

COMMENTS TO AMR SEMINAR#72

Case No.1 – Contributed by Paul Wakely:

Abbas Agaimy: Great and “out of context of a salivary neoplasm”, tough case, very unusual to see the degree of atypia, the myoepithelial phenotype and post-radiation setting on one side, and still a favorable outcome on the other side. Thanks Paul for sharing. I have encountered one or two myoepithelial carcinoma cases in post-radiation setting in the head and neck.

Phil Allen: Radiation induced myoepithelial carcinoma of the right parotid. This tumor fulfills Cahan’s requirements for a radiation induced malignancy, namely: the tumor has occurred in an irradiated field; it is histologically different from any previously treated malignancy, and there has been a latent interval.

Ira Bleiweiss: Agree. Beautiful variety of patterns.

Alberto Cavazza: Agree, very nice case and discussion. I ignored the association with radiotherapy.

Kum Cooper: Great educational case Paul. Much thanks.

Goran Elmberger: Thanks for commenting on my case of myoepithelial carcinoma in parotid gland presented at AMR meeting in Bratislava. Clearly this is a good example of another myoepithelial carcinoma given the metastasis. Looking at the slides I could recognize this as being probably a multinodular myoepithelial SGT but then I struggled with whether it was a myoepithelioma or myoepithelial carcinoma. No obvious destructive type of infiltration, no necrosis and a moderate atypia in combination with seemingly low mitotic index makes assessment of malignant potential difficult in a case like this. In most published series a clearly destructive infiltrative growth has been found in all cases of myoepithelial carcinoma but in latest WHO a pushing border type of infiltration is also recognized. Other indicative features from literature are > 7 mitoses/10 HPF; > 10 % Ki-67; atypical mitoses; necrosis and anaplasia and to be honest I am not sure I can confidently identify any of those even if apoptosis and some mitoses are noted. Since this is obviously a malignant tumor with metastasis those observations only support the well-known fact these are difficult tumors to assess. What I sometimes do to hope for help in cases with difficult invasion patterns is to look for neurite incorporation (NFP; Synaptophysin) and CD 34 positive naïve stroma intratumorally. Sometimes it helps.

Franco Fedeli: In this case, myoepithelial carcinoma shows a fibromyxoid stroma that reminds me of myoepithelial carcinoma of the soft tissue.

Cyril Fisher: Myoepithelial carcinoma, with convincing immunophenotype.

Masaharu Fukunaga: Thank you very much for the beautiful case and discussion of this type of tumor. Myoepithelial carcinomas often show variable histologic patterns.

Thomas Krausz: Agree with diagnosis, very nice case. In places, where acinar pattern dominates, mammary-analog secretory carcinoma also came to my differential. The clinical history makes this case even more educational.

Thomas Mentzel: Thanks for this beautiful example of malignant myoepithelioma that shows a variety of growth pattern and cell types. Is there real any relationship to the radiotherapy more than 50 years ago?

Jesse McKenney: I favored myoepithelial carcinoma, but also considered an unusual high grade pattern of MASC.

Markku Miettinen: Agree on myoepithelial carcinoma.

Cesar Moran: Nice case.

Kyle Perry: Thanks for submitting this case. Since we have subspecialized, I don't see much ENT pathology; however, I've often found myoepithelial neoplasms of soft tissue to be tricky, given the variety of morphologic patterns associated with this tumor.

Fredrik Petersson: My first bet was a myoepithelial carcinoma. Multinodular, secretory, cellular atypia, mitotic activity, multinodular low-grade infiltrative pattern. Nothing to add. Good case.

Murray Resnick: Nice example.

Brian Rubin: Nice case of myoepithelial carcinoma with a very interesting history.

Saul Suster: Very nice case of myoepithelial carcinoma. These are always problematic because the "myo" and epithelial markers are not always clearly demonstrated, in particular the myoid part of it.

Ady Yosepovich: Thank you for sharing this rare case.

Case No.2 – Contributed by Thomas Mentzel:

Abbas Agaimy: Pretty example of GCF/DFSP hybrid, just had a similar pediatric case with suggestive histology but negative FISH, any alternate gene fusions Thomas?

Phil Allen: Myxoid dermatofibrosarcoma protuberans with giant cell fibroblastoma areas, left upper arm. I personally regard giant cell fibroblastoma as one of the histological variants of dermatofibrosarcoma protuberans.

Ira Bleiweiss: Agree. Nice case.

Alberto Cavazza: Thanks for sharing this nice case, with concise and educational comments.

Kum Cooper: Thank you Thomas for the hybrid tumor. I recently saw a DFSP recur as a GCF in a young patient in Africa.

Goran Elmberger: Good case!

Franco Fedeli: Giant cell fibroblastoma; in my experience I saw only one case. The lesion recurred after 8 years as DFSP.

Cyril Fisher: Giant cell fibroblastoma with DFSP areas, nice example.

Masaharu Fukunaga: Thank you very much for the interesting case, Thomas. It is a great hybrid case of giant cell fibroblastoma and DFSP.

Thomas Krausz: In this example even the conventional DFSP portion of the tumor is a bit myxoid in contrast to previous examples I have seen where the DFSP was more compact/cellular.

Jesse McKenney: Nice example GCFB/DFSP.

Markku Miettinen: Agree on giant cell fibroblastoma with DFSP.

Cesar Moran: Great case.

Kyle Perry: This nicely highlights the spectrum of DFSP and giant cell fibroblastoma. Great for teaching. Thanks for sharing.

Fredrik Petersson: DFSP - giant cell fibroblastoma. Very nice pseudovascular spaces.

Brian Rubin: Beautiful case of giant cell fibroblastoma/DFSP.

Ady Yosepovich: Thank you for sharing this rare case – I was not aware of this entity.\

Case No.3 – Contributed by Masaharu Fukunaga:

Abbas Agaimy: Nice and rare example of combined gastric type adenocarcinoma and hepatoid carcinoma. I believe considering this type is the only key to recognize it as the hepatoid differentiation is mainly by IHC. I at first glance thought of dedifferentiated carcinoma. Given that gylpican, AFP and SALL4 as potential hepatoid markers are seen as well in some dedifferentiated SWI/SNF deficient endometrial carcinomas, it would be of interest to see if there is any loss of one of these markers in the solid component of this tumor. Thanks for the interesting case, Masa.

Phil Allen: Combined hepatoid carcinoma and gastric-type mucinous adenocarcinoma of the endometrium. Thanks Masa, for keeping me up-to-date with this gynecological surprise.

Ira Bleiweiss: Really interesting example of 2 different histologies acting independently. The gastric type is in a deep lymphatic channel on my slide. Thanks Masa.

Alberto Cavazza: Spectacular case and very convincing diagnosis! Needless to say, I have never seen this combination before.

Kum Cooper: Thank you Masa. I have not seen either of these sub-types in the endometrium, let alone a combined version! Much thanks for sharing this unusual case.

Goran Elmberger: Unusual and interesting combination. Thanks!

Franco Fedeli: Very rare neoplasm. Never seen hepatoid carcinoma combined with gastric type mucinous carcinoma of endometrium. Her2, frequently overexpressed in hepatoid carcinoma, could be very helpful for diagnosis.

Thomas Krausz: A diagnostically challenging case. Before reading the discussion, I was considering a variant of clear cell carcinoma of the endometrium, however the immuno-profile is convincing for a combined gastric type mucinous and hepatoid carcinoma. It is a superb case, must be published.

Thomas Mentzel: What a combination! I was wondering about a well-differentiated tumor component showing widespread infiltration and the “poorly-differentiated” component with a solid exophytic growth but had no idea about the existence of this combination!

Jesse McKenney: Interesting case of gastric type adenocarcinoma associated with a poorly differentiated component. By H&E, I also considered the possibility of trophoblastic differentiation in the high grade component.

Michal Michal: I missed the hepatoid component in my slide, probably due to sampling.

Markku Miettinen: Poorly differentiated carcinoma, seems to be reasonable to call hepatoid differentiation by markers.

Cesar Moran: Clearly carcinoma, but I'm struggling with the "hepatoid" and mucinous part. I simply don't see them in my slide.

Kyle Perry: Interesting case. I agree that this likely represents a gastric type mucinous adenocarcinoma with hepatoid differentiation.

Fredrik Petersson: Carcinoma, biphasic. The hepatoid component appeared undifferentiated to me and the differentiated tubular component – I was not even aware that gastric type mucinous carcinomas was a reality in the endometrium (only cervix). Spectacular case!

Murray Resnick: Interesting case. At first glance I would not have thought to order hepatocytic markers and would have written it off as an undifferentiated component.

Brian Rubin: Thanks for the interesting case. I have to think these two components are related as you suggested.

Ady Yosepovich: Thank you for sharing this rare case.

Case No.4 – Contributed by Delia Perez-Montiel:

Abbas Agaimy: Very rare case of endometrial carcinoma, I got the YST component, but it was hard for me to recognize the endometrioid pattern in the slide. Given that endometrioid is a pattern in gonadal YST, would this be a genuine endometrioid adenocarcinoma with YST pattern or a germ cell neoplasm (YST) with endometrioid pattern? Just to enhance discussion and controversy. Thanks for a beautiful case.

Phil Allen: Endometrial endometrioid adenocarcinoma with an extensive yolk sac component. My slide did not include much of the endometrioid adenocarcinoma.

Ira Bleiweiss: Agree.

Alberto Cavazza: Very nice case and discussion. As you said, age is an important point to be considered in the differential diagnosis between germ cell tumor and carcinoma with germ cell tumor differentiation.

Kum Cooper: Thank you Delia for this nice example of somatic YST differentiation in an endometrial carcinoma. Dr Glen McCluggage also described a series.

Goran Elmberger: Great educational value. Rare. Beautiful Schiller-Duvall bodies.

Franco Fedeli: Yolk sac tumor component in endometrioid adenocarcinoma is a very rare occurrence. What about your experience with CDX2 antibody in this neoplasia?

Cyril Fisher: Nice example of yolk sac tumor in rare setting with associated raised AFP.

Masaharu Fukunaga: A very nice case and comment. I agree. My case, case 3, might be originated from pluripotential stem cells, too. Thank you very much, Delia.

Ondra Hes: Thank you Hugo. For me it is always a challenge to evaluate spindle cell lesion in breast especially in frozen section (mostly designated as "scar" by surgeons) and it is always been a scary moment for me ☺.

Thomas Krausz: Before reading the history/discussion I only had differential diagnosis between various carcinomas. Serum AFP is very high. I also could see some Schiller-Duval-like bodies. The immunohistochemical result confirms the diagnosis. It is unfortunate that the tissue preservation on this excellent case is suboptimal.

Thomas Mentzel: Another impossible case for a simple dermatopathologist.....many thanks!

Jesse McKenney: Great case of yolk sac differentiation in an endometrial carcinoma.

Markku Miettinen: Agree on endometrioid carcinoma with yolk sac tumor differentiation.

Cesar Moran: Isn't that an unusual association?

Fredrik Petersson: I was not aware of YST as a component of endometrioid/endometrial carcinomas. No definitive endometrioid carcinoma component on my section. Checked the literature; appears extremely rare. Histogenetically intriguing. Amazing case, indeed.

Murray Resnick: Very nice example.

Brian Rubin: Interesting case. It's fascinating to think of how this could occur.

Saul Suster: Wow! Never seen this before. Thank you for sharing this case with us.

Paul Wakely: I think my entire slide is composed of YST and, being unaware of germ cell tumors arising in combination with endometrial carcinoma, is why I was struggling to subclassify this neoplasm. Only after reading your explanation did the entire picture become clear to me.

Ady Yosepovich: This is very interesting – I liked your new description of "retro-differentation" – the plasticity of malignant cells can create almost everything – maybe we can classify this as "carcino-germinoma"?

Case No. 5 – Contributed by Ira Bleiweiss:

Abbas Agaimy: Very interesting case history and discussion. I too initially believed this was hematogenous spread of anthracotic pigment. Thanks Ira for contributing the case of Munchausen syndrome, I hear about this disease occasionally in the MDTs, last month concerning a complex case of refractory hypoglycemia without pancreatic lesion or exaptation and they thought of it as a DDX.

Phil Allen: Munchausen's syndrome causing tattoo induced pigmented right axillary lymphadenopathy. I handled another Munchausen's as a surgical intern in 1960. The patient was a middle-aged woman who repeatedly passed innumerable "renal calculi" which actually consisted of cooked wheat flour. Baron Munchausen is a fictional German nobleman of the 18th century who was created by Rudolf E. Raspe. Incidentally, Rudolf Raspe is not to be confused with the famous and very rich Adelaide resident, the late Charles Rasp, who discovered the ore deposits at Broken Hill and was an original shareholder in the BHP Co. Ltd. (Now BHP Billiton).

Alberto Cavazza: Thanks for sharing this incredible case: the histologic lesion is nice, but the history is fantastic and reminds us there is always something beyond a slide!

Kum Cooper: Thanks Ira. What a great case!

Goran Elmberger: So we finally learned a bit about psychiatry too!

Franco Fedeli: Never heard about Munchausen' Syndrome. AMR slide seminars are also useful to learn about psychiatric disorders. Tattoo induced lymphadenopathy is now occurring very frequently. In Italy more than 12% people have Tattoos!!

Masaharu Fukunaga: An unbelievable story!! This is the first time I see tattoo-induced lymphadenopathy.

Thomas Krausz: What an entertaining history with a "punch-line". Thanks Ira. I will add it to my "pitfalls" list.

Thomas Mentzel: Amazing case, many thanks!

Jesse McKenney: Wow... what a clinical history! That would be quite a medical record to decipher.

Markku Miettinen: Fascinating history. Lymph node with carbon pigment and no cancer.

Cesar Moran: Interesting.

Kyle Perry: Wow. This is an incredible story.

Fredrik Petersson: Madness! Great to hear the story.

Murray Resnick: Fascinating story!! As pathologists we do miss out (for better or for worse) on dealing directly with Munchausen patients.

Brian Rubin: OMG! Great case. I thought I was missing something in the lymph nodes.

Saul Suster: Great case, Ira. Thanks for the education!

Paul Wakely: What a story Ira!!! I may have seen some innocuous-appearing pathology specimens from such patient impostors in the past, but was never made aware of their true nature.

Ady Yosepovich: Ira, this is a masterpiece.

Case No.6 – Contributed by Justin Bishop:

Abbas Agaimy: Nice case of thyroid adamantinoma-like Ewing sarcoma. I attended your nice presentation at the ECP, thanks Justin for the good discussion on the topic.

Phil Allen: Adamantinoma-like Ewing's sarcoma of the thyroid gland. I am afraid I am one of the (generally) silent majority of pathologists who was not aware of the existence of adamantinoma-like Ewing's sarcoma. Thanks for the instruction.

Ira Bleiweiss: Whoa! The squamous component is very subtle and limited to periphery on my slide.

Alberto Cavazza: Thanks for educating me. I saw the keratin differentiation and I considered thymic carcinoma and NUT carcinoma, but I completely missed the right diagnosis. Very educational discussion.

Kum Cooper: Welcome to the group Justin. Was good to meet you on the boat at USCAP recently. What a great case for an introduction into the AMR club!

Goran Elmberger: Interesting diagnosis with important therapeutic implications. I have too little experience to be able to comment on nomenclature but perhaps I would prefer a more generalized nomenclature like adamantinoma like EFT since the alternative would be to come up with separate names in every organ this tumor appears in. If a progression from bona fide thyroid carcinomas like PTC can be proven perhaps the nomenclature suggested by Eloy is to be considered. In the end, perhaps designation as carcinoma or sarcoma become less important than classifying according to driver genes and therapy response...

Franco Fedeli: The first two times I looked at this lesion, my diagnosis was poorly differentiated carcinoma of the thyroid (insular type). Without using numerous antibodies (TTF1, Thyroglobulin, CD99...), the only sampling for CK AE1-AE3 could have been very tricky in this case!!

Cyril Fisher: Ewing sarcoma, genetically proven, with epithelial features, similar to adamantinoma-like ES in bone though whether it should be so called in extra-osseous sites is debatable. Thanks Justin for this lovely example and discussion.

Masaharu Fukunaga: Welcome, Justin. It is a challenging case. My first impression is malignant epithelial tumor, rather than Ewing sarcoma.

Thomas Krausz: Fascinating case. Adamantinoma-like Ewing sarcoma as an entity is new to me. The immuno and molecular results underpin the diagnosis. Thank you very much for the excellent discussion. I feel we need a few more years to see whether this entity will take the European or the other routes of histogenetic thinking.

Thomas Mentzel: Thanks for the great case, but I never understand the term "adamantinoma-like" because for me adamantinoma looks different. Why not call the lesion Ewing's sarcoma with focal squamous differentiation?

Jesse McKenney: Very photogenic example!! Thanks for sharing.

Michal Michal: Nice case. It would be easy to confuse it with insular carcinoma of the thyroid.

Markku Miettinen: Seems convincingly documented Ewing sarcoma, but could easily go as poorly differentiated thyroid carcinoma without IHC.

Cesar Moran: Great case; not familiar with the entity. I was thinking of insular carcinoma.

Kyle Perry: Thanks for sharing this case. It was nice to have a glass slide to show my colleagues in the department after explaining how much overlap this can have with basaloid squamous cell carcinoma. As you mentioned in your discussion on ALES in the salivary glands, I also wonder whether this entity will still be classified as a variant of ES in the distant future (as shared gene rearrangements among different tumors are becoming more common in the literature).

Fredrik Petersson: Solid, a bit insular, quite monotonous malignant tumor with necrosis. I first thought of a poorly differentiated thyroid carcinoma. IHC and EWSR1 FISH nails it. Nosologically and diagnostically, I feel that it is important that these tumors have been identified and that they can be further studied in relation to prognosis and treatment. Nomenclature is to me always secondary. That these tumors express squamous/epithelial markers and have an epithelial light microscopic appearance and with ES/PNET genetic aberration is just a very interesting fact of life. Great case, sneaky CK- and p40-positive. The not so young age makes it even more difficult. Thanks for the great educational case.

Brian Rubin: Thanks Justin! Now I have a case of this rare and fun entity.

Saul Suster: Was not familiar with this entity - than you Justin for contributing this great case and for the education! When I first looked at it I thought this was a follicular carcinoma; I would have been hard-pressed to call this any type of Ewing sarcoma based on histology. The EWSR1 finding is certainly surprising; I wonder how many cases have been diagnosed as follicular carcinoma that harbored this molecular abnormality. This case also begs the question of whether it is legitimate to consider this a rare variant of Ewing sarcoma based solely on the genetic alteration or whether this may not be an example of another neoplasm unrelated to Ewing's that simply shares the same translocation; after all, EWSR1 seems to be quickly becoming the next vimentin as it is now been described in so many unrelated tumors. Great case – welcome to the Club!

Paul Wakely: First time I have run across this neoplasm in this location. With the non-specificity of EWRS1 fusions, I wonder if we should still be using the moniker of "Ewing sarcoma" as part of the name of these new entities just because they harbor the same (but seemingly non-specific) gene rearrangement? What is the long term outlook for these patients – do they behave aggressively like conventional Ewing sarcoma of bone? Wonderful case Justin. Welcome to the Club.

Ady Yosepovich: Thank you for sharing this exceptional case, the overlapping findings of sarcoma and carcinoma are always problematic, probably it is time to admit that we cannot name all tumors properly, especially the rare ones.....

Case No.7 – Contributed by Brian Rubin:

Abbas Agaimy: Great case Brian, never seen this in the gallbladder. I too would have thought of some genetic diseases like NF1. The plexiform neural proliferation is occasionally the cause of serious obstructive jaundice if close to the bile duct. Never seen this combination before.

Phil Allen: Gallbladder with an apparently previously undescribed diffuse mucosal Schwann cell proliferation as well as a small plexiform schwannoma of the cystic duct and chronic cholecystitis. I have never seen this before. I wonder if the patient may also have some other Schwann cell proliferations in the gastrointestinal tract, particularly the colon.

Ira Bleiweiss: Fascinating unique case. I could not figure out what the subepithelial proliferation was.

Alberto Cavazza: Spectacular case. In cholecystitis it is not exceptional to find traumatic neuroma, frequently close to the cystic duct, and I have seen two cases of benign epithelial proliferation inside the nerves, but I have never seen a case similar to yours.

Kum Cooper: This is an amazing case, Brian. Interesting how these W-M corpuscles are present in the villi only. Has NF-1 been ruled out with molecular genetic analysis? Good to catch up with you at USCAP.

Goran Elmberger: Interesting and peculiar finding. Reactive?? Occult syndrome after all?? NF???

Franco Fedeli: Never seen a case like this. Maybe the lesion could be related to the so called "Mucous Schwann cell hamartoma" in colorectal polyps.

Cyril Fisher: Diffuse (and plexiform) neurofibroma in exceptional location. It seems possible that the patient has some form of NF1 and might have other lesions.

Masaharu Fukunaga: I have never seen such a lesion. Thank you very much for sharing with us and for wonderful discussion. I am not sure it represents a reactive process or a neoplastic lesion.

Thomas Krausz: I think the features are those of Schwann cell hamartoma. References: Gibson JA and Hornick, Am J Surg Pathol 2009; 33:781-787; Bae MN et al. Ann Coloproctol 2013; 29:130-134; Das P. Mucosal Schwann cell hamartoma of gall bladder: a novel observation. Pathology 2018; 50(4): 480-482.

Thomas Mentzel: Many thanks, Brian, for this spectacular case! It would be interesting to find out if the patient has more of these tiny lesions in other parts of the gastrointestinal tract or in other locations.

Jesse McKenney: This case looked familiar, and then I realized I'd seen it (it's from Cleveland)!

Michal Michal: Wanger-Meissnerioma of the gallbladder!

Markku Miettinen: Mucosal nerve sheath tumor (neurofibroma?). Could also wonder if there is neurofibromatosis 1.

Cesar Moran: Hev not seen this before. Great case.

Kyle Perry: Thanks for sharing this very odd case. I have never seen anything like that. The Wagner-Meissner corpuscle like areas in the mucosa somewhat remind me of the nodule foci of schwannomatous differentiation in a hybrid neurofibroma/schwannoma. Although a conventional neurofibroma component was not seen here, I wonder if this finding (in conjunction with the plexiform schwannoma) could represent a localized presentation of NF2 or schwannomatosis with mosaicism.

Fredrik Petersson: Mucosal schwannomatosis. Never seen this before. No plexiform schwannoma on my section. Maybe has a syndrome (true Schwannomatosis) that will show up?

Murray Resnick: Very interesting case. I've never seen anything like it. I assume that the patient was worked up for genetic syndromes such as NF.

Brian Rubin: My case – I hope everyone enjoyed it. Looking forward to hearing your thoughts.

Saul Suster: I had never seen this before. Thank you for the collector's item.

Paul Wakely: I have seen mucosal ganglioneuromas in the past, but in answer to your question Brian, I have never seen such a case as yours previously. Nor do I unfortunately have an explanation for this phenomenon in the absence of a syndrome of some kind.

Ady Yosepovich: Thank you very much for sharing this exceptional case. It is my opinion that this is a metaplastic process originating from a pluripotent mesenchymal cell that reacted to the chronic inflammatory process. In the past I described a case with bone metaplasia and with bone marrow formation in the setting of chronic cholecystitis; maybe this is basically a similar process. (Ref: Yosepovich A, Nass D, Zagatsky M, Kopolovic J. Chronic cholecystitis with bone metaplasia. A case report. Pathol Res Pract. 2002;198(11):765-6).

Case No. 8 – Contributed by Thomas Krausz:

Abbas Agaimy: Very nice case and superb description of a rare case of Ménétrier disease, thanks Thomas.

Phil Allen: Menetrier's disease in a total gastrectomy specimen. Thanks for updating me on the literature. I have only seen one case that was about 30 years ago.

Ira Bleiweiss: Agree.

Alberto Cavazza: Very nice example and discussion, thanks.

Kum Cooper: Thomas this case brings back memories of the only case of Menetrier's disease I saw as a resident at autopsy with protein losing enteropathy. I recall that Morson and Dorson (the green GI book) called the gross picture a "bag of worms"!

Goran Elmberger: Long time no see. Thanks!

Franco Fedeli: Menetriere disease...I have studied this entity in medical school, but I have never met it in my practice. Useful and very exhaustive discussion about etiology and clinical aspects.

Cyril Fisher: Striking foveolar hyperplasia, something I rarely see.

Masaharu Fukunaga: Thank you very much for the beautiful case of Menetrier disease, Thomas. I have never seen this type of gastric lesion in Japan.

Ondra Hes: Great case!! I've recently encountered TFE3 rearranged renal cell carcinoma with HMB45 positivity in consultation. Tumor was very strange, more resembled t6;11 RCC than Xp11.2 (TFE3).....real challenge, and PECOMa was one of my differential diagnoses (however morphology of my case was very "carcinomatous").

Thomas Mentzel: Great case and wonderful discussion.

Jesse McKenney: I can't remember the last time I've seen one of these. Thanks for the case.

Markku Miettinen: Never remember seeing Menetrier disease; nice case. One could speculate that it has some overlap with polyposis syndromes.

Cesar Moran: I have known about this condition but I do not recall having seen the histology of it. The gross specimen should be very telling!

Kyle Perry: Nice example of Menetrier.

Fredrik Petersson: Quite innocuous hyperplastic histology with reactive changes. The clinical-endoscopic features/correlation leads further. Great educational case.

Santiago Ramon y Cajal:

Murray Resnick: Very nice example, gross photo and discussion.

Brian Rubin: Fantastic case. Surprised to know that the etiology of Menetrier disease is still unclear.

Saul Suster: Thank you for sharing this case. Although this condition is something we learn about early in medical school and read about in every major textbook, I have only seen cases in slide seminars and collection boxes but have never seen one in real practice.

Ady Yosepovich: Thank you very much for this interesting case.

Case No.9 – Contributed by Ma. Pia Foschini:

Abbas Agaimy: Rare and convincing example of intravascular DLBCL associated with multiple infarction. I have seen a few in the kidney (some in renal biopsies). Thanks Maria for sharing this beautiful slide.

Phil Allen: Intravascular B-cell lymphoma with multiple brain infarcts. The intravascular malignant cells are pretty obvious but I initially missed them.

Ira Bleiweiss: Agree.

Alberto Cavazza: I agree, very nice case. As you said, the diagnostic features can be subtle. We can make this diagnosis in any organ: the first case I saw, many years ago, was in a cholecystectomy.

Kum Cooper: Thank you Maria for this instructive case. Andrew Folpe presented an AMR case with IVL on an esophageal biopsy some years ago. I saw a couple of cases in Africa years ago that involved multiple organs including the adrenal and skin.

Goran Elmberger: Interesting case with difficult antemortem diagnosis. Perhaps an early lung biopsy for infiltrate diagnosis could have contributed...

Franco Fedeli: Intravascular large B cell lymphoma. Curiously a Japanese group studied 96 cases of this entity (Blood 2007, 109, 478-85). In that study, 38% of cases were CD5 positive.

Cyril Fisher: Intravascular B cell lymphoma resulting in cerebral infarction, rare case.

Masaharu Fukunaga: A beautiful case of intravascular B-cell lymphoma. Thank you, Maria. This type of lesion is often presented in autopsy examinations for the Japanese Board of Pathology.

Thomas Mentzel: Many thanks. Very rarely we've seen intravascular B- and T-cell lymphomas in the skin as well.

Jesse McKenney: Nice example of intravascular lymphoma.

Markku Miettinen: Agree on intravascular lymphoma, especially seen in the meninges.

Cesar Moran: Great case.

Fredrik Petersson: Clearly abnormal – malignant intravascular lymphoid cells. Exceedingly difficult to diagnose pre-mortem. Some literature says that one can try "blind" skin or transbronchial biopsy. IHC is of course mandatory. In the skin the H&E differential diagnosis is with intravascular histiocytosis.

Brian Rubin: Intravascular lymphoma. Great example.

Saul Suster: Nice example of intravascular lymphoma. I believe it was Mark Wick who first declared this to be an actual lymphoma. Dr. Rywlin actually wrote the first paper (in the Am J Dermatopathology) demonstrating that the tumor cells in this condition were positive for LCA; he interpreted the process as a phenomenon of bidirectional differentiation (lymphoid and endothelial).

Ady Yosepovich: Thank you very much for this interesting case.

Case No.10 – Contributed by Alberto Cavazza:

Abbas Agaimy: Spectacular case, never seen before and have to admit I found the relevant features only after reading the concise discussion. Interesting to see that the portal tracts are expanded by nodular fibroinflammatory reaction with prominent eosinophils as a pitfall with sclerosing cholangitis. Thanks.

Phil Allen: Amniotic fluid and placental tissue embolism in the liver. I doubt that I would ever have worked this one out. The florid reactive fibroblastic proliferation, the histiocytes and the giant cells simulate a malignancy but on careful inspection, the scanty keratin flakes and the ghost outlines of the placental villi are all there, waiting to be recognized.

Ira Bleiweiss: This is unbelievable. The reactive changes are so intense with atypia, mitoses, epithelioid cells, etc, that I thought it was epithelioid angiosarcoma. Admittedly I passed over the necrotic placental tissue.

Alberto Cavazza: My case. Unfortunately in some slides placental tissue is lost, but epithelial squames are present as a diagnostic clue.

Kum Cooper: I am in total awe! Thank you for sharing. I have seen brain tissue embolus in the lung in a newborn autopsy following vacuum-assisted vaginal delivery. But have never seen anything like this before!!!

Goran ElMBERGER: Fascinating case. Another explanation taking into account superficial process in liver and intestine might be spillage of placental material during caesarean section.

Franco Fedeli: Never seen a case like this....amniotic abscess in the Liver....almost incredible just to think about it...amazing!

Masaharu Fukunaga: This case is also a great case of amniotic fluid and placental tissue embolism. This is the first time I see this. Thank you, Alberto.

Thomas Krausz: I have seen cases involving the lung but never the liver. Thank you very much for submitting it.

Alberto Marchevsky:

Thomas Mentzel: To be honest, I would miss the case.....

Jesse McKenney: What an extraordinary case. It's amazing that the patient did so well.

Markku Miettinen: Difficult to catch without history, but there is clearly necrotic placental tissue in the liver.

Cesar Moran: Interesting case.

Fredrik Petersson: Liver abscess in conjunction with amniotic fluid embolism. Squames and a multitude of foreign body type giant cells on my section. Even ghost villi are present! Thanks for an excellent discussion.

Murray Resnick: Striking case. Very fortunate clinical outcome.

Brian Rubin: What a strange case. I've never heard of this before. Thanks.

Saul Suster: This must be very rare!

Case No.11 – Contributed by Franco Fedeli:

Abbas Agaimy: Very rare case of primary lung meningioma, never seen before, were there meningotheelial nodules in same specimens? Thanks Franco.

Phil Allen: Multiple primary pulmonary and pleural meningiomas in the left lung in a patient with a previous lung carcinoma. I wonder if the sections of the previous lung carcinoma have been reviewed.

Ira Bleiweiss: Agree. Great case.

Alberto Cavazza: Great case and discussion! Occasionally meningotheial-like nodules becomes large enough to be seen as multiple small nodules at CT-scan of the chest, and for this reason they can be excised; in these cases it is worthwhile to exclude clinically a metastasis from a CNS meningioma.

Kum Cooper: Franco, I am still concerned for a neuroendocrine tumor (?metastatic). There is a new meningioma marker SSTR2A which would be useful. Also more broad spectrum keratins may help too.

Goran Elmberger: Difficult and rare diagnosis with very few specific IHC markers. Agree with diagnosis based on morphology and IHC results. NF2 FISH deletion 50 %. Somatostatin receptors?

Franco Fedeli: My Case. Was presented in AMR 2018 in Split. Other slides of the pulmonary parenchyma (aside the lesion and far from it) showed more minute meningotheial nodules.

Cyril Fisher: Pulmonary meningioma, very nice section.

Masaharu Fukunaga: Primary pulmonary meningioma, beautiful case, Thank you, Franco, for the comments.

Thomas Krausz: I have seen minute meningotheial nodules in the lung before, but only one case of metastatic meningioma. Thank you for the excellent discussion.

Thomas Mentzel: Wonderful example of rare pulmonary meningioma.

Jesse McKenney: I assumed that this would be a metastasis... unexpected history.

Markku Miettinen: Looks like atypical meningioma; not clearly malignant.

Cesar Moran: Very interesting case. This may correspond to what has been regarded as "atypical meningioma." Some people would call it malignant based on the 10% in the Ki-67.

Kyle Perry: Thanks for this case. With the focal expression of CD56, it seems like there would be potential to misdiagnose this as neuroendocrine tumor (synaptophysin and chromogranin would of course help with this).

Fredrik Petersson: Meningotheial features are there, albeit a bit subtle (to me). Initially I saw some vague fibrillary processes radiating towards small vessels, vaguely ependymoma-like. Always review the primary. Case worked up by the book and solved!

Murray Resnick: Beautiful example. Great discussion.

Brian Rubin: Really rare case. I wasn't sure what it was but the histology is believable for meningioma.

Saul Suster: Great case. Cesar Moran published a nice series on primary pulmonary meningiomas many years ago.

Paul Wakely: Beautiful case, Franco.

Ady Yosepovich: Thank you very much for this interesting case.

Case No.12 – Contributed by Goran Elmberger:

Abbas Agaimy: What a case! Initially I thought of some type of bland (low-grade!) looking polypoid spindle cell (metaplastic) carcinoma, hard to identify the LD bodies, thanks Göran. Has the patient a relevant geographic history?

Phil Allen: Pseudosarcomatous hypopharyngeal mucosal Leishmaniasis in an immune modulated patient. The organisms are non-easy to see, even when one knows they are there. The Australian pathologists who diagnosed the published case from the same Greek island must have good eyesight.

Ira Bleiweiss: Holy smokes. I never thought I would see this. Goran - how did you even think of this? The amastigotes are even visible on H&E.

Alberto Cavazza: I thought of an inflammatory pseudotumor, but I missed the parasite: only after reading your diagnosis I recognized it. I am particularly guilty because leishmaniasis is not an exceptional disease in my region. I have seen some mucosal cases simulating cancer or other diseases (including an unfortunate patient treated in another institution for nasal Wegener, until the correct diagnosis was performed). Spectacular case!

Kum Cooper: Goran an excellent teaching case. What a great pick-up. I'm assuming that the slide is from the eventual surgical resection, since the organisms are confined to perivascular histiocytes (reduced in number due to amphotericin treatment).

Goran Elmberger: My case. Hope you enjoyed the dots...

Franco Fedeli: Unusual pseudotumor from Leishmania Infection. Local corticosteroid drugs could probably favor the infection?

Masaharu Fukunaga: A challenging case. Leishmaniasis pseudotumor. I have never seen this before, thank you, Goran.

Thomas Krausz: What a brilliant diagnosis, congratulations Goran. I have seen rare cases of mycobacterial spindle cell pseudotumor before, which were misdiagnosed.

Thomas Mentzel: What a great case! I've never seen such tumor-like leishmaniasis before!

Jesse McKenney: Great infectious case!

Michal Michal: All cases of leishmaniasis that came through my hands were much easier to diagnose. I do not remember a case that looked sarcomatous as this one.

Markku Miettinen: Yes, Leishmania is there but could easily be misdiagnosed as tumor.

Cesar Moran: That is what happens when you move to Sweden ☺

Fredrik Petersson: Definitely not sarcomatoid carcinoma. Inflammatory-infective pseudotumor on H&E appearance. Amazing leishmaniasis case! Great positive impact for the patient.

Murray Resnick: Remarkable case. Have diagnosed both cutaneous and visceral leishmaniasis during my time in Israel but have never seen anything like this. The amastigotes were not easy to find initially as their distribution throughout the section was quite regional.

Brian Rubin: Great case and wonderful discussion.

Saul Suster: Goran, this must be the case of the year! Kudos for this brilliant diagnosis; I would have surely missed it.

Paul Wakely: Wonderful example of something that mimics sarcomatoid carcinoma or inflammatory myofibroblastoma at low power until one sees those “critters” at higher magnification; analogous to the entity of mycobacterial spindle cell tumor. What is the name of that island Goran, so I make sure I do not go there?

Case No.13 – Contributed by Santiago Ramon y Cajal:

Abbas Agaimy: Very interesting teaching case, I believe the organ-specific pathology culture and dogmas occasionally are a source of confusion. So, breast pathologists and prostate pathologists are worried to see some basal staining cells. In the head and neck however, it is no matter if organoid basal-luminal differentiation is seen as this is not related to the biology of the lesion at all. In my eyes, this case recapitulates myoepithelial-poor (epithelial-dominant) epithelial-myoepithelial carcinomas for which in the breast the term adenomyoepithelial carcinoma might be used as well. The fibromyxoid desmoplastic stromal reaction is the solid evidence of invasive growth. This tumor possibly represents the apocrine variant, analogous to apocrine epithelial-myoepithelial carcinoma. Thanks for the fine contribution.

Phil Allen: Residual viable infiltrating ductal carcinoma of the breast in a patient with bilateral breast calcifications. I hardly do any breast pathology and in Australia, adjuvant therapy is usually given after the primary tumor has been excised.

Ira Bleiweiss: I am not convinced of invasive carcinoma. Most if not all of this is apocrine intraductal carcinoma involving radial scar, in my opinion. I’m not sure what you mean by “senescent” cells. There are well described chemotherapy-induced cytologic effects on tumor cells - cytoplasmic vacuolization, extreme nuclear atypia with intranuclear vacuolization and eosinophilic globules in both. In such cases, despite the nuclear pleomorphism, there is often a complete lack of mitosis-which of course makes sense. It’s impossible to know if a cell is “viable” unless it is caught in the act of mitosis, and so the cytologic effect may be a degenerative change. So far, however, none of this seems to matter clinically. Only those patients who have a complete pathologic response (no residual invasive carcinoma and no residual lymph node metastases) have a demonstrably better prognosis.

Alberto Cavazza: I agree with your diagnosis, and I suspect a larger component of infiltrating ductal carcinoma (without myoepithelial layer) was present before chemotherapy. I totally agree that very probably not all the residual diseases are the same. In my reports I try to transmit this concept in a descriptive way, but I understand that this is not very satisfactory. I am curious for the other comments.

Kum Cooper: Thank you for sharing this interesting case. I defer to the breast experts for your challenging questions!

Goran Elmberger: Interesting case and discussion. In the field of salivary gland pathology it is well known that a group of biphasic tumor like epithelial myoepithelial carcinoma, adenoid cystic carcinoma and basal cell adenocarcinoma can show infiltration and preserved myoepithelial cells at the periphery of ductal differentiation. In the breast the dogma is that preserved myoepithelial cells imply benign non-infiltrative entities. However, there are some exceptions like nipple syringomatous tumor, salivary gland type tumors and epithelial-myoepithelial carcinoma. In salivary glands one might consider classifying a tumor with similar characteristics as this case as an epithelial-myoepithelial carcinoma of apocrine type.

Franco Fedeli: My favorite diagnosis (based on pure morphology and positivity for basal layer antibody) is tubular adenosis altered by chemotherapeutic drugs.

Masaharu Fukunaga: I hesitate to make a diagnosis of ductal carcinoma, I prefer adenosis with atypia.

Thomas Krausz: I find it difficult to answer your key questions without seeing all the immunostaining in the microscope. However, I think there is residual invasive carcinoma with apocrine differentiation. In places where there is myoepithelial outer layer I believe that the inner layer is "surviving" carcinoma colonizing ductular structure. In my experience in situ carcinoma and carcinoma in intravascular location (vascular invasion) may survive after chemotherapy.

Thomas Mentzel: Given that we dealing with an obvious malignant neoplasm the complete layer of myoepithelial cells may suggest that these cells are part of the neoplasm as well. In regard to the second point it seems reasonable to interpret these residual cells as tumour cells in senescence and if the conditions allow they will grow again.

Jesse McKenney: I found this case difficult given the prior chemotherapy. I would have probably diagnosed this descriptively as: "atypical apocrine proliferation colonizing a complex sclerosing lesion, favor apocrine DCIS with chemotherapy effect".

Markku Miettinen: No definitive invasive carcinoma in my slide.

Cesar Moran: Interesting histology.

Fredrik Petersson: Post-chemotherapy effect in all the tissues. Apocrine adenosis with chemo effect? I would have to see the biopsy to comment on the actual slide. Awaiting Ira's comments.

Brian Rubin: Hard to know how to evaluate the residual disease after therapy. p16 is a stress marker of senescence but not sure if that means that the cells will senesce. I guess I would just say that it shows treatment effect but still has viable cancer.

Ady Yosepovich: I believe that this is a tubular carcinoma. It is not clear to me why chemotherapy was advised.... Lymph node metastasis is an unpleasant surprise...

Case No.14 – Contributed by Phil Allen:

Abbas Agaimy: A case of epithelioid hemangioendothelioma within popliteal aneurysm treated by femoro-popliteal bypasses with metachronous multifocal spread. Tricky case in the primary resection and hard to recognize. I have difficulty distinguishing EHE from epithelioid angiosarcoma in the slides due to extensive regressive changes and presence of some spindling and higher nuclear features in the destructive bony lesions. Brian, Ofer and I have published recently in the Annals of Diagnostic Pathology a small series of epithelioid angiosarcoma in orthopedic and vascular grafts, almost all were diffusely and strongly CK positive and one was initially misinterpreted as poorly differentiated carcinoma at frozen section. Nice illustrations and discussion, thanks Dr. Allen.

Ira Bleiweiss: Agree.

Alberto Cavazza: Very nice case and intriguing hypothesis. I remember having seen an angiosarcoma arising in a popliteal arterial aneurism.

Kum Cooper: Thank you Phil for this challenging case. My initial impression was that of an epithelioid hemangioma. I wonder if FOSB and CAMTA-1 will be helpful in the differential diagnosis with EHE.

Goran Elmberger: Great case. Very easy to overlook the attempts at vascular formation in the form of intracytoplasmic vacuoles, which are characteristic for this tumor.

Franco Fedeli: Very singular case. In my experience it is more frequent to see primitive located bone epithelioid hemangioendothelioma with metastasis elsewhere.

Cyril Fisher: Amazing example of epithelioid hemangioendothelioma in bizarre clinical setting.

Masaharu Fukunaga: Thank you very much, Phil for the challenging case and comments. It is very difficult to make the differential diagnosis between epithelioid hemangioendothelioma and epithelioid angiosarcoma in this particular case.

Thomas Krausz: Phil, I like your idea of proximal feeding artery with tumor leading to multifocal epithelioid hemangioendotheliomas very much.

Thomas Mentzel: Did you perform CAMTA1 and TFE3 staining to exclude well-differentiated epithelioid angiosarcoma?

Jesse McKenney: Difficult case... My differential diagnosis was epithelioid hemangioma (the pattern originally described as "hemorrhagic epithelioid and spindle cell hemangioma") versus angiosarcoma. The multifocal bone disease could go either way. The level of atypia seemed somewhat borderline to me, but the clinical course was obviously malignant. I try to reserve the "epithelioid HE" term for the classic corded tumor with myxoid to hyalinized stroma and associated CAMTA1 fusion. It would be fascinating to know CAMTA1 and FOS family rearrangement status in this case. I have seen similar cases that cycled around the US and were diagnosed variably by different bone experts.

Markku Miettinen: Nice malignant epithelioid vascular tumor, probably epithelioid hemangioendothelioma. Better seen in specimen A.

Cesar Moran: Very nice case.

Fredrik Petersson: Agree with epithelioid hemangioendothelioma in (b). On section (a) not equally convincing tumor.

Brian Rubin: Could this be epithelioid angiosarcoma? It would be a good case for CAMTA1 IHC or genetic analysis for *WWTR1-CAMTA1* gene fusion.

Case No.15 – Contributed by Saul Suster:

Abbas Agaimy: Great case Saul, never seen a similar tumor with this morphology, will check if any adrenal specimens from FAP cases are in our files. It would be great if this distinctive morphology can be confirmed to be FAP-specific. Very beautiful immunostains and images (panel D might be SF-1??? It looks very nuclear to me). The morphology is indeed similar to some sex cord lesions. Thanks again Saul.

Phil Allen: Tubulopapillary adrenocortical adenoma in a patient with familial adenomatous polyposis. Sorry Saul. I have not seen one like this before either.

Ira Bleiweiss: Cool. I've never seen this pattern in adrenal adenoma.

Alberto Cavazza: Thanks for sharing this unique case. Never seen anything similar before.

Kum Cooper: Thanks Saul. Not seen this morphology before. I suspect you may have something similar to the thyroid cribriform-morular carcinoma.

Goran Elmberger: Great case with molecular pathway ramifications.

Franco Fedeli: Morphologically the lesion reminds me of a metanephric adenoma of the kidney. Very good teaching case and interesting case discussion.

Cyril Fisher: Adrenal cortical tumor with remarkable and unusual architecture. Very interesting and genetically supported relationship with FAP. Not seen this before.

Masaharu Fukunaga: Thank you very much for sharing this case with us. Detailed analysis and comments are excellent. I have no cases similar to this cortical tumor.

Thomas Krausz: Saul, I did a quick search of our archive, but so far, no similar case was identified.

Thomas Mentzel: Many thanks for this beautiful case!

Jesse McKenney: We have only seen this rather basaloid-insular or tubulopapillary pattern in myxoid adrenocortical tumors.

Markku Miettinen: Agree on very unusual adenoma.

Cesar Moran: Great case.

Fredrik Petersson: Never seen such a case. The morphology is similar to a pituitary adenoma!

Murray Resnick: Never seen anything like it. Beautiful case.

Brian Rubin: Never seen such a case. Unusual histology and nice discussion. The tumor manifestations of FAP are broad.

Saul Suster: My case. The case was recently e-published in Human Pathology (Tubulo-papillary adrenocortical adenoma in a patient with familial adenomatous polyposis: A morphologic, ultrastructural and molecular study. Huang H, Chang J, Rosati S, Geurts J, Mackinnon AC. Hum Pathol 2018 Aug 30 [Epub ahead of print]).

Paul Wakely: Completely weird looking cortical adenoma Saul, the likes of which I have never seen before.