřej Hes** – Very nice case. I totally agree with diagnosis. For me also is difficult to confirm invasive growth in bladder/kidney pelvis cases with extensive mucin production. I believe those very rare cases of bladder/kidney pelvis tumors arising from pure colonic metaplasia can behave similar way, like colloid breast adenocarcinoma (dissection of stroma by abundant mucin production). In such situation is almost impossible to tell difference between active invasive growth pattern and extension of mucin into the stroma (pseudoinvasion).

**Thomas Krausz** – I was not aware of the paper about invasive urothelial carcinoma with chordoid feature. On this case, I probably would have concluded with a diagnosis of urothelial carcinoma with focal plasmacytoid features and myxoid stroma.

**Jesse McKenney** – Agree, nice example.

**Thomas Mentzel** – A nice case with an unusual phenotype, many thanks!

**Markku Miettinen** – High-grade urothelial carcinoma. Perhaps it could be also classified as high-grade urothelial carcinoma with sarcomatoid features.

**Fredrik Petersson** – My sections show abundance of plasmacytoid cells. We have seen some cases over the years, sometimes with a component of rhabdoid cells. Myxoid or loose edematous stroma is regularly present. On my sections, very focal cord-/extraskelatal myxoid chondrosarcoma-like arrangement. I am wondering if these (plasmacytoid/rhabdoid/chordoid histopathologic appearances are not overlapping

patterns in high-grade urothelial carcinomas with “progression/dedifferentiation/sarcomatoid - epithelial to mesenchymal transformation”)? There is CIS on my section.

**Brian Rubin** – Interesting case with nice discussion.