

## **COMMENTS FOR AMR SEMINAR #74**

### **CASE NO. 1 – CONTRIBUTED BY: Abbas Agaimy, M.D.**

**Gerald Berry** – Nice example of a localized malignant mesothelioma. It is very similar to my case in Seminar #60. The challenge is often to think about the possibility of mesothelioma on small samples (FNA or cores) and not assume TTF-1/Napsin negative adenocarcinoma.

**Justin Bishop** – Interesting case and tumor. I was not familiar with this variant. Has an almost hepatoid appearance.

**Ira Bleiweiss** – Agree. Why is it that mesothelioma is always one of those diagnoses that can look like anything and you just have to always keep it in mind, like melanoma? Is it that they are “m” diagnoses?

**Alberto Cavazza** – I perfectly agree, very nice case. Localized malignant mesothelioma tends to have a better prognosis than classical diffuse mesothelioma. I have seen a few cases, including two of the lymphohistiocytoid variant.

**Kum Cooper** – Thank you Abbas for sharing this case. I have not seen this variant of mesothelioma before. Thanks for the great write up.

**Göran Elmberger** – Great case. Agree. We just got BAP-1 IHC up and running in Umeå... Looking forward to additional diagnostic tool in this difficult diagnosis.

**Franco Fedeli** – Very interesting case. I am wondering if this type of mesothelioma is defined by a better prognosis than the usual one.

**Cyril Fisher** – Adenomatoid-like localized epithelioid mesothelioma, great case and discussion, thanks Abbas.

**Maria Pia Foschini** – I agree with the final diagnosis of mesothelioma with adenomatoid-like features. BAP-1 loss is interesting. Some papers suggest a possible role of BAP1 loss in the diagnosis of mesothelioma.

**Masaharu Fukunaga** – Thank you very much for the interesting case of localized malignant epithelioid mesothelioma, adenomatoid-like variant, Abbas. Your comment on BAP1-deficient is very informative and interesting.

**Barbara Gazic** – An excellent case to remind us that BAP-1 deficient cases are not only for melanocytic lesions and renal cell carcinomas which we have in our archives and that BAP-1 lost cases tend to show epithelioid morphology.

**Ondra Hes** – This is a very nice case...however I have mixed feelings ☺...Several years ago we published a series of adenomatoid tumors, where we suggested that bridging strands (delicate thread-like structures) are highly specific for adenomatoid tumor (regardless of localization) ☺. I've never seen such a mesothelioma.

**Thomas Krausz** – Great case. Credible examples of localized malignant mesothelioma are rare. The combination of being localized (convincingly illustrated both by imaging and gross photo), “adenomatoid” pattern and BAP1 loss makes this case real special. I hope you will publish it.

**Brandon Larsen** – I agree. A beautiful case of localized malignant mesothelioma, with great adenomatoid morphology. I'm not sure that I've seen adenomatoid morphology before in a localized mesothelioma, but now I have. It would be fascinating to know whether it harbors a BAP1 germline mutation, given the history of a prior renal tumor.

**Jesse McKenney** – It would be interesting to know if these lack the TRAF7 mutation of adenomatoid tumor.

**Thomas Mentzel** – Many thanks for this spectacular case increasing the number of BAP1 deficient neoplasms.

**Michal Michal** – I have seen recently 3 such adenomatoid-like mesotheliomas. In all cases it was very difficult to say the level of malignancy.

**Markku Miettinen** – Agree on malignant mesothelioma, epithelioid type, with adenomatoid tumor-like features.

**Delia Perez-Montiel** – Very difficult case, the adenomatoid pattern is impressive. I don't know if have missed one of these cases in the fallopian tube.

**Cesar Moran** – Interesting case.

**Fredrik Petersson** – Unusual tumor with unusual morphology in an unusual location = difficult. Adenomatoid tumor-like features are obvious, including "thread-like bridging strands", but too cytologically atypical and mitotically active. The scan image looks as though the tumor could be related to the pleura – what was the intraoperative impression? Other "mesothelial IHC markers" done, ?D240, ?WT-1. Impressive case and good concise discussion. It is my understanding that despite the localized disease, the prognosis has to be "guarded".

**Murray Resnick** – Nice example and great discussion on BAP1.

**Brian Rubin** – Excellent case Abbas. Without loss of BAP1 I might have favored an adenomatoid tumor. The histology is very benign/low-grade.

**Niels Rupp** – Very nice case of an unusual type of mesothelioma; good that BAP1 immunohistochemistry is available now to corroborate the diagnosis.

**Saul Suster** – Pretty spectacular case! Thanks for sharing it. We published a very similar case many years ago that was located in the anterior mediastinum and which we interpreted as a "cystic adenomatoid tumor" of the mediastinum, but it may well have arisen from the pericardium or mediastinal pleura (Plaza JA et al. Am J Surg Pathol 28:132-138, 2004). The only mesotheliomas I've seen previously with this adenomatoid tumor-like architecture were all invasive and malignant.

#### **CASE NO. 2 – CONTRIBUTED BY: Phil Allen, M.D.**

**Abbas Agaimy** – Pretty example of carcinoma cuniculatum. I agree this is not the same as verrucous carcinoma although inverted verrucous carcinoma may closely mimic this variant, albeit lacking the prominent keratin cyst-pattern which is a hallmark of carcinoma cuniculatum.

**Gerald Berry** – Not a diagnostic term that I use very often! We did raise this possibility for a recent intra-oral lesion, but that term came from our oral pathologist.

**Justin Bishop** – Lovely example of carcinoma cuniculatum. We see this with some frequency in the oral cavity, where it is probably underdiagnosed.

**Ira Bleiweiss** – Agree with well differentiated squamous cell carcinoma.

**Alberto Cavazza** – Spectacular case! My humble opinion is this is slightly different from verrucous carcinoma, although the two may be part of a spectrum. I remember a case in the oesophagus, shown me by Giovanni De Petris.

**Kum Cooper** – Thank you Phil. I have only seen this once each in the oral mucosa and esophagus. By the way I showed the case to David Elder too.

**Göran Elmberger** – Interesting and very unusual case. I am sure you are right, but I can't help thinking about necrotizing syringometaplasia as a differential diagnosis. Lots of eccrine glands with peculiar changes intermingled. A tint of lobular arrangement. Short history (8w.) The history including foreign body and needle picking is a bit odd for a neoplasm, but we all know we cannot always trust. Any signs on IHC for a connection to eccrine glands?? The few cases of carcinoma cuniculatum I have seen were all in the oral cavity including one last week and they had a slightly different kind of debris centrally in the burrows and a more disorganized growth, but I see in the literature also this kind of lamellated keratin in CC. Follow up will probably not help given the radical surgery.

**Franco Fedeli** – Usually carcinoma cuniculatum occurs in acral areas where the stratum corneum is thicker.

**Cyril Fisher** – Carcinoma cuniculatum on finger, nice case Phil. I have seen cases in the foot usually with prominent inflammatory infiltrate, as here.

**Maria Pia Foschini** – This case is interesting, but I have some trouble in accepting this as carcinoma cuniculatum. The present case is composed of well differentiated nests and cystic-like spaces clearly invading the dermis, surrounded by inflammation. As far I can understand a clear example of carcinoma cuniculatum is the one reported by McArdle, et al. International Journal of Surgical Pathology 2017, Vol. 25(5) 438–442.

**Masaharu Fukunaga** – It seems that there is no epidermal carcinomatous component. Verrucous carcinoma is different from this case.

**Barbara Gazic** – Interesting case, of course never seen before.

**Ondra Hes** – Great case...just question...is there any chance for association with Carney's syndrome? Having strange myxoma...I always consider this possibility. Thank you.

**Thomas Krausz** – I agree with all the points you mentioned, and I believe that carcinoma cuniculatum is a different clinicopathologic entity than verrucous carcinoma.

**Brandon Larsen** – Great case. Thanks for sharing. I've not encountered this unusual presentation of SqCC before, but it certainly seems compatible with published descriptions of carcinoma cuniculatum.

**Jesse McKenney** – This looks identical to the "pseudohyperplastic" and "carcinoma cuniculatum" variants of squamous cell carcinoma that we see in the penis. Our group thinks that these two variants have a lot of overlap but are distinct from (although probably closely related to) verrucous carcinoma. We probably see 1-2 penile cancers a year that is one of these two subtypes.

**Thomas Mentzel** – The well-differentiated neoplasm shows features we see also in keratoacanthoma-like neoplasms in acral, especially periungual location and despite the bland morphology these neoplasms are locally aggressive.

**Markku Miettinen** – Well-differentiated squamous cell carcinoma, keratinizing.

**Delia Perez-Montiel** – Agree, I have never seen one case before. Thank you.

**Cesar Moran** – I would have called this lesion squamous cell carcinoma. In my opinion this is not a verrucous carcinoma.

**Fredrik Petersson** – I think carcinoma cuniculatum is a suitable diagnosis. Clearly infiltrative and cytologically bland. These tumors may also occur in non-cutaneous sites. We have published a case in the tongue as well as in the esophagus (both tumors lacked TP53 mutations). (Ref: Carcinoma cuniculatum of the esophagus and tongue: report of two cases, including TP53 mutational analysis. Head Neck Pathol. 2014; 8:261-8). These tumors are non-metastasizing (when pure), slowly growing, but relentlessly destructive. One third of the tongue was “eaten up” in our lingual case. Cytologically bland throughout (no component of conventional SCC – e.g. hybrid tumor). Of note, the sinuses/burrows frequently become infected and the acute inflammation may give rise to significant cytologic atypia which can make the distinction from a component of conventional SCC (with metastatic capacity). Thanks for this case.

**Brian Rubin** – I never heard of carcinoma cuniculatum before. Thanks for the interesting case.

**Niels Rupp** – A scary case, given the biopsy morphology and context of manipulation, potential foreign body and apparently inconspicuous clinical presentation. I have seen very few cases of this "cuniculatum" pattern in the genital tract and oral mucosa, but all of them were very deeply invading despite this bland cytology. In this context, I personally believe that this is a different tumor from typical verrucous carcinoma, as it may be observed together with verrucous carcinoma, but then better be described as "hybrid carcinoma" due to a conventional infiltrative growth. Probably the metastatic risk is low, but I am not sure if it is as low as in conventional verrucous carcinoma.

### **CASE NO. 3 – CONTRIBUTED BY: Gerald J. Berry, M.D.**

**Abbas Agaimy** – Very unusual neoplasm; why thymoma if pankeratin is negative!!! The consistent calretinin expression is another unusual feature, although it might represent a possible link to underlying myxoma which is usually calretinin positive. This rare lesion (I have to admit I have never seen one before) might represent just an unusual (metaplastic!!!) pattern of myxoma.

**Justin Bishop** – Truly bizarre. It does appear to be the same tumor as described by Miller, et al. but the immunoprofile suggests that it is not truly a thymoma (similar to ectopic hamartomatous “thymoma” which probably isn’t).

**Ira Bleiweiss** – Wow! I had no clue. Didn’t know this could occur.

**Alberto Cavazza** – Fascinating case indeed! Before reading your diagnosis, I thought a peculiar myxoma, but my experience in cardiac pathology is almost zero. I have some concern for the diagnosis of thymoma, particularly due to the immunostains, but I have no good ideas.

**Kum Cooper** – Fascinating case Gerry. Like your interpretation. Question: was the tumor really 32.8 cm?

**Göran Elmberger** – Rare case. Difficult. I see myxoma variant but have a hard time recognize convincing thymoma component. Also find your IHC studies with negative results for CK’s and PAX8 disturbing. This is in opposition with the published results from the Miller paper. It does show some overlapping features at histology with the published cases.

**Franco Fedeli** – CK negative thymoma. Very unusual staining pattern or a thymoma. Could it be an epithelioid variant of myxoma?

**Cyril Fisher** – Cardiac myxoma with thymoma, new to me, great slide.

**Maria Pia Foschini** – Really interesting and unique case! Cardiac myxomas are quite rare and when show features like these they are almost impossible to diagnose.

**Masaharu Fukunaga** – A fascinating case. I had no idea of thecoma at all. I am not sure there is cardiac myxoma element in the slide.

**Barbara Gazic** – Really unusual case. The morphology fits with thymoma. Regarding the neoplasms arising in cardiac myxoma I am only familiar with the case of a large B cell lymphoma arising in cardiac myxoma reported by Aguilar, but we have never seen any case of cardiac myxoma with a secondary tumour arising in it.

**Thomas Krausz** – This is a diagnostically difficult case. However, according to the discussion, only calretinin was positive by IHC. Calretinin is expressed in about 75% of cardiac myxomas. I have never seen a thymoma without keratin immunoreactivity, so I don't think this is a thymoma in a cardiac myxoma. Rarely cardiac myxoma may exhibit pseudomalignant changes (see AFIP atlas of tumor pathology on heart and great vessels, 1995) as a result of hypercellularity without nuclear pleomorphism or brisk mitotic activity. I favor the diagnosis of cardiac myxoma with hypercellularity.

**Brandon Larsen** – Fascinating cardiac myxoma. I haven't encountered a myxoma before with this peculiar change. I'd be reluctant to call this "thymoma", given that this term implies potential malignant behavior and could raise undue alarm clinically, but it certainly could be... and I don't have a better term to suggest, nor am I convinced that it would NOT have the potential for malignant behavior. Maybe this is just some type of epithelial metaplastic change, rather than true thymic differentiation? It seems to lack many other thymic markers and TdT etc. are negative. In any event, it's reassuring that the patient is okay 3 years later. Very strange. Thanks for sharing, Gerry.

**Jesse McKenney** – Wow... fascinating case (I hadn't seen that reference). Could this represent an unusual hypercellular variant form of atrial myxoma?

**Thomas Mentzel** – What a case! However, isn't it unusual that tumour cells are negative for cytokeratins?

**Michal Michal** – Amazing case. The question is, whether it does not represent some hitherto undescribed thymoma-like tumor arising in cardiac myxoma.

**Markku Miettinen** – Thymoma type B3. No definite myxoma on the slide.

**Cesar Moran** – Unusual thymoma.

**Fredrik Petersson** – Could this be a mucin poor atrial myxoma??? Eagerly awaiting the thoracic specialists' views.

**Murray Resnick** – Fascinating case.

**Brian Rubin** – Very strange and interesting case. Your diagnosis seems plausible and I don't have a better suggestion.

**Niels Rupp** – This is a really fascinating case, as I do not have any association to put that in.

**Saul Suster** – I have never seen a tumor like this before in the heart, and I most certainly have never seen a thymoma that looked like this. I can accept a PAX8-negative thymoma because some B3's have loss of expression, but I have NEVER seen a CK or p63-negative thymoma! I don't know what this tumor is but it's very hard for me to accept it as a thymoma. It also does not look like a cardiac myxoma gone bad; the tumor cells are quite bland, and I couldn't find mitoses. Have no idea what this may be!

**Paul Wakely** – Case 3. Extraordinary case. Completely unaware of this entity.

**CASE NO. 4 – CONTRIBUTED BY: Justin Bishop, M.D.**

**Abbas Agaimy** – Beautiful example of classical sclerosing polycystic adenosis in the submandibular gland, thanks Justin.

**Gerald Berry** – The timing for receiving this case was perfect as I had been struggling to find a good name for a similar salivary gland lesion. It is a great term as it encompasses all the diagnostic features of a benign process that is possibly an intersection of duct obstruction and peculiar metaplasia.

**Ira Bleiweiss** – The resemblance here to apocrine lesions of the breast is striking. If it were in breast, I would require necrosis before making a diagnosis of intraductal carcinoma despite the significant nuclear atypia which is seen. Perhaps it might be a useful criterion here as well.

**Alberto Cavazza** – Very interesting case and discussion, thanks for sharing. The ductal component is quite atypical, but I understand that prognosis is excellent if the lesion is completely excised.

**Kum Cooper** – Thank you Justin. I have waited a long time to see one of these lesions after reading about them in the 90s! The lobular configuration in the less cellular areas was useful. Thank you for the succinct summary of the literature on this entity.

**Göran Elmberger** – Beautiful, rare classical case of SPA.

**Franco Fedeli** – Unusual case of sclerosing polycystic adenosis/adenoma. I have never seen a case like this. It is an interesting entity well described. This is another lesion originally described in the breast.

**Cyril Fisher** – Unusual salivary gland lesion, thanks for great discussion Justin.

**Maria Pia Foschini** – Sclerosing polycystic adenosis\adenoma. Thank you for contributing this very rare and interesting case. I have seen one previous case only, that presented in situ duct carcinoma (Fulciniti F, Losito NS, Ionna F, Longo F, Aversa C, Botti G, Foschini MP. Sclerosing polycystic adenosis of the parotid gland: report of one case diagnosed by fine-needle cytology with in situ malignant transformation. Diagn Cytopathol. 2010 May;38(5):368-73).

**Masaharu Fukunaga** – I have never seen sclerosing polycystic adenosis/adenoma. Some parts look like acinic cell carcinoma. Thank you very much.

**Barbara Gazic** – Interesting case. In the breast we do not expect DCIS to arise from fibrocystic changes/adenosis so polycystic adenosis is not very suitable term for the changes in salivary gland.

**Thomas Krausz** – Very nice case with superb discussion, thank you very much. So educational, especially for those who also practice breast pathology, seeing the overlapping features but also the differences, including the various cytoplasmic granules, both zymogen and apocrine. I am sure this entity can be quite challenging on frozen section.

**Brandon Larsen** – This case stumped me, probably because I wasn't familiar with this entity before. Despite its circumscribed border, the disorganized and somewhat infiltrative appearance of the glands made me nervous for a low-grade malignancy. I'd definitely be asking for help from my H&N colleagues if this were my case! Thanks for sharing.

**Jesse McKenney** – I'm surprised more of these don't progress to carcinoma.

**Thomas Mentzel** – Many thanks for sharing this rare case. Has anyone seen a similar lesion in the skin? I'm not aware of a sclerosing adenoma/adenomatosis in the world of cutaneous adnexal neoplasms.

**Markku Miettinen** – Atypical oncocytoid ductal proliferation, suspect low-grade intraductal carcinoma.

**Delia Perez-Montiel** – Very nice case.

**Cesar Moran** – Great case, thanks for sharing it.

**Fredrik Petersson** – Agree. Very nice case. IHC for myoepithelial cells of tremendous value because of the frequent distortion of the atypical proliferation – adenosis as well as ADH/DCIS (Sclerosing polycystic adenosis of the parotid gland: report of a bifocal, paucicystic variant with ductal carcinoma in situ and pronounced stromal distortion mimicking invasive carcinoma. *Head Neck Pathol.* 2011 Jun;5(2):188-92). Of note, SPA may be non-cystic! Reference: Non-cystic Sclerosing Polycystic Adenosis: Diagnosis of a Hitherto Undescribed Pattern. Petersson F. *Head Neck Pathol. In Press.* Recently I saw what I am convinced is a SPA with extensive cancerization of the adenosis component – another pattern that may mimic invasive carcinoma ex-SPA. We wrote up the case, but I was not able to get the reviewer on board.

**Murray Resnick** – Beautiful example.

**Brian Rubin** – New entity for me. Thanks.

**Niels Rupp** – A great case of this really rare entity. Also, very interesting to see some atypical intraductal features, almost identical to breast lesions, and probably a similar way of development as in “intraductal” carcinoma ex pleomorphic adenoma. Thanks for sharing.

**Saul Suster** – Great case! It can sometimes be very easy to confuse this for low-grade mucoepidermoid carcinoma. The lack of infiltration or perineurial invasion is a helpful clue.

#### **CASE NO. 5 – CONTRIBUTED BY: Ira Bleiweiss, M.D.**

**Abbas Agaimy** – Good name for this uncommon lesion and good teaching discussion, it carries somewhat a resemblance to chalazion of the eyelid.

**Gerald Berry** – Nice example. They can get large enough to raise clinical concern.

**Alberto Cavazza** – Very interesting, I ignored the lesion.

**Kum Cooper** – Thank you Ira. Another entity that I’ve read about but never seen before. Thanks for sharing “through the club”!

**Göran Elmberger** – Interesting case and discussion. Ira you forgot to tell it was a breast lesion but for us who know you well that goes without saying... Unfortunately, not characteristic cystic micro abscesses in my slide so I am happy you included a photo... Regarding problematic stains for microorganism detection I had an anecdotal case where my molecular wizard Mehran Ghaderi did 16srRNA sequencing and found evidence of Corynebacteria on blasting sequence. I was truly impressed and perhaps this could be a highly sensitive general technique for detecting microorganisms...

**Franco Fedeli** – In this case the infiltrate is richer in plasma cells than in granulocytes.

**Cyril Fisher** – Cystic neutrophilic granulomatous mastitis, a distinctive appearance. New to me.

**Maria Pia Foschini** – Unfortunately my slide lacked the typical features of neutrophilic granulomatous mastitis. It showed just non-specific acute and chronic inflammation.

**Masaharu Fukunaga** – It is very nice to share the case of cystic neutrophilic granulomatous mastitis, Ira. My slide shows beautifully the representative changes.

**Barbara Gazic** – The morphology reminds me of 'doughnut' shaped micro abscesses seen in the bone marrow of the patients with Q fever.

**Thomas Krausz** – This entity is new to me. Thank you very much for submitting it.

**Brandon Larsen** – Agree. Great case.

**Jesse McKenney** – I have no experience with well-circumscribed inflammatory lesions like this in the breast.

**Thomas Mentzel** – I'm so lucky to have in my slide a doughnut-like microabscess!

**Markku Miettinen** – Slide shows chronic neutrophil-containing inflammation with granulomatous features.

**Delia Perez-Montiel** – Interesting case. In Mexico we have a very high prevalence of tuberculosis, so, in some cases with granulomatous mastitis we do PCR studies for mycobacteria and a few cases have been positive.

**Cesar Moran** – Nice case.

**Fredrik Petersson** – Unaware of this entity. Now enlightened. Thanks Ira, for educating me/us.

**Murray Resnick** – Nice case. We had one a few months ago. Fortunately, our pathologist was aware of the entity as the bugs were difficult to find as you mentioned.

**Brian Rubin** – Thanks for the nice discussion. This is another new entity for me.

**Niels Rupp** – A really unique pattern, I have seen an identical case a few years ago, including the described Gram-positive bacteria.

#### **CASE NO. 6 CONTRIBUTED BY: Fátima Carneiro, M.D.**

**Abbas Agaimy** – Rare example of primary signet ring carcinoma of colon, extensive disease in contrast to subtle endoscopic findings. Thanks Fatima, for a beautiful slide and concise discussion. What about the frequency of E-cad germlines in those very young patients?

**Gerald Berry** – I can't remember the last time I saw a pure signet ring cell carcinoma of the colon! Nice to see a case to reinforce that they can and do occur in the colon!

**Ira Bleiweiss** – Agree. Beautiful case.

**Alberto Cavazza** – Thanks for sharing this rare tumor.

**Kum Cooper** – Thank you Dr. Carneiro for this great example in the colon. Good to see cases with classical pathology in this group! In Africa I have seen signet ring cell carcinoma in the rectum in young men. I don't think they were ever characterized any further though. I wonder if they were MSI high?

**Göran Elmberger** – Thanks for showing classical but in this location rare case. Good to know about differential MUC staining patterns.



**Franco Fedeli** – Signet ring cell carcinoma of the colon. Very rare case. The type of MUC is important for the differential diagnosis between stomach and colon.

**Cyril Fisher** – Signet ring adenocarcinoma of colon, striking appearance.

**Maria Pia Foschini** – Interesting and rare case. The features of these neoplastic cells are “true signet ring” and not simply “*bona fide* signet ring”!

**Masaharu Fukunaga** – A beautiful case of signet-ring cell carcinoma of the colon. Welcome Fatima! Mucin Immunoprofiles of colon and gastric signet-ring cell carcinomas are very informative. Thank you.

**Barbara Gazic** – Very useful information regarding MUC2, MUC5A and MUC6 regarding the origin. We’ll try to use this in the few cases from our archives.

**Ondra Hes** – Very interesting case. One question from a routine pathologist: Is there any chance to rule out origin in the stomach by means of some immunohistochemical/other panel? Thank you.

**Thomas Krausz** – Agree with diagnosis, striking morphology. Historically, I remember a case of a pseudotumor in the rectal wall, closely mimicking signet ring cell carcinoma and diagnosed as such, which in reality was a benign histiocytic infiltrate as a result of injected polyvinylpyrrolidone. Polyvinylpyrrolidone is positive with mucicarmine and colloidal iron. However, in contrast to mucin, it also stains with Congo red.

**Brandon Larsen** – Beautiful case. Thanks for sharing.

**Jesse McKenney** – Agree, signet ring cell adenocarcinoma.

**Thomas Mentzel** – Nice example of a rare lesion, many thanks!

**Markku Miettinen** – Signet ring cell carcinoma, ?primary in the colon.

**Delia Perez-Montiel** – Very nice case, only a question, because the previous history of high grade papillary urothelial carcinoma of the bladder, was a signet ring cell variant ruled out? Sometimes urothelial carcinomas can have a signet ring cell component with CDX2 expression and recurrence can be atypical.

**Cesar Moran** – Nice case.

**Fredrik Petersson** – Very unusual colorectal primary. In most centers spread from a gastric primary would have to be excluded – despite the different MUC-pattern. Thank you.

**Murray Resnick** – Great case and excellent discussion on differentiating colonic signet ring from gastric signet ring adenocarcinoma. As you mentioned it was critical in this case to differentiate between the two as I could not identify a precursor adenoma in the slides sent.

**Brian Rubin** – Beautiful case.

**Niels Rupp** – This is a very unusual purely signet ring differentiated carcinoma, I have not seen before in this location. Recently, I encountered a similar purely signet ring cell intestinal-type adenocarcinoma in the sinonasal tract.

**Saul Suster** – Nice and rare presentation of signet ring adenocarcinoma. Welcome to the Club Fatima!

**CASE NO 7. – CONTRIBUTED BY: Alberto Cavazza, M.D.**

**Abbas Agaimy** – Rare lesion with even more unusual terminology, I wonder if S100 and CD1a is relevant in such lesions to rule out LCH.

**Gerald Berry** – Nice example. We rarely see it here because of so few smokers!

**Justin Bishop** – Very strange. I had not heard of this, but my colleague Dr. Mariano de Vito did – he remembered Prof. Cavazza presenting this case at a conference!

**Ira Bleiweiss** – I’ve heard of this, but I don’t recall ever seeing one. What a strange misnomer.

**Kum Cooper** – Thank you Alberto you for sharing this case. I have only seen this entity twice before and on both occasions, I failed to recognize it; primarily since, as you say, it does not truly resemble the placenta!

**Göran Elmberger** – Interesting and rare lesion. In my slide one good villiform structure. Interesting hypothesis on etiology and pathogenesis. Need further studies. Similarities to “free floating septae” - a finding I personally use in definition of emphysema. The clinicopathological circumstances for PTM clearly stands out from traditional bullous emphysema.

**Franco Fedeli** – I think that this lesion is related to alveolar adenoma. In both lesions mesenchymal cells are present inside the interstitium.

**Cyril Fisher** – Very interesting case and discussion.

**Maria Pia Foschini** – Very interesting and rare case. Thank you for sharing, I had never seen this before and I was not aware of these lesions. Indeed, these clear cells are quite intriguing, and they do not resemble placental cells. We found two further papers dealing with this entity. [1]: Naureen Narula, Sam Ngu, Dikshya Sharma, Faraz Siddiqui, Michel Chalhoub: Placental transmogrification of the lung associated with unilateral pleural effusion: A case report with a comprehensive review of the literature. *Respiratory Medicine Case Reports* 26 (2019) 161–164, and [2]: Man Yang, MM, Xue-Ting Zhang, MM, Xiao-Fang Liu, MD, Xu-Yong Lin, MD: Placental transmogrification of the lung presenting as a peripheral solitary nodule in a male with the history of trauma. *Medicine* (2018) 97:18.

**Masaharu Fukunaga** – Placental transmogrification (PT) of the lung is very difficult to understand. In this case the interstitial clear cell proliferation is prominent and very interesting. Thank you, Alberto.

**Barbara Gazic** – Thank you for very interesting case, never seen before.

**Thomas Krausz** – I have seen only one case before (in a slide seminar). I am not sure what the interstitial cells are, but would do additional IHC markers for beta catenin, CD31/ERG.

**Brandon Larsen** – Tough case, Alberto. It certainly resembles placental transmogrification in many respects, but I would actually favor cystic metastasis of a low-grade fibrohistiocytic neoplasm, either metastatic DFSP or metastatic dermatofibroma / fibrous histiocytoma, or something in the differential diagnosis of what was called “cystic fibrohistiocytic tumor of the lung” in the past. It might be interesting to test for PDGFB gene rearrangements in this case and inquire about any history of previous skin lesions. Tom Colby collected a handful of cases over the years, which we still have in our collection, and I would be happy to collaborate on a project if you’re interested.

**Jesse McKenney** – I was worried about LAM.

**Thomas Mentzel** – What a strange name indeed! Good luck for the characterization of the lesional mesenchymal cells!

**Markku Miettinen** – Reactive changes. Seems to be consistent with “placental transmogrification”.

**Cesar Moran** – Nice case.

**Fredrik Petersson** – Great case highlighting an important aspect - the interstitial cells - of this rare condition. Just based on the morphology my concern was with LAM. But the pattern of the lesion was not right. Thanks.

**Brian Rubin** – Not sure I understand this case. Kind of looks like benign fibrous histiocytoma.

**Niels Rupp** – An extraordinary and exciting case. I have seen once a case of placental transmogrification in our department, also presenting as bullous emphysema. Interestingly, the paraffin blocks from an initial resection in the 1970s were available and showed a similar picture. This case has been published here, for anyone who is interested: <https://www.ncbi.nlm.nih.gov/pubmed/27609748>

**Saul Suster** – Thanks for sharing this rare case. This doesn't look quite like the previous cases of placental transmogrification I've seen, but it comes close for lack of a better explanation!

#### **CASE NO 8. – CONTRIBUTED BY: Göran Elmberger, M.D.**

**Abbas Agaimy** – Great and very rare case Göran. Critical assessment of superficial urothelium to rule out a papillary component and CIS is mandatory for diagnosis. We recently reported frequent SWI/SNF loss including rare SMARCB1 loss in dedifferentiated and undifferentiated urothelial carcinoma so now another differential diagnosis in this context.

**Gerald Berry** – This is another first for me. I always find the hardest part of making the diagnosis of epithelioid sarcoma is remembering to think of the possibility outside of the limbs!

**Ira Bleiweiss** – Wow! History really is everything – impossible diagnosis without it. I recently saw a metastatic lobular carcinoma to bladder in a patient with a long(ago) history of bilateral invasive lobular carcinoma. Equally necessary history.

**Alberto Cavazza** – A rare tumor in an exceptional location! No hope for me to think of the right diagnosis without clinical information.

**Kum Cooper** – Wow Goran...what a case!!! Fascinating morphology and write up. Thank you!

**Göran Elmberger** – My case. I hope you reviewed it blindly! Not easy unless you know previous history up-front... Unfortunately, the young man is now DOD 6 months after diagnoses of bladder metastasis.

**Franco Fedeli** – Very unusual presentation of metastatic epithelioid sarcoma. The clear cell appearance is unusual. What about Pax 8. INI1 is negative in rare tumors of the kidney like medullary carcinoma.

**Cyril Fisher** – Amazing case with unusual location for epithelioid sarcoma metastasis and striking appearance with clear cells in sheets. I do not recall seeing prominent glycogenic vacuolation before in some 300 ES over the years. Clear cell morphology with glycogen was not mentioned in the AFIP series of 241 cases (AJSP 1985; 4: 241-26). It would be interesting to know whether the primary tumor had similar morphology.

**Maria Pia Foschini** – Really interesting case and difficult diagnosis, especially in absence of clinical history.

**Masaharu Fukunaga** – A tough case to make a diagnosis. Initially I had no idea of metastatic epithelioid sarcoma. Thank you very much for the detailed discussion.

**Barbara Gazic** – Most probably it would be impossible to diagnose this case without knowing the history of ES.

**Thomas Krausz** – Diagnostically challenging case. I agree, clinical history is critical to exclude dedifferentiated urothelial carcinoma with INI1 loss.

**Brandon Larsen** – Fascinating case. From a morphologic standpoint, I was wondering about PEComa, but it's hard to argue with your stains! I haven't encountered metastatic ES in the urinary bladder before. Thanks.

**Jesse McKenney** – Great case! It is very interesting that the low-power pattern resembles the benign reactive lesion described as "papillary cystitis", but the malignant cells fill the lamina propria. I was expecting a clear cell sarcoma family tumor by H&E.

**Thomas Mentzel** – Many thanks for the case and for the excellent discussion. I have only a brief historic comment. Epithelioid sarcoma was most likely first described by Josef Laskowski (in a polish paper he published a series of 7 cases of an entity he called "aponeurotic sarcoma" that represents epithelioid sarcoma in Polish Medical Journal Vol X No1/1971) and at least the polish pathologists are very proud of this.

**Markku Miettinen** – Clear cell neoplasm, carcinoma. Could not possibly get to epithelioid sarcoma by histology. Of course, this might be right based on your studies.

**Delia Perez-Montiel** – Very nice discussion, thank you.

**Cesar Moran** – Very interesting case. Did not think about epithelioid sarcoma.

**Kyle Perry** – Great case. It's interesting that many of the metastatic tumor cells appear to take on a more clear or vacuolated morphology.

**Fredrik Petersson** – Sneaky case if the history was not provided. The papillomatous urothelial lesion looks a bit atypical with areas of mucinous metaplasia. Tumor to tumor metastasis?

**Murray Resnick** – Amazing case.

**Brian Rubin** – Hmm. I've never seen epithelioid sarcoma metastasize to bladder. The immunophenotype supports this conclusion.

**Niels Rupp** – An interesting case to discuss the broad differential diagnosis of clear cell neoplasms and to always keep possible metastatic manifestations in mind.

**Saul Suster** – I would have not been able to make this diagnosis, even with knowledge of the history of an epithelioid sarcoma of the foot. Despite the immunophenotype, it just doesn't look like one on the H&E.

#### **CASE NO. 9 – CONTRIBUTED BY: Franco Fedeli, M.D.**

**Abbas Agaimy** – Rare example of Müllerian-type clear cell carcinoma of renal pelvis. Aggressive type 2 papillary carcinoma and collecting duct carcinoma are relevant DDX, was NapsinA positive? AMACR?

**Gerald Berry** – Agree.

**Ira Bleiweiss** – Agree. Very nice.

**Alberto Cavazza** – This kind of morphology in this location can be mistaken for a more trivial parenchymal renal tumor, but I suspect the location can be a diagnostic clue. Spectacular case!

**Kum Cooper** – Fascinating case Franco. I showed the case to my GU pathology colleague who showed me a similar case in the bladder (PAX8, Napsin-1, Racemase all positive; GATA-3 negative).

**Göran Elmberger** – Interesting and rare case. Histology quite compatible with NA like variant of Mullerian clear cell carcinoma of renal pelvis. However, I have some difficulty to differentiate it from renal papillary carcinoma type 2. The latter tumor is perhaps more common, and this tumor seems also to grow within the renal parenchyma. Overlapping histology and IHC; according to Immunoquery the only differentiating antigens would be Lewis Y, PDGFR alpha, Mesothelin and OCT4. Curious of outcome or additional IHC studies.

**Maria Pia Foschini** – The microscopic findings of this lesion and the immunohistochemical features are consistent with the diagnosis of a Mullerian type clear cell tumour involving the urinary tract, very unusual in a male patient.

**Cyril Fisher** – Rare variant of renal carcinoma, very interesting.

**Masaharu Fukunaga** – Thank you, Franco. I have never seen case of clear cell adenocarcinoma, Mullerian type of the renal pelvis.

**Barbara Gazic** – Very interesting case and useful information regarding PAX8 positive tumors in a male.

**Ondra Hes** – I've never seen Mullerian type clear cell adenocarcinoma in the kidney (if I did, for sure I missed it). I have great difficulties to differentiate this case from "papillary" renal cell carcinoma (however we mostly agree that papillary RCC is rather a group of similar tumors rather than a compact entity). From a practical point of view, I would very carefully check the renal pelvis to rule out urothelial origin (however this seems highly unlikely to me).

**Thomas Krausz** – Before reading the discussion, I was considering type II papillary renal cell carcinoma and even FH-deficient renal cell carcinoma.

**Brandon Larsen** – Interesting case. I would have probably made the mistake of favoring an odd variant of papillary RCC, and might've looked for one of those translocation-associated RCCs.

**Jesse McKenney** – Rare case!

**Thomas Mentzel** – Many thanks!

**Markku Miettinen** – Renal papillary clear cell carcinoma of renal pelvis. Did not know of Mullerian type.

**Cesar Moran** – Great case, thanks for sharing.

**Kyle Perry** – Very interesting case. Given that these can stain for Pax8, it seems there would be a real potential to mistake this for other primary renal neoplasms.

**Fredrik Petersson** – Infiltrative carcinoma with papillary structures and a fair component of clear cells. Any more IHC done to support clear cell carcinoma of Mullerian differentiation? HNF1-beta, Napsin A?

**Brian Rubin** – Very unusual case.

**Niels Rupp** – Certainly, a rare but very important differential diagnosis is with nephrogenic adenoma. I recently saw a consult case of a clear cell carcinoma, which was in the vicinity to the urinary bladder and therefore initially (in a

small biopsy) mistaken as nephrogenic adenoma. I would be curious about the ARID1a and DNA-Mismatch-Repair protein status of your case.

**Saul Suster** – Agree with the diagnosis; excellent case!

**CASE NO. 10 – CONTRIBUTED BY: Maria Pia Foschini, M.D.**

**Abbas Agaimy** – Anaplastic plasmacytoma. Tough and mainly IHC diagnosis, in particular at such unexpected site.

**Gerald Berry** – Anaplastic plasmacytoma, let alone extramedullary plasmacytoma in this location is so rare. Another example of needing to keep a broad differential diagnosis.

**Justin Bishop** – Wow, scary case!

**Ira Bleiweiss** – Nice case. I doubt that I would have thought of the diagnosis- it looks so epithelioid.

**Alberto Cavazza** – A very unusual tumor, thanks for sharing!

**Kum Cooper** – Thank you Maria. I have seen only one plasmacytoma in the meninges which I called meningioma on frozen! And it was much better differentiated than yours. Great case! Thanks for sharing.

**Göran Elmberger** – Nice case with some neuro-hematopathology. Value of systematic evaluation including IHC fishing. Also illustrates paradigm that anything can occur everywhere... In retrospect I see a hint of cartwheel pattern chromatin, focal hof and a bluish cytoplasm of typical character. No Russel or Dutcher bodies. Great case!

**Franco Fedeli** – Anaplastic plasmacytoma. Very rare location for this tumor.

**Cyril Fisher** – Extramedullary anaplastic plasmacytoma, very rare case.

**Masaharu Fukunaga** – Thank you very much for the beautiful case of meningeal anaplastic plasmacytoma. I have never seen this type of tumor in this location.

**Barbara Gazic** – Classical case of plasmacytoma in unusual location, nice case.

**Thomas Krausz** – Agree with diagnosis, though the tumor cells do not appear too anaplastic to me. I am also wondering whether there is focal amyloid deposition in the sclerotic stroma?

**Brandon Larsen** – Wow. Spectacular case. Thanks.

**Jesse McKenney** – Agree, plasmacytoma.

**Thomas Mentzel** – To be honest I had no idea....

**Markku Miettinen** – Plasmacytoid neoplasm. CD38 would be nice to have, kappa restriction is ok. Differential diagnosis may also include marginal zone lymphoma with plasmacytoid differentiation.

**Cesar Moran** – Very interesting case.

**Kyle Perry** – Very nice example of anaplastic plasmacytoma. Thank you for sharing.

**Fredrik Petersson** – Great case. Hematolymphoid impression on H&E. Convincing IHC for plasma cell neoplasm.

**Brian Rubin** – Fooled me. I wasn't thinking plasmacytoma but in retrospect the diagnosis is plausible.

**Niels Rupp** – A really difficult case, as the typical plasmacytoid morphology is barely visible. Did you test for EBV?

**CASE NO. 11 – CONTRIBUTED BY: Masaharu Fukunaga, M.D.**

**Abbas Agaimy** – Classical example of adenomatoid tumor of broad ligament, thanks Masa.

**Gerald Berry** – Agree.

**Justin Bishop** – Lovely case.

**Ira Bleiweiss** – Very impressive indeed. The diagnosis is much easier in testis, though.

**Alberto Cavazza** – Very impressive and photogenic example of adenomatoid tumor.

**Kum Cooper** – Thank you for sharing this case in an unusual site Masa.

**Göran Elmberger** – Agree. Don't see that tumor often and never in the broad ligament. Thanks for sharing!

**Franco Fedeli** – Educational case. In some areas the lesion is cystic and morphologically looks like a serous cystadenoma of the pancreas.

**Cyril Fisher** – Lovely adenomatoid tumor.

**Maria Pia Foschini** – Adenomatoid tumor of the broad ligament. I agree with the diagnosis. I did not know that it can arise in the broad ligament also. I have seen uterine cases only.

**Barbara Gazic** – Nice case, between many cases of adenomatoid tumour I don't remember a case in the broad ligament.

**Ondra Hes** – This is nice case of adenomatoid tumor (with bridging strands) ☺ Thank you!

**Thomas Krausz** – Very nice example, thank you very much.

**Brandon Larsen** – Agree. Beautiful adenomatoid tumor. Great case. Thanks for sharing.

**Jesse McKenney** – Agree, adenomatoid tumor with unusual cystic component.

**Thomas Mentzel** – What a beautiful example!

**Markku Miettinen** – Adenomatoid tumor, nice example.

**Delia Perez-Montiel** – Thank you, I can compare with case 1.

**Cesar Moran** – Same discussion as for case #1.

**Fredrik Petersson** – Interesting case indeed. It looks to me that part of the tumor shows features of a multicystic mesothelioma and another part looks like an adenomatoid tumor. A few "hybrid mesothelial tumors" are described in a recent paper: Sun M et al. Ann Diagn Pathol. 2019 Feb;38:43-50.

**Murray Resnick** – Nice example.

**Brian Rubin** – Great case. Finally recognized a case.

**Niels Rupp** – A very nice case to compare the morphology to case 1. I personally believe that these tumors are related to WDPPM (or vice versa), as I recently saw a case of WDPPM with small foci of adenomatoid tumor like differentiation (no p16 loss, BAP1 positive), which has also been described in a large cohort of 75 WDPPM cases (Sun et al., Annals of Diagnostic Pathology, 38:43-50, 2018).

**Saul Suster** – Nice case Masa, very striking.

**CASE NO. 12 – CONTRIBUTED BY: Thomas Krausz, M.D.**

**Abbas Agaimy** – Fully agree, SMARCA4-deficient dedifferentiated endometrioid adenocarcinoma, superb discussion, thanks Thomas. Were CD117 and SALL4 diffusely positive? That was my experience with these tumors.

**Gerald Berry** – Agree. I can't keep up with all the new molecular categories of endometrial carcinomas.

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – Very interesting case and discussion.

**Kum Cooper** – Thank you Thomas. Nice case and great write-up too covering all the recent publications in this field. There is another series by Nucci in Mod Pathol with pure rhabdoid morphology and SMARCA4 deficient (young woman, endometrium, aggressive). Saw one case last year in consultation.

**Göran Elmberger** – Great and important case. New and useful information to me about how to use components of the SWI/SNF complex; SMARCB1, SMARCA1 and SMARCA2, as help in identifying dedifferentiated/undifferentiated endometrial carcinoma.

**Franco Fedeli** – Dedifferentiated endometrial carcinoma with loss of SMARCA4. This tumor has a poor prognosis as well as other tumors with the same loss of SMARCA4.

**Cyril Fisher** – Rare variant of endometrial carcinoma.

**Maria Pia Foschini** – Dedifferentiated endometrioid carcinoma with SMARCA4 loss. The case is very interesting, I was not aware of this entity. On the basis of the data here shown, should genetic investigation be suggested?

**Masaharu Fukunaga** – Dedifferentiated endometrioid carcinoma, a very interesting case. The discussion is very informative. Recently I encountered dedifferentiated carcinoma associated with atypical polypoid adenomyoma.

**Barbara Gazic** – Interesting information regarding SMARCA genes in dedifferentiated endometrioid carcinoma. We don't perform immuno for SMARCA routinely in those cases.

**Brandon Larsen** – Great case. I had a virtually identical case of dedifferentiated endometrioid Ca with SMARCA4 loss just a few months ago, with brain mets, and have had several cases in the lung and one in the GI tract. Ever since we validated the BRG1 antibody in our own lab, we've been finding similar cases in our own practice in various organ systems, virtually always with high-grade rhabdoid morphology. Seems to be another example of a "not as uncommon as we initially thought" problem. Once you have the tool, the cases start coming out of the woodwork! Thanks for sharing.



**Jesse McKenney** – Agree. We are starting to recognize a lot more of these SMARCA4 deficient malignant tumors.

**Thomas Mentzel** – A wonderful example of another dedifferentiated neoplasm! Many thanks.

**Delia Perez-Montiel** – Interesting association with loss of SMARCA4 (BRG1), SMARCA2 (BRM), and SMARCB1 (INI1), I wonder if these kinds of lesions are part of some group in molecular classification.

**Markku Miettinen** – Endometrial adenocarcinoma, dedifferentiated. BRG1 noted (not histologically assessable).

**Cesar Moran** – Why dedifferentiated? Why not just an adenocarcinoma with different growth patterns?

**Fredrik Petersson** – Very nice example, illustration and characterization of the phenotypic result of tumor genetic instability. The patient has poor prognosis.

**Murray Resnick** – Beautiful case and excellent discussion.

**Brian Rubin** – Interesting case and nice discussion. It's cool when you can correlate morphology with genetics as in loss of SMARCA4 in this case.

**Niels Rupp** – Another exciting case out of the spectrum of SWI/SNF complex alterations.

**Paul Wakely** – Thank you Thomas for the summary description of SWI/SNF complex. Neoplasms harboring this abnormality seem to be occurring on a regular basis nowadays.

#### **CASE NO. 13 – CONTRIBUTED BY: Alberto Marchevsky, M.D.**

**Abbas Agaimy** – Lung carcinoma showing STAS, I believe this is a genuine pattern of spread of detached tumor cells within the lung and may mirror the trans-alveolar spreading along the alveolar septae seen in bronchoalveolar carcinoma. This finding however is still not TNM-reflected.

**Gerald Berry** – I thought this looked more like artifactual displacement along the airway than convincing airway spread. I am looking forward to more definable/reproducible criteria in future publications.

**Justin Bishop** – I am out of the thoracic path field now, and this concept is still new to me. It sure looks like artifact to me.

**Ira Bleiweiss** – Alberto, I would suspect this is artifactual and probably of no consequence, but I'm not sure how to prove it.

**Alberto Cavazza** – I have not a strong opinion on STAT. I tend to think it is an artefact, but maybe it is facilitated by the fact that in some tumors neoplastic cells are less cohesive, and this may have a prognostic impact. For sure in a significant proportion of cases I would not be able to distinguish real STAT from an artefact. Another problem may be to distinguish in practice STAT from micropapillary features. I am curious to know the opinions of the other members.

**Kum Cooper** – Alberto, I thought that aerogenous spread was a recognized form of tumor dissemination for many decades!

**Göran Elmberger** – Slide shows a mixed pulmonary adenocarcinoma with a dominant lepidic pattern component. Macrophage filling of adjacent alveolar spaces of "golden pneumonia" character. Few STAS tumor cells floating apparently discontinuous from body of cancer. Useful artifact? Loss of cohesion? Papers claim adverse prognostic finding.

**Franco Fedeli** – Detached cells are present in many types of tumors and the prognosis is usually worse.

**Maria Pia Foschini** – Spread through air spaces is a debated morphological feature. Many studies are emerging, demonstrating its importance as a predictive factor of poor prognosis in lung cancer. I am not an expert in lung pathology, but, in the present case I would consider it a way of spread rather than an artifact.

**Masaharu Fukunaga** – I favor spread through air spaces. I can find atypical cells in the alveolar space.

**Barbara Gazic** – For me it is an artefact...

**Thomas Krausz** – Yes, there are foci of adenocarcinoma with a predominantly acinar pattern. Conceptually I believe that carcinoma may spread through air-spaces, but on my slide I could not see good example of such a phenomenon.

**Brandon Larsen** – Agree. Nice case of STAS. Thanks for sharing, Alberto. In my opinion, STAS is sometimes real... except when it's just an artifact! And I never really know for sure which one is true in any particular case. I'm just glad our surgeons haven't started to ask us to look for STAS on frozen sections... at least not yet.

**Jesse McKenney** – My opinion is that I think "we" are making our job unnecessarily complicated.

**Thomas Mentzel** – I think it's a reasonable mode of cancer spreading if I have an exophytic growing neoplasm.

**Markku Miettinen** – Well-differentiated adenocarcinoma, seems to be in the airspaces.

**Cesar Moran** – I'd rather stay silent!!!

**Fredrik Petersson** – Too esoteric pulmo-oncological question/issue for my knowledge. Awaiting (again) the more well versed (in thoracic pathology) colleagues' comments.

**Brian Rubin** – I have to think that STAS is artifact but proof is required. Seems like a good question for a mouse model.

**Niels Rupp** – A major point for discussion: in micropapillary pattern, I would agree to an airway spread, but I do not know if it is the same for more conventional patterns.

**Saul Suster** – This is a rather contentious subject on which the jury is still out. Dr. Rywlin used to talk of "tubular" spread of cancer in the airways, particularly for lepidic type of adenocarcinoma, but deciding whether some of these foci are artifact or tubular spread can be quite arbitrary in many cases. Until we have a more reliable way than just "because I said so" to tell them apart, I think its premature to try to establish this as a new standard of practice.

#### **CASE NO. 14 – CONTRIBUTED BY: Thomas Mentzel, M.D.**

**Abbas Agaimy** – Very rare example of huge retroperitoneal LGFMS with progression/dedifferentiation and pleomorphic cells, closely mimicking dedifferentiated liposarcoma. Thanks Thomas, for sharing.

**Justin Bishop** – Very interesting case, illustrating why putting "low-grade" in a tumor name can be problematic! (similar to polymorphous low-grade adenocarcinoma of salivary glands)

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – A phenomenon I ignored, thanks for the interesting discussion.

**Kum Cooper** – Thank you Thomas for sharing this interesting morphology of LGFMS. I have seen a few cases with LGFMS/SEF but not a LGFMS with progression as in your case. Interesting morphology resembling perineurioma too. In the old days before the translocation discovery, relation between LGFMS and perineurioma was talked about.

**Göran Elmberger** – LGFMS with progression. Not as well-known as dedifferentiated lipogenic neoplasms. By the way I too prefer the term progression.

**Franco Fedeli** – One example of this fascinating tumor with hyperchromasia of the neoplastic cells and necrosis.

**Maria Pia Foschini** – Low grade fibromyxoid sarcoma with morphological signs of progression. Interesting case, on rare occasions it can affect the head and neck region.

**Cyril Fisher** – Nice example of LGFMS with increased cellularity and nuclear pleomorphism. Sometimes there is marled cellularity at first presentation, making interpretation difficult. We are recognizing a wider range of morphology in this tumor type than was originally described. It would be of interest to know the fusion transcripts in this tumour as there are hybrid forms with sclerosing epithelioid fibrosarcoma

**Masaharu Fukunaga** – A challenging case. Initially without history, it seemed to be a malignant perineurioma. Thank you very much for sharing this tough case.

**Barbara Gazic** – Very interesting comparison to lipogenic neoplasms.

**Thomas Krausz** – Highly educational case. I agree that at this anatomic site and age group one needs to exclude dedifferentiated liposarcoma.

**Brandon Larsen** – Nice case of LGFMS, arising in an unusual location.

**Jesse McKenney** – I'm glad we have MUC4 now.

**Markku Miettinen** – Myxoid sarcoma. Can't see mitoses but due to necrosis seems to automatically go to intermediate grade (both slides). B not a perfect look for LGFMS but believable with documentation.

**Cesar Moran** – Nice case.

**Kyle Perry** – Thanks for sharing this case. I suspect that as NGS becomes more prevalent, the recognized morphologic and clinical spectrum of LGFMS will continue to expand. As noted in the discussion, I think there could be a real potential to confuse this tumor for a dedifferentiated liposarcoma on a limited biopsy of a retroperitoneal tumor.

**Fredrik Petersson** – Low-grade fibromyxoid sarcoma with progression to a higher grade. Low-power I was thinking of LGFMS, but the cytonuclear atypia, etc. put me off. Was there any classic low-grade component seen? It would have been interesting to see if and what extra mutational changes that a case like this has compared to a conventional LGFMS. This and similar phenomenon of progression seems to have been illustrated in Harry Evans paper: Am J Surg Pathol. 2011 Oct;35(10):1450-62. Low-grade fibromyxoid sarcoma: a clinicopathologic study of 33 cases with long-term follow-up.

**Brian Rubin** – Cool case. I'm impressed by how much the histology reminds me of perineurioma.

**Niels Rupp** – A very nice case. I have not seen this kind of spectrum of "LG" FMS before.

**Saul Suster** – It would have been interesting to do electron microscopy in this case. The histology in the low-grade areas reminds me of perineurioma, and the cells were reportedly positive for EMA which can also be positive in perineurioma. I haven't had much luck with MUC4, it seems to stain too many things indiscriminately. Can you do FISH for *FUS*? I think the case could benefit from further workup.

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

**Abbas Agaimy** – Dysplastic lipoma, I see now these tumors on an almost daily basis. Very uniform histology. Thanks Michal.

**Gerald Berry** – The variation in the size of the adipocytes was the clue for me. I was not aware of the association with ocular tumors.

**Justin Bishop** – Fascinating, thank you!

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – Very interesting case.

**Kum Cooper** – Thank you Michal for this case. Abbas also showed a nice example in Split last year.

**Göran Elmberger** – Good case. I like the terminology of dysplastic lipoma even if the previous term anisometric cell lipoma is very good from a descriptive point of view. Given RB1 genetical changes dysplastic seem to better reflect possible premalignant biology.

**Franco Fedeli** – Anisometric cell lipoma. What about CD34 in this tumor?

**Maria Pia Foschini** – Dysplastic lipoma. Interesting case. Differential diagnosis with atypical lipomatous tumor not easy.

**Cyril Fisher** – A recently proposed variant, dysplastic (anisometric) lipoma. The variation in adipocyte size is striking here.

**Masaharu Fukunaga** – Dysplastic or anisometric cell lipoma is new to me. Thank you very for sharing the interesting tumor, Michal.

**Thomas Krausz** – The discovery of association of dysplastic (anisometric) lipoma with retinoblastoma is fascinating. Of course, in view of heterozygous loss of RB, it does make sense.

**Brandon Larsen** – Interesting case. I would have probably just called this a lipoma with degenerative or reactive changes related to its large size. Thanks for sharing.

**Jesse McKenney** – Very interesting case!

**Thomas Mentzel** – Many thanks for sharing an example of a new entity. The neoplasm looks like classical atypical lipomatous tumour but has obviously different genetic changes (as it is the case with atypical spindle cell lipomatous tumour and atypical pleomorphic lipomatous tumour). Given that we have at the moment three different kinds of "atypical lipomatous tumours".

**Markku Miettinen** – Agree with dysplastic lipoma.

**Cesar Moran** – Interesting case.

**Fredrik Petersson** – Highly characteristic morphology. Since Michal's paper we have seen a couple of cases – one sent for consultation to confirm that we are correctly "calibrated". They seem to be "not that rare". P53 IHC very helpful.

**Brian Rubin** – I'm still not sure these are a thing. They might just be lipomas with fat necrosis, but Harry Evans is always right so I'm leaning toward believing.

**Niels Rupp** – This is an important differential diagnosis with ALT. I have seen an identical case from the shoulder recently, also showing this strong p53 staining. I totally agree with your findings. Another case was diagnosed as "traumatic" lipoma, due to the lack of mdm2 amplification.

**Saul Suster** – Yes, the tumor does look very disorganized for normal fat. "Dysplastic" sounds a bit aggressive; "anisometric" sounds more elegant and dignified.

#### **CASE NO. 16 – CONTRIBUTED BY: Michal Michal, M.D.**

**Abbas Agaimy** – Another fine contribution of Michal, mucin-filled cells in plexiform neurofibroma, remarkably associated with more myxoid intraneural foci. I have overlooked them prior to Michal's publication.

**Justin Bishop** – Diffuse and plexiform neurofibroma, not sure I would have noticed the muciphage-like cells in question

**Ira Bleiweiss** – Neurofibroma for sure. Why aren't the myxoid areas just degenerated nerves?

**Alberto Cavazza** – Interesting case, with a potentially useful diagnostic clue.

**Kum Cooper** – Thank you Michal. I have not observed these microvacuolated cells before.

**Göran Elmberger** – Peculiar and characteristic finding. Degenerative? Are these interspersed bulbous nerve-like structures parts of tumor or merely entrapped reactive normal nerve bundles?

**Franco Fedeli** – Thank you for this interesting observation about this type of tumor.

**Cyril Fisher** – Plexiform and diffuse neurofibroma with multivacuolated cells, very nice slide. Ultrastructural examination might be of interest.

**Maria Pia Foschini** – Plexiform neurofibroma with multivacuolated mucin-filled cells. Interesting finding. Same cells can be seen in mucinous peripheral neuropathy.

**Masaharu Fukunaga** – Plexiform neurofibroma, a very beautiful case. Multivacuolated cells looked histiocytes, but they are positive for CD34 and Glut1.

**Barbara Gazic** – Very interesting, haven't seen yet.

**Thomas Krausz** – Great observation.

**Brandon Larsen** – Nice case of plexiform NF. I haven't noticed this additional finding before. To me, the cells look like vacuolated macrophages collecting between the perineurium and nerve trunks, but it appears from your paper in Human Pathology that they are something else entirely.

**Jesse McKenney** – I have to admit that I haven't been looking for this. Now I will.

**Thomas Mentzel** – A very interesting finding that represents probably a degenerative phenomenon

**Delia Perez-Montiel** – Nice case.

**Markku Miettinen** – Neurofibroma with diffuse and intraneural components.

**Cesar Moran** – Nice example.

**Kyle Perry** – Thanks for this case (and marking the area of the mucin filled cells). These seem reminiscent of the muciphage like cells that can be seen in an intramuscular myxoma, further emphasizing the potential morphologic overlap between myxoma/nerve sheath tumor on a limited needle core biopsy.

**Fredrik Petersson** – Interesting observation. In addition to the plexiform morphology, prominent diffuse growth pattern of neurofibroma on my section.

**Brian Rubin** – Aren't the myxoid nodules degenerate nerves? I've never stained them but perhaps the CD34 positive/Glut1 positive cells are degenerate perineurial cells. I need to read your paper.

**Niels Rupp** – An intriguing detail, which really can be of diagnostic help.

**Saul Suster** – Very interesting and unusual case! We reported a few years ago with Paul Wakely similar tumor that contained scattered signet-ring lipoblast-like cells filled with fat (Plaza JA, Wakely P Jr, Suster S: Lipoblastic nerve sheath tumors. Am J Surg Pathol 30:337-344, 2006). The cells resembled mucin-filled metastatic carcinoma cells.

#### **CASE NO. 17 – CONTRIBUTED BY: Delia Perez-Montiel, M.D.**

**Abbas Agaimy** – Non-calcifying fibrous pseudotumor of testis/paratesticular, similarity to IgG4-related pseudotumor is remarkable. I think i have seen one multifocal case with foci of calcifications in single nodules as well.

**Gerald Berry** – Agree with the diagnosis of paratesticular fibrous pseudotumor. I was not aware of the IgG4 connection. A great learning case for me.

**Justin Bishop** – Very cool! Looks similar to eosinophilic angiocentric fibrosis of the sinonasal tract, another IgG4-related disease.

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – Another location for an in vogue lesion! Interesting case and discussion.

**Kum Cooper** – Lovely example Delia with IHC and serum confirmation.

**Göran Elmberger** – PTFP great case. Expanding spectrum of IGG4 sclerosing disease. Inactive fibrotic variant without classical features such as obliterative endophlebitis and pronounced storiform fibrosis. Shows value of low threshold for ordering IgG4 and an updated knowledge of literature. Had an interesting case myself a few weeks ago in young male with testicular torsion and necrosis where I found a funicular myofibroblastic pseudotumor with in active cellular phase. I kind of thought this was secondary to torsion but perhaps it was the other way around. Will go back and check the IgG4!

**Franco Fedeli** – IgG4 related disease. Another location for this pseudotumor.

**Cyril Fisher** – Fibrous pseudotumor and hyperIgG4– an expanding disease category.

**Maria Pia Foschini** – The diagnosis of paratesticular fibrous pseudotumour associated to IgG4 related disease is consistent with the clinical presentation and the histologic features of the mass. I wonder if the patient had further lesions in other organs.

**Masaharu Fukunaga** – Paratesticular fibrous pseudotumor associated with IgG4 related disease. This is my first time to see IgG4 related lesion in this location, thank you Della.

**Barbara Gazic** – Nice case of IgG4 presentation.

**Thomas Krausz** – Nice example. I have seen a few cases before.

**Brandon Larsen** – Interesting. The morphology is certainly in keeping with IgG4-related fibrous lesions elsewhere, but if this were my case, I would definitely be worried about a regressed GCT! It's certainly helpful that his serum markers were negative... and his IgG4 serum level was high.

**Jesse McKenney** – I agree with "fibrous pseudotumor"/ "nodular periorchitis" with increased IgG4 plasma cells. I'm not sure what this diagnosis means for the patient long-term. It will be interesting to see studies that evaluate how well IgG4 plasma cell infiltrates (when seen in combination with increased serum IgG4 levels) predict for the development of more systemic disease.

**Thomas Mentzel** – Irrespective of the IgG4 association the lesion looks like the borrelia-associated fibroid nodules we see frequently at the elbow. Is there any clinical or serological evidence of borrelia infection in this case?

**Michal Michal** – Nice case. I have some cases of the same morphology. All the cases revealed dendritic AE1-AE3 positive cells. It would be interesting for me to know, whether you saw the cytokeratin positive cells in the lesion as well.

**Markku Miettinen** – Benign fibroinflammatory lesion, could be IgG4-associated.

**Cesar Moran** – Nice case.

**Fredrik Petersson** – Fibrous pseudotumor of the paratestis, agree. IgG4 IHC convincing. Not classical IgG4 sclerosing morphology though.

**Murray Resnick** – Nice example.

**Brian Rubin** – Nice case. I'm still trying to figure out IgG4 –related pseudotumors.

**Niels Rupp** – A very nice case with the typical features. I recently learned that also a lot of neoplastic processes can be associated with increased IgG4+ plasma cells, so that is something I always keep in mind, especially in small biopsies.

**Saul Suster** – Nice case; this is what we used to call (in simpler times) fibrous pseudotumor of the testis. Now we have to do IgG and IgG4 stains and count ratios and percentages – gevald!

**CASE NO. 18 – CONTRIBUTED BY: Cesar Moran, M.D.**

**Abbas Agaimy** – Unusual and difficult case with striking nuclear grooves/coffee bean nuclei. No exact idea Cesar but vacuoles suggested for me either an intermediate epithelioid vascular neoplasm or mesothelioma.

**Justin Bishop** – Strange appearance, could be a funny mesothelioma but question metastasis. Resembles meningioma, but rather atypical.

**Ira Bleiweiss** – Cesar, is this a quiz case? Myoepithelial carcinoma?

**Alberto Cavazza** – A quiz case I suspect, and I suspect I do not know the answer! There are some nuclear inclusions, and in some areas, the tumor, reminds me of a meningioma: a primary or metastatic meningioma with microcystic features is my first possibility. Another idea could be a peculiar thymoma. It does not look very much like a mesothelioma, but just for the location this is another possibility I would like to exclude. No other ideas crossed my mind. I definitely would need immunostains, and I am curious to know the answer!

**Kum Cooper** – ?mesothelial ?mesenchymal

**Göran Elmberger** – That's a difficult one without any hints. I would need more info and IHC to make a diagnosis. In my differential are ectopic/metastatic meningioma, some variant of dendritic cell tumor, variant of SFT or possibly extraordinary thymic tumor. Hope you have the answer to still my curiosity...

**Franco Fedeli** – Meningioma could be a possible diagnosis. This type of sclerosis is also seen in thymoma.

**Masaharu Fukunaga** – Metastatic meningioma.

**Brandon Larsen** – Looks like a beautiful example of primary pleural (or pulmonary) meningioma to me. Fantastic case!

**Jesse McKenney** – I would do an initial IHC panel to assess for lineage: mesothelial, epithelial, and meningioma.

**Thomas Mentzel** – ?

**Markku Miettinen** – Suspect an unusual thymoma variant. Needs immunostains.

**Cesar Moran** – My case, not sure why it is that the diagnosis and the IHC that I did was not transcribed but, in any case, I am sorry I did not mean to test anybody or to be disrespectful. In any case the diagnosis is primary pleural malignant meningioma.

**Fredrik Petersson** – When I got to know the dx. Awestruck!

**Brian Rubin** – I'd like to get some IHC but I'm wondering about mesothelioma. It's vacuolated so I also thought about something adipocytic (? Very odd myxoid liposarcoma) or vascular tumor (? Very very odd EHE without the typical chondromyxoid/fibrous stroma).

**Niels Rupp** – An infiltrating neoplasia with weird koilocytic-like, microcystic cells and some whorls. Immunohistochemistry?



**CASE NO. 19 – CONTRIBUTED BY: Vania Nose, M.D.**

**Abbas Agaimy** – Rare and illustrative case of Cowden disease with multiple microfollicular adenomatous nodules in the thyroid. I have circulated a comparable case in the AMR#67, thanks Vania for the very informative discussion.

**Gerald Berry** – I think the young age and family history in this case is particularly helpful. We don't routinely stain for PTEN, but I think we will bring it up in our IHC Lab. Great case and thanks for the detailed discussion.

**Justin Bishop** – Classic Cowden thyroid. Vania's talks and papers have raised my awareness of the thyroid findings. I have spotted several with Vania's and PTEN IHC assistance!

**Ira Bleiweiss** – Wow, Vania, what an encyclopedic writeup. Thanks.

**Alberto Cavazza** – Very interesting and exhaustive discussion, thanks.

**Kum Cooper** – Thank you Vania for the comprehensive review of Cowden Syndrome.

**Göran Elmberger** – Very interesting survey of PTEN hamartoma syndromes and a reminder of the value of going "behind" the slide.

**Franco Fedeli** – Thank you Vania for this interesting lesson about PTEN hamartomatous tumor syndrome.

**Cyril Fisher** – Minimally invasive follicular carcinoma of thyroid in PHTS – very informative discussion, many thanks.

**Maria Pia Foschini** – PTNE Hamartoma tumor syndrome. Really interesting case of thyroid pathology related to Cowden disease in a young patient. Unfortunately, the slide sent to the club show only features of multiple adenomatous nodules and thyroiditis. The presence of a focal capsular invasion is not clear.

**Masaharu Fukunaga** – Multiple adenomatous nodules. PTEN hamartoma tumor syndrome (PHTS) is quite new to me. This is a golden opportunity to study PHTS. Thank you very much. Vania.

**Barbara Gazic** – Not sure from our slide this fulfils criteria for carcinoma. Anyway, very nice presentation of PHTS! Thank you.

**Thomas Krausz** – Superb, comprehensive, highly educational discussion, thank you very much.

**Brandon Larsen** – Her clinical and family history are certainly worrisome for a hereditary tumor predisposition syndrome, like PTEN hamartoma tumor syndrome. Nice case. Thanks for sharing.

**Jesse McKenney** – Thank you! It is great to see these hereditary cases.

**Thomas Mentzel** – Many thanks for the detailed discussion, very much appreciated!

**Delia Perez-Montiel** – Thank you for your nice discussion.

**Markku Miettinen** – Follicular neoplasm, cannot find evidence for carcinoma on this slide.

**Cesar Moran** – In my slide I am able to see only the multiple adenomatous nodules but cannot see the lymphocytic thyroiditis or the follicular carcinoma. As a matter of fact, I do not see any capsule in my slide. However, the discussion provided by Dr. Nose is great.

**Fredrik Petersson** – Multiple adenomatoid nodules; no obvious carcinoma or thyroiditis on my section. Fascinatingly complex manifestations of PTEN hamartoma syndrome!

**Brian Rubin** – Great discussion!

**Niels Rupp** – This is really an extraordinary case, so you start scratching your head, as it is distinct, but difficult to classify.

**Saul Suster** – Thank you Vania for this great case and the erudite discussion!

**CASE NO. 20 – CONTRIBUTED BY: Brian Rubin, M.D.**

**Abbas Agaimy** – Soft tissue angiofibroma, a rare entity with many faces and sometimes difficult to diagnose. I recall a peculiar huge gluteal tumor in a very old woman which I missed on HE and sent for fusion testing showing then the AAHR-NCOA2 gene fusion. Thanks Brian.

**Justin Bishop** – Thank you for educating me on this lesion.

**Ira Bleiweiss** – A new one for me. Spindle cell and benign. I was thinking of neurofibroma or schwannoma.

**Alberto Cavazza** – Very nice case and discussion.

**Kum Cooper** – Thanks Brian for sharing this case and a great write up of this recently described entity. I have seen one in the calf of a 24-year-old woman and one intra-abdominally that had a well circumscribed focus of cellular atypia. The latter case I sent to Chris too. The latter feature has also been described in these tumors.

**Göran Elmberger** – Another translocation tumor with indistinctive histology and IHC. I am happy since we recently established NGS with Archer chemistry including fusion plex at Umeå...

**Franco Fedeli** – Angiofibroma of the soft tissue. Another myofibroblastic tumor with a non-specific histology but with a specific gene fusion.

**Cyril Fisher** – Angiofibroma of soft tissue with molecular confirmation. The examples I have seen have had a more prominent vascular pattern, as originally described. This case is very difficult but confirmed by demonstrating the gene fusion – a very good call Brian.

**Maria Pia Foschini** – Really interesting case and difficult diagnosis. The vascular component of the lesion is very subtle.

**Masaharu Fukunaga** – Histologically challenging spindle cell tumor. Without history I assumed myofibroblastic tumor or low-grade smooth muscle tumor. Thank you very much for the very informative discussion.

**Barbara Gazic** – Nothing without NGS in such cases... Very good case!

**Thomas Krausz** – Agree with diagnosis. The rare cases I have seen before caused me differential diagnostic dilemma prompting me to reach out for molecular help.

**Brandon Larsen** – Beautiful example of angiofibroma of ST. I would've struggled to get there, but it sure helps that there's a fusion to test for. Thanks for sharing.

**Jesse McKenney** – Nice to see a molecularly confirmed case.

**Thomas Mentzel** – Many thanks for this nice example of an angiofibroma of soft tissues, and in this case solitary fibrous tumour represents a real differential diagnosis.

**Markku Miettinen** – Looks benign myofibroblastic tumor, needs genetics for proper distinction.

**Cesar Moran** – Nice case.

**Fredrik Petersson** – Nice case! Any info on the genetics on nasopharyngeal (juvenile) angiofibromas? NGS generates a multitude of new translocations. I wonder how much the next blue book on soft tissue tumors will be (re-)written.

**Brian Rubin** – My case – hope you enjoyed it.

**Saul Suster** – Thank you for sharing this case Brian, although in all honesty, I doubt whether I'll be able to recognize this the next time I see one. Very generic bland spindle cell tumor; without the results of NGS I don't think I would be able to diagnose one.

#### **CASE NO. 21 – CONTRIBUTED BY: Niels Rupp, M.D.**

**Abbas Agaimy** – I agree, low-grade epi-myoeptithelial carcinoma, in areas mainly low-grade myoeptithelial with paucity of ducts, I agree HRAS mutation is helpful in rare equivocal cases including predominantly apocrine cases.

**Justin Bishop** – Very interesting pattern and genetics in this EMC.

**Ira Bleiweiss** – Agree. Similar, not surprisingly, to malignant adenomyoeptithelioma of breast.

**Alberto Cavazza** – Morphologically, I agree with the diagnosis.

**Kum Cooper** – EMC with HRAS mutations have recently been shown to have a more heterogeneous morphology.

**Göran Elmberger** – Nice case of encapsulated epithelial myoeptithelial carcinoma apocrine solid variant. Small component garden variety. Solid component hard to classify by itself without IHC. Interesting update on molecular pathogenesis and novel molecular finding! I was not aware that most cases of EMEC is ex PA. Good new knowledge.

**Franco Fedeli** – This tumor is composed by two different patterns: nested and classical epithelial-myoeptithelial aspect. Where is the ARID1A (partial loss)?

**Maria Pia Foschini** – Low-grade epithelial myoeptithelial carcinoma, with HRAS-mutation with additional heterogeneous terminating *ARID1A-Mutation*. Very interesting case. I have some doubts on the "low-grade" definition: indeed, the case is surrounded by a complete capsule, but cells show mild atypia, prominent nucleolus. In addition, we counted at least 6 mitotic figures per 10HPF. It is difficult to understand the value of the additional mutation, it should be searched on a series. Why did you look for this specific mutation?

**Masaharu Fukunaga** – Welcome, Niels. Thank you very much for the great case with detailed analysis. It seems to be difficult to distinguish histologically myoeptithelial cells from ductal epithelial cells in this case.

**Barbara Gazic** – Our diagnosis (without NGS) would be epithelial myoeptithelial carcinoma.

**Thomas Krausz** – Agree with diagnosis. I am so pleased to see an example of low-grade epithelial-myoeptithelial carcinoma, especially with molecular underpinning, as in contrast to the classic high-grade epithelial- myoeptithelial carcinoma of salivary glands, the low-grade ones in my experience are diagnostically more challenging.

**Brandon Larsen** – Strange tumor. I would have begged for the help of our H&N pathologists on this one.

**Jesse McKenney** – Agree, epi-myoepithelial carcinoma.

**Thomas Mentzel** – Many thanks for the nice case, and these myoepithelial neoplasms harbour indeed different genetic changes.

**Markku Miettinen** – Looks like an oncocytoid neoplasm, UMP. This slide looks monomorphic.

**Cesar Moran** – I did not know that E-M carcinoma could be positive for ARID1A.

**Fredrik Petersson** – EMECA agree. Typical multinodular pattern – deceptively benign. Some myoepithelial overgrowth? Interesting genetic findings. Great case!

**Brian Rubin** – Agree with epithelial-myoepithelial carcinoma.

**Saul Suster** – Difficult case! Typical epithelial-myoepithelial carcinoma is present only in a small portion of the slide at the periphery of the lesion; the rest looks quite monomorphous and lacking the outer clear myoepithelial cell layer. The good circumscription is also misleading and suggests a benign process. It's a good thing we now have all the fancy translocations for cases like this. Welcome to the Club Niels!

#### **CASE NO. 22 – CONTRIBUTED BY: Paul Wakely, Jr., M.D.**

**Abbas Agaimy** – PLOC, HIV-related, thanks Paul.

**Justin Bishop** – Nice case Paul.

**Ira Bleiweiss** – Agree. Beautiful case.

**Alberto Cavazza** – Very nice and concise discussion.

**Kum Cooper** – Thank you Paul. Great that the terminology has stood the test of time!

**Göran Elmberger** – Important case. Cells very fragile and difficult to see. Clinicopathological correlation. Plasma cell phenotype elusive and can easily be missed on routine IHC work up for CUO. Need include specific plasma cell markers.

**Franco Fedeli** – I saw a case of leishmania with plasma cell proliferation in a HIV patient. It was a very similar case.

**Maria Pia Foschini** – Interesting case. In this case the age of the patient and knowledge of HIV + are leading in the diagnostic procedure.

**Masaharu Fukunaga** – Plasmablastic lymphoma. Paul, thank you very much for the beautiful case. This type of lymphoma is rare in Japan probably because of low rate of HIV positive patients.

**Barbara Gazic** – Nice case. The first thought in HIV+ patients with plasmacytoid tumour.

**Thomas Krausz** – Plasmablastic lymphoma is often a diagnostic challenge. I remember a case which was misdiagnosed as epithelioid angiosarcoma of the skin because of CD31 immunoreactivity (plasma cells, plasmablasts are usually positive for endothelial marker CD31). Thank you very much for the excellent discussion.

**Brandon Larsen** – Nice case. Agree.

**Jesse McKenney** – Nice case!

**Thomas Mentzel** – A nice example of a rare entity.

**Delia Perez-Montiel** – Great example of this lesion.

**Markku Miettinen** – Looks like lymphoma, I thought of ALCL, immune needed for classification.

**Cesar Moran** – Interesting case.

**Fredrik Petersson** – Great educational case and discussion, thanks.

**Brian Rubin** – Interesting case and great discussion.

**Niels Rupp** – Nice example of an oral PBL. I would be interested if there was also epitheliotropic EBV visible in the corresponding EBER in situ hybridization?

**Saul Suster** – Great case of plasmablastic lymphoma, Paul; thanks for sharing it. We first reported the association between oral plasmablastic lymphomas and HHV8 in HIV+ patients from Ohio State University by PCR in-situ performed by Dr. Gerard Nuovo (Cioc AM et al. Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. Am J Surg Pathol 28:41-46, 2004). These can be very difficult to diagnose.

**CASE NO. 23 – CONTRIBUTED BY: Paul E. Wakely, Jr., M.D. (courtesy of Martha Yearsley, M.D.)**

**Abbas Agaimy** – Very unusual case of florid reactive "kaposiform" angioendotheliomatosis limited to the mucosa covering the submucosal fibroma. never seen with this floridness and diffuse pattern, thanks Paul for sharing this beautiful slide.

**Ira Bleiweiss** – Weird.

**Alberto Cavazza** – Very unusual phenomenon for which I have no name. I imagine this is a peculiar reactive vascular proliferation.

**Kum Cooper** – I thought this was an inflammatory fibroid polyp. Another name that might fit is that of reactive angioendotheliomatosis (in this case secondary to the transient ischemia of the intussusception).

**Göran Elmberger** – Given the focal nature and the long history of intussusception I favor a secondary reactive pathogenesis but of course difficult to tell which is the hen and egg (Swedish saying). Found also other reports on this theme (Ramsden KL 1993; Popovska S 2013; Cu MJ 2013).

**Franco Fedeli** – I have never seen this type of lesion. It could be related to the lesion described in the article in Modern Pathology.

**Maria Pia Foschini** – Really interesting case. Searching for related literature, we have found out some case reports of CMV- related polypoid lesions, some showing aspects of vascular proliferation angiosarcoma- like in the mucosa. In other papers this aspect is considered as a possible reaction to ischemia (H. Park, S.Park et al. Cytomegalovirus-Associated Intussusception with Florid Vascular Proliferation in an Infant. Journal of Pathology and Translational Medicine 2015; 49: 270-273; K L Ramsden, J Newman, A Moran: Florid vascular proliferation in repeated intussusception mimicking primary angiomatous lesion. T Clin Pathol 1993;46:91-92).

**Masaharu Fukunaga** – Very interesting case with a prominent vascular proliferation of the mucosa propria. (I have no idea of “formal name”).

**Barbara Gazic** – We saw a few cases of submucosal fibromas with ileal intussusception. I don’t remember vascular proliferation in the overlying mucosa. Perhaps we should revise the slides...

**Thomas Krausz** – I feel that the vascular proliferation in the mucosa is reactive (pyogenic granuloma-like), perhaps due to “chronic” intussusception, rather than a specific preexisting vascular lesion. I consulted some of our GI pathologists and they feel the same way.

**Brandon Larsen** – This case is truly strange. I’ve never seen anything like this before. I would call this some kind of mucosal angiomatosis, too, for lack of a better term, but I’m not sure what this is. It would be interesting to know if the patient has HHT or some other syndrome with hamartomatous or angiomatous proliferations.

**Jesse McKenney** – I don’t have a name... I would have signed it as benign with some description.

**Thomas Mentzel** – The lesion shows features of an angiofibroma not otherwise specified.

**Markku Miettinen** – Agree on benign. Mucosal vascular proliferation looks hemangiomatous. Hard to determine if reactive or neoplastic. Fibrosclerosing mass underneath.

**Cesar Moran** – I do not think I had seen this before and would not have a name for it any more than what you have nicely done. Thanks for sharing this case.

**Kyle Perry** – I haven’t seen anything like this in the GI tract before. For some reason the features remind me a little of sclerosing angiomatoid nodular transformation of the spleen or some sort of long standing/sclerotic IMT.

**Fredrik Petersson** – Is this a sclerosed Vanek’s tumor? I have never seen such a striking benign mucosal vascular proliferation before.

**Murray Resnick** – Very impressive case. Have seen this before in intussusception but the process was primarily transmural.

**Brian Rubin** – I don’t have a name for this. It looks reactive, not neoplastic to me.

**Niels Rupp** – That is florid! Although HIV-, I would have felt more comfortable ruling out Kaposi sarcoma.

**Saul Suster** – I also favor that the vascular proliferation in the submucosa is reactive – scary but reactive! Please give my regards to Martha.

**CASE NO. 24 – CONTRIBUTED BY: Brandon Larsen, M.D., Ph.D.**

**Abbas Agaimy** – Diffuse intrapulmonary epithelioid mesothelioma, very rare presentation, needs be considered and distinguished from solid pattern TTF1-negative adenocarcinoma.

**Justin Bishop** – Tough case.

**Ira Bleiweiss** – I've never seen or heard of this before. I would not have been able to make this diagnosis.

**Alberto Cavazza** – Spectacular example of a tumor that can be unrecognized in this location! Another rare intrapulmonary pattern of mesothelioma that can be misleading is a lepidic growth, simulating an in-situ adenocarcinoma.

**Kum Cooper** – Fascinating; never seen such a presentation of mesotheliomas before. Thank you!

**Göran Elmberger** – Great case. Looks clearly a mesothelioma but clinical circumstances extraordinary. Thanks. Good to know.

**Franco Fedeli** – Intrapulmonary malignant mesothelioma, classical morphology in atypical location.

**Cyril Fisher** – Intrapulmonary diffuse malignant epithelioid mesothelioma, very nice case. Many thanks.

**Maria Pia Foschini** – Really fascinating case. A truly mesothelial tumor with a diffuse involvement of tissue and no or subtle pleural involvement. Really hard diagnosis.

**Masaharu Fukunaga** – Diffuse intrapulmonary malignant mesothelioma, epithelioid type. I have never seen this type of mesothelioma. It looks like adenocarcinoma. Thank you very much, Brandon.

**Barbara Gazic** – Beautiful case, very interesting.

**Thomas Krausz** – I have seen a few cases of malignant mesothelioma with interstitial intrapulmonary spread, mimicking interstitial lung disease. However, in all those cases there was also pleural disease. Thank you very much for submitting this superb case.

**Jesse McKenney** – Striking case!

**Thomas Mentzel** – Many, many thanks for sharing this rare and interesting case!

**Markku Miettinen** – Agree on mesothelioma involving lung.

**Cesar Moran** – Interesting case.

**Kyle Perry** – Very nice case.

**Fredrik Petersson** – Wow, spectacular. Thanks for an extraordinary case.

**Brian Rubin** – Fascinating case. I would have never thought of mesothelioma since I wasn't aware of cases that were entirely intrapulmonary.

**Niels Rupp** – A good example, how important the clinicopathological correlation is, but also to keep uncommon spreading patterns in mind.

**Saul Suster** – Never seen this before but seems quite convincing! Would be hard to explain the pathogenesis (although Dr. Katzenstein had no problem in explaining sclerosing pneumocytomas as being derived from "entrapped" mesothelial rests in the lung many years ago). Welcome Brandon to the Club!

**QUIZ CASE NO. 1 – CONTRIBUTED BY: Saul Suster, M.D.**

**Abbas Agaimy** – No real idea Saul, without seeing the gender, I thought of atrophic "Sertoli-only" inguinal testis, maybe there is some missing data?

**Justin Bishop** – Looks like a Sertoli cell tumor.

**Alberto Cavazza** – It looks like an immature testis to me, and if this is correct this may be an example of androgen-insensitivity syndrome (something I read in the books but I have never seen before). Great case whatever this is!

**Kum Cooper** – Immature testis. Defer to molecular and genetic testing/counseling.

**Göran Elmberger** – Cryptorchid testes. Sexual status? Hermaphrodite?

**Franco Fedeli** – Ectopic atrophic testis, hermaphrodite?

**Maria Pia Foschini** – The lesion seems composed of benign looking Sertoli cells. I would look for testicular feminization or other androgen insensitivity syndromes.

**Masaharu Fukunaga** – Ectopic Sertoli cell tumor, well differentiated?

**Barbara Gazic** – Searching..., still searching...

**Ondra Hes** – Saul, is the patient XX girl?? ☺ Lesion looks like Sertoli cell nodule....

**Brandon Larsen** – Looks like fetal testis to me... in a teenage girl. Must be a congenital remnant or vestige. I wonder if she was exposed to alterations in sex hormones in utero or if she has some other interesting clinical history. Fascinating!

**Jesse McKenney** – Prepubertal type testis, suspect male under-masculinization such as an androgen insensitivity syndrome.

**Thomas Mentzel** – Benign clear cell lesion?

**Markku Miettinen** – Testis retention, androgen insensitivity syndrome (testicular feminization).

**Delia Perez-Montiel** – Groin prepubertal testis.

**Cesar Moran** – Not sure what this is but it looks like a Sertoli cell tumor.

**Kyle Perry** – Cryptorchid testis in patient with androgen insensitivity syndrome.

**Frederik Petersson** – Looks like immature seminiferous tubules. Androgen insensitivity syndrome?

**Brian Rubin** – No idea. Looks like a sex-cord stromal tumor of some type but it's from the groin. I'll be interested to see the comments.

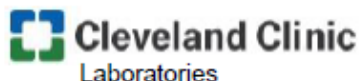
**Niels Rupp** – Testicular feminization syndrome?

**Paul Wakely** – Immature testis compatible with androgen-insensitivity syndrome (Testicular Feminization).



**Saul Suster** – My case. This is an example of pseudo hermaphroditism with androgenic insensitivity syndrome. The patient is an XX female. This condition is most often encountered in young women who are phenotypically female, but are usually taller than normal for age, have scant pubic hair and a small vagina due to the effect of a circulating anti-Mullerian hormone which causes immaturity of the female Mullerian system. The patients usually display bilateral cryptorchid testes that are located intraabdominally, but they can also be present in the inguinal canal or within the labia. Because of the high risk for malignant transformation (30%) in these patients, it is recommended to remove the atrophic testes. The histology is quite characteristic; the testes are small and atrophic and characteristically show absent lumens in the seminiferous tubules. We performed a stain for androgen receptors in this case which was negative; inhibin was strongly positive. This is the first case I've seen of this condition. It was submitted in consultation by a colleague from Ecuador, Dr. Romel Ortega and I thought I'd share it with you. I'd like to acknowledge my colleague Dr. Kenneth Iczkowski here at MCW who reviewed the case with me and was the one who made the diagnosis.

**FOLLOW-UP INFORMATION – CASE NO. 13, AMR SEMINAR #73**



2119 E. 93rd / L15  
Cleveland, OH 44106  
216.444.5755 or 800.628.6816

**Sarcoma Fusion NGS Detection Panel**

Demographic Information			
Name:	RESEARCH_BR	Tumor Percent:	90%
Patient ID:	S09-24728	Accession Date:	6/19/2019
Unique ID:	19SARv1_0195	Received Date:	6/19/2019
Acc/Copath:	S09-24728 D2	Reported Date:	06/23/2019

**Reportable Fusions**

Fusion: EWSR1 - FLI1 fusion junction: chr22:29688158 - chr11:128651853			
Filter: Strong, Quiver, Inframe: TRUE GSP2: <small>EWSR1_chr22_29688126_27+_A1_GSP2</small>	Reads: 134 Percent: 12.2 Start Sites: 22	Genes: EWSR1(+) NM_005243 exon:10 FLI1(+) NM_001167681.2 exon:6	Segments: chr22:29688126 - 29688158 chr11:128651853 - 128651918

Fusion: EWSR1 - FLI1 fusion junction: chr22:29688595 - chr11:128651853			
Filter: Quiver, Inframe: FALSE GSP2: <small>EWSR1_chr22_29688542_35+_A1_GSP2</small>	Reads: 18 Percent: 3.5 Start Sites: 7	Genes: EWSR1(+) NM_005243 exon:11 FLI1(+) NM_001167681.2 exon:6	Segments: chr22:29688477 - 29688595 chr11:128651853 - 128651918

**Data Quality Control**

Sample QC			RNA Fusion QC		
Pre-Sequence Control 1 (<30)	26.18	PASS	Fusion Reads Percent (>=10)	12.2	PASS
Pre-Sequence Control 2 (<30)	25.96	PASS	RNA Unique Start Sites (>=3)	22	PASS
Total RNA Percentage (>30)	38.64	PASS	RNA Unique Reads (>=5)	134	PASS
RNA AvgUniqueStartSitePerGSP2Ctrl (>=10)	42.12	PASS			

**REVIEWED**  
By Christine Revay at 11:52 am, Jun 24, 2019

**APPROVED**  
By Yu-Wei Cheng at 10:18 am, Jun 24, 2019

**Saul Suster:** This is the case I submitted in AMR seminar #73 concerning a nasal mass in a young man with a history of Ewing sarcoma. The case was diagnosed as metastatic Ewing sarcoma due to the EWSR1 translocation. The problem I had when I reviewed the case is that the histology was all wrong for Ewing sarcoma and the tumor was histologically and by immunohistochemistry a quite typical neuroblastoma. The FISH test for EWSR1 was repeated at the Cleveland Clinic courtesy of Dr. Brian Rubin, and it was also positive in their hands for EWSR1/FLI1. Is it at all possible that neuroblastoma can also have, on occasion, the same translocation as Ewing sarcoma?