COMMENTS TO AMR SEMINAR #78

CASE NO. 1 – CONTRIBUTED BY: KUM COOPPER.

Reza Alaghehbandan: Very nice case, thanks for sharing! The multi-nodular architecture is striking.

Phil Allen: I am not sure from my layman's interpretation of the organ imaging which tissue plane is involved. Is it in the joint capsule, the subcutis or even intra-articular with sparing of the subcutis? The operative and cytogenetic findings would also be of great interest. The nodules are more sharply defined, and the inflammatory cells are not as numerous as in the few cases I have recognized. My view on the relationship between the pleomorphic myxoinflammatory hemosiderotic gang of three mirrors Churchill's 1939 impression of the Soviet Union**,** it is "a riddle wrapped in a mystery inside an enigma."

Ira Bleiweiss: Interesting. Quite a chronic inflammatory response.

Alberto Cavazza: Interesting case and comments, including the controversial relationship with hemosiderotic fibrolipomatous tumor and pleomorphic hyalinizing tumor.

Goran Elmberger: Nice case. Good fit with typical description. Morphological features make one suspicious of viral change. Any good reason for naming the entity fibroblastic sarcoma?? Another translocation defined tumor?

Franco Fedeli: Myxoinflammatory fibroblastic sarcoma. The peculiar Reed-Sternberg cell-like component is the hallmark of this tumor.

Masaharu Fukunaga: Thank you very much for the interesting and beautiful case and the historical background of MIFS. Kum, it is clinically and radiologically very impressive. The histogenesis must be interesting.

Anais Malpica: First time I see in real life an example of myxoinflammatory fibrosarcoma. Have you seen cases associated with hemosiderotic fibrolipomatous tumor?

Thomas Mentzel: Dear Kum, many thanks for the nice textbook-like case of this interesting entity!

Jesse McKenney: My differential diagnosis was epithelioid sarcoma versus MIFS.

Michael Michal: I wonder if this is not a so called nodular necrotizing variant of MIFS, a recently introduced novel subtype of MIFS with *YAP1::MAML2* fusions (Perret et al, Modern Pathology 2022). Many of the observed morphological features would favor that (nodular architecture, scattered foci of necrosis in the centers of small nodules, predominance of large RS like cells, others less so (still quite prominent myxoid areas which are supposed to be rare). I think Raul Perret is now a member of the group to comment on this.

Michal Michal (Sr): Nodular necrotic variant of myxoinflammatory fibroblastic sarcoma (with *YAP1::MAML2* fusion?). See: Perret R, Tallegas M, Velasco V, Soubeyran I, Coindre JM, Azmani R, Baud J, Bacle G, De Pinieux G, Le Loarer F. Recurrent YAP1::MAML2 fusions in "nodular necrotizing" variants of myxoinflammatory fibroblastic sarcoma. Modern Pathology 2022:35: 1398.

Markku Miettinen: Myxoinflammatory fibroblastic sarcoma. Could also consider myxofibrosarcoma in the differential.

Vania Nose: Myxofibroblastic tumor - after treatment? (Difficult to make a dx by he; need a BST expert).

Fredrik Petersson: Malignant epithelioid/spindle cell mesenchymal tumor, nodular/plexiform, myxoid with vacuolated cells and variable inflammatory cell background. Some of the larger epithelioid cells have "virus-like" prominent nucleoli. I think there is emperipolesis. Small punctate focus of necrosis on my slide. Excellent case to remind us, non-soft tissue people that the acral location has been "dropped".

Kyle Perry: Very nice case of MIFS. On my H&E level I thought there might have been a focal area of necrosis? It will be interesting to see the relative frequency of *YAP1:MAML2* fusions in the nodular necrotizing variant of this tumor.

Preetha Ramalingam: In the provided section, the histologic features are compatible with myxoinflammatory fibrosarcoma. I have not seen such a case before.

Tiziana Salviato: Very interesting case. Too bad I could not see Dr. Lamovec's case. At first glance, because of the presence of adipocytes I had thought of an HFLT, but the presence of 'virocyte-like cells' and immunohistochemistry skewed the diagnosis. The diagnosis of PHAT could also have been possible, but there are too few vessels. I always think about this differential diagnosis, although some people think these are two variants of the same entity.

David Suster: Nice case and agree with diagnosis. I wonder if sequenced if it would have MGEA5 or possible Raul's *YAP1::MAML2* rearranged variant. Also given that the clinical was that of a tenosynovial giant cell tumor and the histologic shows prominent areas of xanthoma cells I'd even wonder about a malignant TGCT.

Saul Suster: Agree with the diagnosis of MIFS. The tumor shows a striking nodular growth pattern, which I haven't seen in other typical cases of MIFS. It also has central areas of comedo-like necrosis which is distinctively unusual in MIFS. The xanthomatous component may be due to its location near a joint. Could this correspond to the variant of MIFS ("nodular necrotic variant") recently described by Dr. Perret, a new member of our Club. Welcome Raul!

Daniel Wong: Thank you Dr Cooper for this very nice example of myxoinflammatory fibroblastic sarcoma, which appears to show all the classical histological features of this rare entity.

CASE NO. 2 – CONTRIBUTED BY: ALBERTO CAVAZZA.

Reza Alaghehbandan: Very interesting case, never seen HCC with sarcomatoid features before.

Phil Allen: I agree that there is no convincing support for epithelioid hemangioendothelioma.

Ira Bleiweiss: Quite the conundrum. I have a hard time conceiving of these vessels as benign given their infiltrative appearance but quite a unique case.

Goran Elmberger: Tough case. My initial impression was like yours of an angioformative epitheliod tumor with intracytoplasmic vacuoles. Given the clinical history, background cirrhosis and component of classical HCC in the periphery as well as the cited IHC results your final interpretation seems very probable.

Franco Fedeli: In this tumor the metaplastic cells are very bland. I have never seen this type of differentiation in liver.

Masaharu Fukunaga: Welcome, Alberto. Thank you very much for the challenging case and detailed discussion. My initial diagnosis was epithelioid hemangioendothelioma (EHE) and HCC. On second look, I thought that EHE-component could be HCC.

Anais Malpica: I think that this is an epithelioid hemangioendothelioma of liver associated with a hepatocellular carcinoma in spite of the negative CAMTA1. Is there any information about the histology of the metastatic tumor in bone?

Thomas Mentzel: Many thanks for this honest case report and it seems true that rare things are rare and frequent things are frequent…. I only have a question regarding the immunohistochemistry of the epithelioid haemangioendothelioma-like nodule; did these epithelioid cells really stain positively for ERG, CD31 and podoplanin?

Jesse McKenney: I am glad this was not my case! I originally thought the central area within the hepatocellular carcinoma represented benign florid reactive changes or some weird pattern of "mesenchymal hamartoma" … but it would be interesting to try to pick out different cellular components by IHC (Cam5.2, CK7, ERG, CD31, arginase, etc..). After reading the clinical outcome, I think this case is just too hard.

Michael Michal: A very challenging case. First I saw the EHE-like parts and thought it is an EHE but then I saw the full blown carcinoma component and rejected that idea. Then I read about the EHE diagnosis and was shocked that this is a collision tumor. Then I finally read the full discussion to the case and got the right diagnosis 😊 This case nicely shows the importance of CAMTA1 stain.

Michal Michal (Sr): Hepatocellular carcinoma associated with angiosarcoma.

Markku Miettinen: Cholangiocarcinoma with a sclerosing component.

Vania Nose: Hepatocellular carcinoma with endothelial lesion? Difficult to dx by H&E alone.

Fredrik Petersson: Very difficult case. I think there is a morphological transition from the bona-fide HCC to the atypical (heavily collagenized) spindle cell component, supporting your interpretation of sarcomatoid transformation. The abundant collagenous stroma does not make it easy (ddx fibrosing, reactive myofibroblastic process). The strong CK expression I think is very supportive (+ metastasis with similar morphology). In the H&N region, it is well known that sarcomatoid SCC can be very collagen-rich – "paucicellular" spindle cell/sarcomatoid SCC.

Kyle Perry: Thanks for this interesting case and discussion. I was recently talking with a colleague who was recounting her experience validating the CAMTA1 stain on archived "epithelioid hemangioendotheliomas" of the liver. She remarked how a subset of tumors historically identified as EHE were negative for CAMTA1 staining. I'm wondering if this phenomenon might account for some of those cases.

Preetha Ramalingam: This case is challenging. The infiltrative tumor has small tubular structures reminiscent of a cholangiocarcinoma. The haphazard vascular like structures raise the possibility of epithelioid hemangioendothelioma, though morphology it is not classical.

Tiziana Salviato: Very interesting and didactic case because in the end (perhaps) the diagnosis was 'simpler' than expected and only after the metastasis were we able to understand that it was a dedifferentiation of the primary tumor, related to 'suffering,' where only the most dedifferentiated cells could survive.

David Suster: I can totally see why the idea of EHE was entertained here, even has some sclerotic/myxohyaline background stroma.

Saul Suster: I would consider an hepatocholangiocarcinoma, desmoplastic variant. Small poorly formed ductules are seen scattered throughout the sclerotic areas. I would expect a more dense and florid spindle cell proliferation with marked cytologic atypia for a sarcomatoid carcinoma. Very difficult and unusual case! Thank you for sharing it.

Daniel Wong: Thank you Dr Cavazza for sharing this fascinating case. I agree with you that this is most likely sarcomatoid carcinoma. However, given that some of the spindle cells appear to be forming compressed gland-like structures (presumably what was initially interpreted to be vascular spaces), the positive staining for CK7 and the presence of atypia in some ducts, I wondered whether the sarcomatoid change may have occurred in a mixed HCC-cholangiocarcinoma.

CASE NO. 3 – BRANDON LARSEN.

Reza Alaghehbandan: Great case!

Phil Allen: What a beauty. I don't remember ever seeing one of these before, but my memory now is more fallible than most. I think I would have called this a high-grade malignancy but for Dr Larsen's excellent contribution.

Ira Bleiweiss: Sarcoma, NOS to us non-soft tissue gurus. Looks vascular despite the IHC.

Alberto Cavazza: Yes Brandon, I enjoyed it! A rare but important entity to be aware of, for the reasons you mention.

Goran Elmberger: Thanks. Good to know. I could easily understand previous diagnosis of USTS based on pleomorphism. Very good to establish entity described by Andrew et al first place and of you to recognize discrepancy of look and behavior. To make it into WHO based on 40 cases must be a record. Maybe more cases will be recognized but a more specific marker than CD34 would not hurt.

Franco Fedeli: Did you perform STAT-6? The morphology looks like an atypical solitary fibrous tumor.

Masaharu Fukunaga: Welcome, Brandon. It is also a challenging case. Superficial CD34-positive fibroblastic tumor. This case shows the most prominent cytological pleomorphism of superficial CD34 positive fibroblastic tumor I have ever seen. Differential diagnosis includes pleomorphic hyalinizing tumor. Thank you very much for sharing this educational case.

Anais Malpica: Classic example of superficial CD34-positive fibroblastic tumor, as expected marked pleomorphism and no mitoses.

Thomas Mentzel: Great example of a newly described entity (see also AJSP 2022; 46: 1329 with 59 more cases) and it seems that these lesions constitute with PRDM10-rearranged soft tissue tumours a single entity. In the literature CADM3 and WT1 are mentioned as useful markers in the differential diagnosis.

Jesse McKenney: Just based on the H&E slide, I was strongly considering aneurysmal fibrous histiocytoma with atypia. I was surprised by the CD34. Has anyone else diagnosed "CD34-positive fibroblastic tumor" with this type of vascular change?

Michael Michal: Nice case. The hemorrhagic areas and pigmentation make the diagnosis much more challenging.

Markku Miettinen: Low-grade mesenchymal neoplasm with features of hemosiderotic fibrolipomatous tumor. Also, concurrent papillary endothelial hyperplasia. Would do RNA sequencing.

Vania Nose: Pigmented fibroblastic tumor. (Difficult to make a dx by H&E – need IHC).

Fredrik Petersson: Thank you for this excellent case and write up. The thrombosed vascular component is a red herring that led my diagnostic thinking astray. Striking nuclear pleomorphism, scarcity of mitotic figure + the IHC nails it. Again, thank for reminding me about this entity.

Kyle Perry: Thanks Brandon. I remember that Andrew would sometimes like to call these a "Carter" tumor after Jodi Carter who described the superficial CD34 positive fibroblastic tumor. I agree these are probably underrecognized. When I was at Henry Ford (about 100,000 case volume), we usually had one case per year (that we were able to successfully identify). I also had a PRDM10 tumor with prominent vascular spaces and perivascular hyalinization. I wonder if some of these tumors (with prominent vascular spaces) might originally have been classified as pleomorphic hyalinizing angiectatic tumor?

Preetha Ramalingam: This is a nice example of superficial CD34-positive fibroblastic tumor. I have not seen such a case and it was quite educational to read about it. It was interesting to learn that SCD34FT and PRDM10-rearranged soft tissue tumors are likely the same entity. CADM3 expression in this tumor would have added more academic interest to the case but I presume it is not widely commercially available?

Tiziana Salviato: Very interesting case. Never seen it before. My first impression, given the hematoma and the presence of marginal hyalinized and thrombosed ectatic vessels and the rich component of hemosiderophages, I felt that it could enter into the differential diagnosis of a pleomorphic hyalinizing angiectatic tumor, but surely the site and positivity for keratins as well as the anamnestic data, help in the diagnosis.

David Suster: This is a great case! And it looks like an emerging entity since there is some stuff in the literature called pleomorphic sarcoma with PRDM10 and "PRDM10 soft tissue tumors", it is kind of confusing. Raul Perret (New AMR member) had a nice study of 20 cases of these tumors in Histopathology 3 years ago showing they are all likely related/spectrum.

Saul Suster: Thank you Brandon for submitting this case. I do not recall having seen a tumor quite like this before and it does look very distinctive. The superficial location, good circumscription, and absence of mitotic activity in my opinion indicate a likely benign behavior. I have now seen a couple of tumors diagnosed as "CD34+ fibroblastic tumor" in slide seminars and exchange clubs and they all looked different, so it seems like we're still trekking up the proverbial curve to achieving consensus and learning to recognize it. But I'm glad you showed it to Dr. Folpe, because at least now we know that this is what the tumors he described look like. I'm afraid a case like this I would have to regard as a OGK (only God knows). I never thought that in this day and age we would see another entity being named after a single IHC marker (feels like we're back to the days of "Ki-1 lymphoma"), but I'm sure we'll soon learn about some exotic fusion or mutation that will provide us with a better name.

Daniel Wong: Thank you Dr Larsen for this very nice example of superficial CD34+ fibroblastic tumor. We wrote up two cases in 2015 (PMID: 26126039) soon after the original series by Dr Folpe, and examined these at an ultrastructural level, which confirmed the fibroblastic lineage. The cells with abundant eosinophilic cytoplasm showed the expected paranuclear whorls of intermediate filament, similar to what is seen in rhabdoid cells.

CASE NO. 4 – DELIA PEREZ-MONTIEL.

Reza Alaghehbandan: Thank you for sharing! Some epithelioid LM have certainly been called STUMP…

Phil Allen: I agree. It looks horrible but as there are no mitoses or necrosis, it should be benign even with a longer follow-up than two years.

Ira Bleiweiss: Soo epithelioid. At low power looks very concerning for a lot of mitoses, which turn out not to be at high power.

Alberto Cavazza: Interesting case. The practical point here is to be sure this is benign, but I agree it is.

Goran Elmberger: My first thought ESS LG. Problem with subspecialization is spectrum of ddx in other organ systems is easy to forget. Good always to render list of ddx's and perform IHC to nail down! I love Esthers title "the remarkable spectrum of smooth muscle neoplasia"! Good case!

Franco Fedeli: I suspected an endometrial stromal sarcoma but the immunohistochemical study confirms the diagnosis of epithelioid leiomyoma.

Masaharu Fukunaga: Uterine epithelioid leiomyoma, thank you very much for the beautiful case. Differential diagnosis includes uterine tumor resembling ovarian sex-cord tumor.

Anais Malpica: This epithelioid uterine smooth muscle tumor measured 5.6 cm and has more than 4 mitoses per 10 HPFs. According to a recent study, an epithelioid leiomyoma should measure < 5 cm and show a mitotic index < 4 mitoses per 10 HPFs. In addition, it should not have moderate or severe atypia, necrosis, atypical mitoses, lymphovascular invasion or irregular borders. Based on the tumor size and the mitotic index, this tumor would be better categorized as a STUMP.
Chapel, D. , Nucci, M. , Quade, B. & Parra-Herran, C. (2022). Epithelioid Leiomyosarcoma of the Uterus. *The American Journal of Surgical Pathology, 46* (4), 464-475.

Thomas Mentzel: It's a difficult case on H&E…. given that there is some degree of nuclear atypia and some mitoses I would label the lesion probably as atypical epithelioid leiomyoma. Are the morphological criteria for the entity similar as for spindle cell smooth neoplasms in the uterus?

Jesse McKenney: I would be worried about a fusion-related uterine mesenchymal tumor in this case.

Markku Miettinen: Low-grade mesenchymal neoplasm, could be leiomyoma variant. No report on desmin-positivity.

Vania Nose: Leiomyoma.

Fredrik Petersson: Great case. Honestly, I initially thought some kind of stromal sarcoma.

Kyle Perry: Thanks for submitting this case. It's interesting to see just how "epithelioid" these things have become.

Preetha Ramalingam: This was a challenging case. While there is no marked atypia, the nuclei appear to be more atypical than that seen in usual epithelioid leiomyoma. Additionally, I found up to 5 mitoses/10hpfs in one area. I think a diagnosis of at least epithelioid STUMP may be considered in this case.

Tiziana Salviato: Really interesting case: I have no better ideas to offer. Stressing the imagination, I might say that a differential diagnosis can be made with endometrial stromal tumor. Desmin is not mentioned. Has it been performed? it would be also interesting to have other suggestions from other experts.

David Suster: Nice example!

Saul Suster: Thank you Delia for this nice case. When I looked at it blind, I initially thought of endometrial stromal sarcoma, but the negative CD10 and bcl1 do not support that diagnosis. Did you try PR? Given the sharp circumscription and low mitotic activity the patient hopefully will do quite well.

Daniel Wong: Thank you Dr Perez-Montiel for sharing this interesting case.

CASE NO. 5 – FRANCO FEDELI:

Reza Alaghehbandan: Thank you for sharing.

Phil Allen: I could see no mature rhabdomyoblastic differentiation in the H and E, only the immature eosinophilic cells that Franco mentions. The myxoid change and the patient's age also suggest rhabdomyosarcoma which is confirmed by the immunohistochemistry. I would be a bit cautious about the prognosis. The location and poor differentiation are not favorable signs.

Ira Bleiweiss: Agree with rhabdomyosarcoma.

Alberto Cavazza: A beautiful example of spindle cell embryonal rhabdomyosarcoma.

Goran Elmberger: Interesting case but from pure morphological viewpoint to me not an easy diagnosis. I hardy see any rhabdomyoblasts or myotubules. To me would be a differential ddx solved by IHC and molecular pathology just the way you did. I admit I am not a soft tissue or pediatric pathologist. I read in differential of malignant myxoid spindle cell tumors are also MPNST, SS, FS, ASPS and DSRCT. Happy to learn prognosis is better than it looks from pleomorphism. Any follow-up?

Masaharu Fukunaga: Thank you very much for the interesting case, Franco. I have never seen spindle cell rhabdomyosarcoma with myxoid change so it is a challenging case for me.

Anais Malpica: The tumor does not show the distinct fascicular pattern of spindle cell rhabdomyosarcoma. I think this is an embryonal rhabdomyosarcoma with the commonly seen myxoid background and spindle cells.

Thomas Mentzel: Given the variable cytomorphology, the myxoid stroma and the presence of scattered enlarged tumour cells and multinucleated giant cells I favor the diagnosis of embryonal rhabdomyosarcoma with anaplasia. Spindle cell rhabdomyosarcoma includes different subgroups with different genetics and prognosis (spindle cell RMS with *VGLL2/NCOA2* rearrangements, spindle cell RMS with *MyoD1* mutations).

Jesse McKenney: I would classify this as "embryonal RMS, NOS".

Markku Miettinen: Undifferentiated sarcoma, MPNST could be in the differential. But with the immunostain results it has to be rhabdomyosarcomatous tumor. Has anaplastic features raising the possibility of Li-Fraumeni syndrome.

Vania Nose: Rhabdomyosarcoma vs. myxoid tumor (need IHC and molecular).

Fredrik Petersson: Immature pediatric spindle cell sarcoma. On low-power, a bit of a "tigroid"pattern reminiscent of high-grade MPNST. IHC convincing.

Kyle Perry: This is an interesting case. I remember that Carina Dehner and Andrew Folpe recently published a series of fusion driven spindle cell rhabdomyosarcomas with a few of those also exhibiting myxoid features.

Preetha Ramalingam: This case was interesting in that there was a prominent myxoid background, insignificant collagen fibers and lack of fascicular pattern. It would be interesting to know the genetics of the tumor as MYOD1 mutated tumors are reportedly associated with worse outcomes.

Tiziana Salviato: Difficult case, compatible with high-grade sarcomatous lesion. Morphologically and by immunohistochemistry compatible with embryonal RMS.

David Suster: Nice case of spindle cell rhabdomyosarcoma, would be interesting to see the genetics.

Saul Suster: Very nice case, Franco; than you for sharing it. I agree with the diagnosis given the results of the immunohistochemical stains. It is interesting how these tumors refuse to "read the books" and keep showing variations on the theme. This case shows numerous scattered pleomorphic cells which are more common in the solid variant of alveolar RMS and pleomorphic RMS but are not "supposed" to be present in spindle and embryonal RMS. Although we insist on trying to create rigid categories for tuors, in practice they continue to defy our books and do whatever they wish. The famous surgical pathology wizard from our previous generation, Dr. Mamoru Kaneko from Mount Sinai Hospital in New York used to say, "Cancer like thief – does whatever it wants".

Daniel Wong: Thank you Dr Fedeli for this interesting case. Although historically regarded as a variant of embryonal RMS, spindle cell/sclerosing RMS is now classified separately in the current WHO Classification of Soft Tissue Tumors. Under this classification, I probably would have considered this tumor to be embryonal RMS with multifocal anaplasia based on the myxoid stroma, alternating cellularity and perivascular condensation of cells (although admittedly, sometimes the distinction from spindle cell RMS without molecular genetics is subjective).

CASE NO. 6 – GERALD BERRY:

Reza Alaghehbandan: Fascinating MASC!

Phil Allen: Another open and shut case in an unusual location. I doubt that I would have recognized it.

Ira Bleiweiss: Looking at the slide, without looking at the history or site, I thought this was breast cancer, ductal or apocrine. Frankly it does not really look like the secretory carcinomas that I've seen. If you tell me it's thyroid, I would have to believe you, but I don't see any thyroid tissue. I'd want to be sure she doesn't have a breast cancer. While I can't argue with the ETV-6 result, this looks mostly necrotic rather than "secretory" to me with much larger cells and larger glandular formations than usual secretory carcinoma, perhaps an aggressive variant.

Alberto Cavazza: Spectacular case, never seen it before in the thyroid!

Goran Elmberger: Rare unique case! With IHC profile and ETV6 translocation not much room for diagnostic doubt. Micropapillary pattern with small psammomatous calcifications. Still negativity for S100

and SOX10 a bit unusual, at least in SGT. Also, a bit unusual morphology. More mucinous than "secretory"? Comedo necrosis! SC with HG features? In cited articles stated co-existent with PTC in significant number of cases (TTF; Thyroglobulin; BRAF positive), also sharing ETV6 gene fusions! Hybrid tumor??

Franco Fedeli: Great case! I have never seen a case in this location.

Masaharu Fukunaga: Thank you, Gerald. A wonderful and interesting case. I have never seen secretory carcinoma of the thyroid. My initial impression was mucoepidermoid carcinoma.

Anais Malpica: Areas of the tumor could be mistaken for a papillary thyroid carcinoma as the nuclei show clearing of the chromatin and grooves; however, the presence of intraluminal basophilic and bright eosinophilic material should trigger the request of the IHC stains to make the correct diagnosis.

Thomas Mentzel: Now we see cases of secretory carcinoma more and more and in more and more uncommon locations….

Jesse McKenney: Agree, great case!

Michael Michal: Although I know generally very little about thyroid pathology, this was a very easy one for me – I just came back from one of our weekly intradepartmental multihead sessions where we show interesting cases from the past week. One of my colleagues presented a case of thyroid MASC. Totally identical morphology!

Markku Miettinen: Carcinoma, mucoepidermoid variant. Could not recognize this as a secretory carcinoma, which it has to be due to the fusion.

Vania Nose: Secretory carcinoma thyroid (Beautiful!).

Fredrik Petersson: Superb case! Looks more aggressive than the cases of SC in salivary glands that I have seen. Highly infiltrative. Focally micropapillary architecture with some hob-nailing.

Kyle Perry: Very interesting (and unique) presentation of this tumor.

Preetha Ramalingam: The tumor has glandular, papillary and squamoid areas as well as mucin. In some areas it appears to be reminiscent of mucoepidermoid carcinoma and in other areas the nuclear features raise the possibility of papillary thyroid carcinoma. The ETV6 rearrangement facilitates the diagnosis.

Tiziana Salviato: Very interesting case. I have never seen it in the thyroid. I have only seen it in salivary glands and breast, or in books.

David Suster: Beautiful example.

Saul Suster: Beautiful example of mammary-analogue secretory carcinoma (MASC); agree with the diagnosis. I have not seen it before in the thyroid. Although there is no normal thyroid tissue on the slide, the surrounding lymphoid elements do contain small solid cell rests and abortive follicular lumens, a finding that is commonly seen in Hashimoto's thyroiditis. The size and extent of this tumors appears to indicate this may be a particularly aggressive variant. Did all the sections show the same features?

Daniel Wong: Thank you Dr Berry for sharing this interesting case.

CASE NO. 7 – IRA BLEIWEISS:

Reza Alaghehbandan: Beautiful case! Have seen it being misdiagnosed as carcinoma...

Phil Allen: I cannot be sure that it is benign, particularly in view of the nerve invasion. I would be interested in Saul's opinion as he has written on this topic. If excision was complete, I expect the patient will be cured.

Alberto Cavazza: I agree. What is really striking in this case is the location in the axilla in a supernumerary nipple!

Goran Elmberger: Difficult case. Would like to see clinical picture, extended IHC and more sampling. Even if your history could be indicative of SyT (syringomatous adenoma of the nipple) I do not see firm evidence of nipple or breast tissue in my slide. Could be sampling error. Based on what I see I could not rule out a dermal adnexal eccrine apocrine tumor. Similarities between breast tumors, nipple tumors and skin adnexal tumors as well as salivary gland tumors is sometimes just too much. Subtle differences in CK expression patterns have been described in the literature but I have no personal experience. If we consider possibility of a sweat gland tumor given the infiltrative character and perineural growth, this tumor shows similarities with microcystic adnexal carcinoma. This tumor is however more commonly occurring in the central face. Extrafacial lesions are rare but described also in the axilla. It is interesting that SyT in the breast is not considered a malignancy even if it shows infiltrative and perineural growth but MAC of sweat gland origin is considered a LG malignant tumor. Otherwise very similar tumors.

Franco Fedeli: My first diagnosis was an infiltrative epitheliosis, a term coined by Azzopardi in 70's.

Masaharu Fukunaga: Syringomatous adenoma. I have never seen it in accessory breast. Thank you, Ira.

Anais Malpica: Interesting to see how the glands do not infiltrate the adipose tissue in spite of extending deep. Syringomatous adenoma of the nipple, in some articles they have added the word infiltrating to it.

Thomas Mentzel: This case is a real diagnostic pitfall also given the anatomic location….

Jesse McKenney: I was really worried about low-grade adenosquamous carcinoma of breast type or some type of low-grade adnexal adenocarcinoma (eccrine?).

Michael Michal: I completely forgot this entity exists. Thanks for teaching me!

Michal Michal (Sr): It seems to me that the tumor shows considerable atypia and desmoplastic reaction. I might call it syringomatoid well differentiated carcinoma.

Markku Miettinen: Low-grade sweat gland tumor (low-grade carcinoma).

Vania Nose: ? smooth muscle proliferation? (Difficult to make a dx by H&E).

Fredrik Petersson: I too considered initially low-grade adenosquamous carcinoma and also sclerosing sweat duct carcinoma/microcystic adnexal carcinoma. The IHC and clinicopathologic correlation supportive of SyT.

Preetha Ramalingam: The location of the tumor in the dermis rather than within the breast tissue, from what I read, also favors syringomatous tumor of the nipple over adenosquamous carcinoma.

Tiziana Salviato: Very tricky case! Given the location you have to think about it. it's not that immediate. How do you explain the perineural invasion in core biopsy?

David Suster: Wow, tough case! When examining the slide before reading the clinical history provided, I thought this was invasive carcinoma vs displaced epithelium involving a scar, but once the p63 was positive I would have likely backed off and asked for someone with more breast experience to look at this.

Saul Suster: Agree with Ira that this is benign. I'm not sure I would have been as imaginative in interpreting it as arising in ectopic breast tissue. I was not able to see any convincing breast epithelium in my slide; instead, I see apocrine ducts typical of skin adnexa normally seen in this location. If this was truly breast, then you would be obligated to call it malignant (aka, low-grade adenosquamous carcinoma). In my youth, we published a study on similar lesions in breast parenchyma that we designated "syringomatous squamous tumors of the breast" (Suster S et al. Cancer, 1991; 67:2350-2355). Our cases showed identical features to Rosen's "low-grade adenosquamous carcinoma" but all behaved indolently. Perhaps they stand on the "spectrum"?

Daniel Wong: Thank you Dr Bleiweiss for sharing this interesting case.

CASE NO. 8 – JOHN GROSS:

Reza Alaghehbandan: Great case!

Phil Allen: I could not see any glomus cell differentiation in the H&E and doubt that perivascular growth in a tumor with smooth muscle features is sufficient to establish glomus cell differentiation, even if there are some genetic abnormalities. The existence of a malignant glomus cell tumor is tinged with a certain degree of uncertainty, as indicated in the 7th edition of Enzinger. It is also of interest that the mythical hemangiopericytoma has reappeared in protean form as a myopericytoma on page 850 of Enzinger, just after the discussion on "malignant" glomus tumors.

Ira Bleiweiss: Wow. I had no idea what this was.

Alberto Cavazza: My impression was a peculiar leiomyosarcoma, or perhaps an EBV-associated smooth muscle tumor, but in retrospect I think you are right. Very beautiful case!

Goran Elmberger: Rare case. Difficult dx! Great Job! Does not look like garden-variety glomus tumor at all and malignant variants in esophagus must be exceedingly rare. Still peculiar vascular look made me think of vascular tumors. IHC and molecular finding together with metastasis surely confirms dx of malignant glomus tumor. It has been described that malignant variants often show spindle cell morphology.

Franco Fedeli: I presented a similar case in the duodenum in an International AMR Slide Seminar 10 years ago.

Masaharu Fukunaga: Malignant glomus tumor. Perivascular proliferation, myomatous cells and a lobular arrangement are consistent with glomus tumor.

Anais Malpica: This example of malignant glomus tumor shows an important component with spindle cells; however, there areas of typical glomus tumor which facilitates its recognition.

Thomas Mentzel: Many thanks for this example of a rare malignant glomus tumour, a diagnosis confirmed by molecular analysis. Did you find somewhere a benign glomus tumour component?

Jesse McKenney: My differential diagnosis was quite broad in this case. I was strongly considering a "funny looking" GIST, possibly SDH deficient given the nodular growth and lymph node involvement. I was surprised by the fusion… but I guess that is why we do the testing.

Michael Michal: Great case. I am surprised how much cytologically different this case is from a classic glomus tumor.

Markku Miettinen: Malignant glomus tumor (did not recognize this histologically as tumor is spindled and somewhat pleomorphic), but SMA+ and fusion gets it to glomus tumor.

Vania Nose: ?smooth muscle tumor? Glomus-type tumor? (Need IHC).

Fredrik Petersson: First considerations were AS/KS. But did not really fit. This case confirms why I need to be in the group! Thank you very much for this highly educational case.

Kyle Perry: Nice case John. I recently saw a case of metastatic/recurrent malignant glomus tumor which was originally called melanoma (maybe because these can also sometimes carry a BRAF V600E mutation?).

Preetha Ramalingam: This case of malignant glomus tumor shows sarcomatoid morphology which could bring several other tumors in the differential, including malignant smooth muscle tumor, especially if it were on a biopsy. In the provided section, the presence of more typical areas of glomus tumor helps with its recognition.

Tiziana Salviato: Never seen a case like this. Very interesting and educational! To keep in mind. Differential diagnosis arises with solitary fibrous tumor (STAT6+ and CD34+).

David Suster: A very rare case, super nice example. See John Gross's recent study on this entity!

Saul Suster: I think this is quite believable as a malignant glomus tumor. Other than malignant transformation in an angiomyoma, I cannot think of any other condition to place in the differential diagnosis. Pardon my utter ignorance but, is there a particular significance to the identified translocation? Is it "distinctive" for glomus tumors?

Daniel Wong: Thank you Dr Gross for sharing this very interesting case.

CASE NO. 9 – MARI PIA FOSCHINI:

Reza Alaghehbandan: Nice case!

Phil Allen: It looks as though the tumor arose in a submucous minor salivary gland in the right cheek. The Italian plastic surgeons must be World leaders to have filled in the huge facial defect and keep the patient alive for more than a year post operatively so that the thoracic surgeons could also show their mettle.

Ira Bleiweiss: Agree.

Alberto Cavazza: I am not an expert, but I agree, I think it is a beautiful example of high-grade transformation in a low-grade malignant salivary gland tumor. The patient may be another indirect victim of COVID infection!

Goran Elmberger: Difficult case. I am not sure about suggested diagnosis of polymorphous adenocarcinoma of minor salivary gland with HGT based on single selected slide. To establish this diagnosis, I would like to see a component of conventional PAC or molecular evidence of PRKD mutations. S100 positivity would not hurt since 97% should be positive. On the contrary here we have a biphasic adenocarcinoma with suggested peripheral basal/myoepithelial component and a central ductal differentiation. With malignant tumors of this size involving skin, cheek, lips, maxillary bone and oral mucosa it can sometimes be very hard tom localize origin and differentiation between SGT and skin adnexal tumor can be difficult and sometimes impossible. I am not sure where the submitted slide is taken from. Seems like lip with one part being mucosal and other part probably being skin with solar elastosis and suggestive sweat gland ducts in epidermis. Superficial connection with epidermis and superficial suggested squamoid differentiation. An alternative diagnosis here could be a skin adnexal carcinoma derived from apocrine or eccrine ducts. One entity that come to mind is squamoid eccrine ductal carcinoma. I am sure you have many blocks so perhaps in other parts evidence would look different. Still maybe something to consider.

Franco Fedeli: Polymorphous adenocarcinoma, S-100 negative. Very strange negativity.

Masaharu Fukunaga: Polymorphous adenocarcinoma of minor salivary gland with high grade transformation. It is characterized by various proliferative patterns and focal glandular formation. A targetoid perineural invasion is very cute. Thank you very much for a beautiful case.

Anais Malpica: The tumor has high grade features throughout. I think this represents an example of high grade epithelial-myoepithelial carcinoma.

Thomas Mentzel: Great case and it is interesting that these diffusely infiltrating neoplasms behave relatively indolent despite morphological high-grade transformation.

Jesse McKenney: High grade salivary gland-type adenocarcinoma… by H&E, I was strongly favoring epithelial-myoepithelial carcinoma.

Markku Miettinen: Carcinoma, poorly differentiated, possibly adenoid cystic, certainly accept polymorphous adenocarcinoma.

Vania Nose: High grade salivary gland carcinoma (Polymorphous adenocarcinoma vs. EMC).

Fredrik Petersson: Challenging case indeed. No low-grade component on my slide. Basal cell adenocarcinoma/adenoid cystic carcinoma with HGT are also considerations. ?beta-cateinin. Molecular genetic would be helpful/interesting.

Kyle Perry: Nice case!

Preetha Ramalingam: The tumor has uniform high grade features in the provided slide and has some overlapping features with a high grade epithelial-myoepithelial carcinoma. Additionally, S100 negativity is unusual for polymorphous low grade adenocarcinoma. In this case PRKD testing may be helpful.

Tiziana Salviato: Very interesting and unusual case.

Saul Suster: Very convincing case.

Daniel Wong: Thank you Dr Foschini for sharing this very interesting case.

Reza Alaghehbandan: Nice case!

Phil Allen: Have all our birthdays come at once? This looks the same to me as case 3 of this seminar and not at all like the real myxoinflammatory fibroblastic sarcoma (case 1) in this same seminar. Will Dr Larsen agree?

Ira Bleiweiss: Agree.

Alberto Cavazza: Hard case to me. My humble opinion is you are right: I would have called it MIFS.

Goran Elmberger: I am not an expert but it fits reasonably well with description of MIFS. I guess today molecular studies could be performed with some characteristic changes reported such as VGLL3 amplifications, t(1;10) or BRAF fusions. Maybe Markku has some experience with methylation profiling?

Franco Fedeli: The high percentage of eosinophils need for molecular biology study.

Masaharu Fukunaga: This is a challenging case. My impression of H&E includes the possibility of inflammatory myofibroblastic tumor, myxoinflammatory fibroblastic sarcoma, malignant granular cell tumor and superficial CD34-positve fibroblastic tumor. I prefer superficial CD34-positive fibroblastic tumor.

Anais Malpica: The case does not have the myxoid background usually seen in myxoinflammatory fibroblastic sarcoma. In my opinion, this case is similar to case #3. Therefore, my diagnosis is CD34 positive fibroblastic tumor.

Thomas Mentzel: A very unusual pleomorphic neoplasm with numerous eosinophils. I don´t know the diagnosis but myxoinflammatory fibroblastic sarcoma is very hard to prove.

Jesse McKenney: I had a very broad differential diagnosis for this case. It is interesting that it had a lower grade component in the original biopsy. Any chance it could be a very unusual pattern of "dedifferentiated/malignant" solitary fibrous tumor given the original diagnosis on the biopsy and the CD34 expression (STAT6)? Other things that crossed my mind: superficial CD34-positive fibroblastic tumor (relationship to skin?), funny pattern of liposarcoma (MDM2 amplification?), and histiocyte rich rhabdomyoblastic tumor (desmin/myogenin?). Otherwise, I probably would have just given a descriptive sarcoma diagnosis.

Michael Michal: MIFS is definitely one of the top differentials here, but I think this case is more likely to correspond to a superficial CD34+ fibroblastic tumor (good circumscription, lack of myxoid zones and mainly the typical glassy cytoplasm). When reviewing our archival cases of MIFS (some 70+ cases), I found several spf. CD34+ tumors originally classified as MIFS - the morphological overlap is very high.

Michal Michal (Sr): Superficial, CD34 positive fibroblastic tumor. These tumors often bear close similarity to myxoinflammatory fibroblastic sarcomas.

Markku Miettinen: Pleomorphic sarcoma, low-grade. Would be great to have sequencing. Due to low-grade features, MIFS would be in consideration although this is not typical.

Vania Nose: Sarcoma with inflammation (need BST pathologist to better classify these lesions).

Fredrik Petersson: I am eagerly awaiting the comments of the soft tissue specialists.

Kyle Perry: Thanks for sharing this interesting case. As the tumor shares some features (glass cytoplasm) with Brandon's (case #2), I think it would be interesting to sequence for PRDM10 for a PRDM10 rearranged soft tissue tumor. Apparently, these tumors can often have a prominent eosinophilic component (Am J Surg Pathol 2019;43:504–513).

Preetha Ramalingam: In the provided section, the tumor shows some prominent inflammation and areas of emperipolesis suggestive of myxoinflammatory fibroblastic sarcoma (MiFS), however, there is absence of typical myxoid background. It appears that these tumors may have overlapping histology with CD34 positive fibroblastic tumors with t(1;10) translocation being reported in some cases. I don't have much experience with the spectrum of these tumors, and I presume the marked inflammation would favor MiFS.

Tiziana Salviato: Unlike case 1 this one has an inflammatory infiltrate and most importantly we do not have the lobulate appearance; however, 'virocytic like cells' are present. the cells are much more spindle-like and there is much more hemosiderin/hemosiderophages. Why not a hemosiderotic fibrolipomatous tumor?

David Suster: Nice example of MIFS, this example has minimal or no myxoid areas, but that pattern has been described.

Saul Suster: Beautiful and typical example of MIFS, myxoid stroma-poor (at least in this slide). I've also seen this striking degree of eosinophilia before several times in MIFS. In addition to the virocyte-like nucleoli, the extensive emperipolesis is quite distinctive for these tumors. Given the overlap between MIFS, CD34+ fibroblastic tumor, PHAT, and hemosiderotic fibrolipomatous tumor, why don't we declare them a single entity within a spectrum (MIDSCD34PHATHFT – or MCPHT for short). Just kidding, Paul!

Daniel Wong: Thank you Dr Wakely for sharing this interesting case. For me, the features seem to be a nice fit for superficial CD34+ fibroblastic tumor, similar to case 3 of the current Seminar. The fascicular growth, glassy eosinophilic cytoplasm, intranuclear pseudo-inclusions, eosinophil-rich inflammation, marked pleomorphism but only rare mitotic activity are typical features for this entity and the diagnosis is supported by the diffuse CD34 expression reported. It would be useful to confirm that the lesion is subcutaneous in location.

CASE NO. 11– REZA ALAGHEHBANDAN:

Phil Allen: The use of the terms "uncertain malignant potential" and "low grade cancer" endows the pathologist with almost papal prognostic infallibility. My parents maintained that honesty is the best policy, but I still see people described as honest but poor. Perhaps a degree of ambivalence is necessary in pathology reports.

Ira Bleiweiss: So bland looking.

Alberto Cavazza: Thanks for sharing this example of oncocytic renal neoplasm, and for your comments on this difficult topic. My diagnostic impression was LOT, but you correctly pointed out there are some worrisome features. A diagnosis of low-grade malignancy seems reasonable to me.

Goran Elmberger: Oncocytic renal tumors… Evolving difficult field. I did not follow the latest developments. Oncocytic tumors unfortunately are allowed to sometimes demonstrate fat and vascular invasion even if benign and are all known to be prone to necrosis even if the latter finding is not accepted according to WHO in oncocytomas. Where exactly to draw the line between recently reported low-grade tumors and carcinomas not fulfilling definition of chromophobe RCC? Is there any help from molecular evaluation of genetic complexity CGH arrays etc?

Franco Fedeli: It is with great sadness that I miss Hes' comment.

Masaharu Fukunaga: I was very glad to meet you in Venice, Reza. I am not a renal pathologist, but it is a good opportunity to know the recent information of kidney tumors. Thank you for sharing this interesting case.

Anais Malpica: Low grade oncocytic neoplasm, the presence of necrosis -not seen in the slide available to us, warrants the diagnosis of renal cell carcinoma with oncocytic features.

Thomas Mentzel: Many thanks for the nice discussion on oncocytic renal neoplasms!

Jesse McKenney: These "other oncocytic tumors" of the kidney are very frequent. Someone needs to solve/simplify this problem… (hint … hint).

Markku Miettinen: Low-grade oncocytoid renal carcinoma. Has some features of Oncocytoma-Chromophobe carcinoma hybrid tumor (possibly Birt Hogg Dube syndrome-associated).

Vania Nose: RCC (need molecular to better classify these renal tumors).

Fredrik Petersson: Low-grade eosinophilic/oncocytoid renal tumor. Predominantly solid, focally cystic on my slide. No "leishmanioid" cytoplasmic bodies (Ondra's designation) as in eosinophilic solid-cysticRCC. A difficult field. Cytologically bland, but apparently aggressive growth. Warrants designation as low-grade carcinoma. Good clinic-pathologic correlation. Thanks.

Kyle Perry: I find these eosinophilic tumors of the kidney very challenging. I guess there are still mutations waiting to be found 😊

Preetha Ramalingam: Low grade oncocytic tumor. Given the presence of necrosis, may be best to classify as renal cell carcinoma with oncocytic features, probably low risk. It could be syndrome associated given young age of the patient.

Tiziana Salviato: Difficult case. The cytologic appearance is very bland and could suggest the possibility of a benign lesion; nevertheless, infiltration of the renal sinus fat leads to a diagnosis of low-grade malignancy.

David Suster: This looks oncocytic and low- grade but I could not further classify it and would likely send it out for another opinion.

Saul Suster: Thank you Reza for this great case! This area of renal pathology is getting more and more complicated by the day!

Daniel Wong: Thank you Dr Alaghehbandan for sharing this very interesting case.

CASE NO. 12 – RICARDO LASTRA:

Reza Alaghehbandan: Fantastic case!

Phil Allen: Despite years of application, I am still unable to accurately diagnose difficult ovarian tumors.

Ira Bleiweiss: Agree. A new one for me.

Alberto Cavazza: Beautiful and well documented case! Never seen in the ovary.

Goran Elmberger: Very interesting. Seems to be what you suggest even if not reported in ovary before. Not even chatGPT could find reported case. You could report it! Congratulations!

Franco Fedeli: The morphology reminds me of a proliferating nephrogenic adenoma. Can it occur in the ovary?

Masaharu Fukunaga: It was great to meet you in Venice, Ricardo. My impression was papillary mesothelioma. It is a challenging case. I have never seen ovarian clear cell papillary cystadenoma. Thank you very much for the beautiful slide and detailed comments.

Anais Malpica: An example of ovarian clear cell papillary cystadenoma that initially represented a diagnostic challenge as it was simultaneously detected with a renal mass in a middled age woman without significant medical history. Another confounding factor was the ovarian location rather than a location in the mesosalpinx or broad ligament as it is typically seen. Interestingly, there is a previous report of two cases of clear cell papillary cystadenoma of the epididymis where the initial diagnosis of metastatic renal cell carcinoma was rendered, one of these two cases also had a somatic mutation of the *VHL* gene.(1) Regarding the behavior of this tumor, it is usually indolent with a caveat that a rare case had omental disease as reported by the group of Dr. Nogales. Such a case presented with periadnexal tumor and 2 additional omental nodules 2-3 cm each. Of note, the patient was with no evidence of disease after 15 years in spite of the omental disease at presentation. In my opinion, the designation of the omental disease as "benign implants" may be misleading as the experience with this type of case is very limited. (2)

1. Gilcrease MZ, Schmidt L, Zbar B, Truong L, Rutledge M, Wheeler TM. Somatic von Hippel-Lindau mutation in clear cell papillary cystadenoma of the epididymis. Hum Pathol. 1995 Dec;26(12):1341-6. doi: 10.1016/0046-8177(95)90299-6. PMID: 8522307.
2. Nogales FF, Goyenaga P, Preda O, Nicolae A, Vieites B, Ruiz-Marcellan MC, Pedrosa A, Merino MJ. An analysis of five clear cell papillary cystadenomas of mesosalpinx and broad ligament: four associated with von Hippel-Lindau disease and one aggressive sporadic type. Histopathology. 2012 Apr;60(5):748-57. doi: 10.1111/j.1365-2559.2011.04151.x. Epub 2012 Feb 1. PMID: 22296276; PMCID: PMC7489309.

Thomas Mentzel: What an interesting case! Did you perform molecular analysis on the renal tumour as well?

Jesse McKenney: Classic case… we rarely ever get to see these.

Michael Michal: Terrific case. We recently published a series on clear cell mesotheliomas (PMID: 36515470) where the morphological, IHC and genetic overlap (both CC-mesothelioma and CC-cystadenoma have VHL mutations) is very high but this lesion indeed looks very bland and clear cell cystadenoma seems to be the best fit. We also found consistent near haploid genome of CC-mesotheliomas which should be able to differentiate between the two lesions if needed.

Markku Miettinen: Low-grade papillary clear cell carcinoma.

Vania Nose: Benign ovarian papillary neoplasm.

Fredrik Petersson: Very good case. Looks very much like endolymphatic sac tumor. Erudite comments.

Kyle Perry: Great case! I shared this with my colleagues who do GYN and they got a kick out of this.

Preetha Ramalingam: This is such an uncommon tumor and a very nice example. Several confounding factors including a renal mass and ovarian rather than paraovarian location.

Tiziana Salviato: Very interesting case. I never saw it in the ovary and honestly the first thought was of a metastasis from renal carcinoma. The association with VHLD is also important.

David Suster: Beautiful case. I have not yet seen one these in actual practice.

Saul Suster: Beautiful case Ricardo. Looks just like the Heffner tumor in the ear.

Daniel Wong: Thank you Dr. Lastra for sharing this very interesting case.

CASE NO. 13 – THOMAS MENTZEL:

Reza Alaghehbandan: Thanks for sharing!

Phil Allen: I have never seen one of these before. The fourth series AFIP fascicle mentions it only briefly. Thanks, Thomas, for the informative discussion and references.

Ira Bleiweiss: Cases like this make me so glad I don't do dermatopathology.

Alberto Cavazza: Spectacular case. I have no specific comments.

Goran Elmberger: Certainly good to be aware of the age. Clinically and histologically a dangerous trap for the unwary.

Franco Fedeli: Very unusual case with varied morphology.

Masaharu Fukunaga: Cutaneous neurocristic hamartoma, thank you very much for sharing this case. This is the first time I see this type of lesion.

Anais Malpica: Indeed, an unusual neurocristic hamartoma as it shows very prominent vessels and Schwannian differentiation. The spindle cell component is less prominent that the only case of this entity that I had seen before.

Jesse McKenney: I try to avoid anything with atypical melanocytes, regardless of age.

Michael Michal: I don't think I have seen one before, thanks for showing this wonderful case!

Markku Miettinen: Low-grade congenital melanocytic neoplasm.

Vania Nose: Classic-type tumor (for dermatopathologists); it is some pigmented benign lesion.

Fredrik Petersson: Complex, predominantly epithelioid and spindle cell, congenital melanocytic lesion. "Hamartoma" seems to me a misnomer. Very educational Discussion!

Kyle Perry: This is a very instructive case. I will make sure to keep this in mind when assessing a vascular lesion in young patients.

Preetha Ramalingam: This case has the spectrum of changes of neurocristic hamartoma. The prominent vessels are unusual. Again, another case that I have not previously encountered.

Tiziana Salviato: Very interesting case. I never saw this before.

Saul Suster: A simple way to conceptualize neurocristic hamartoma is as a combination of a blue nevus with a neurofibroma. This case certainly fulfills the criteria. We recently had a case here that showed the development of a malignant peripheral nerve sheath tumor in the background of a neurocristic hamartoma.

Daniel Wong: Thank you Dr Mentzel for sharing this very interesting case. I've read about these but have never encountered one in my practice. It's great to have an H&E copy – thank you.

CASE NO. 14 – FREDRIK PETERSSON:

Reza Alaghehbandan: Thanks for sharing!

Phil Allen: Thanks for the updated nomenclature and extensive discussion. My slide had a black ink spot marking a pleural scar which is adjacent to but separate from the tumor. It's on the underside of the slide so I assume that it is an accidental mark.

Ira Bleiweiss: Agree. This would be a nightmare frozen section.

Alberto Cavazza: A complete and accurate discussion on mucinous adenocarcinoma of the lung. My main rules of thumb on this entity are the following:
- In the lung, a monotonous proliferation of pure mucinous cells is diagnostic of adenocarcinoma, no matter how bland the cells are (they frequently are very bland!).
- In a lung biopsy, even a few mucinous cells floating in the mucin are suspicious for adenocarcinoma. In these situations, I generally do CK20: if negative it is not useful, but if positive in the epithelial cells it strongly supports malignancy.
- Particularly in small biopsies, bronchiolar adenoma and peribronchiolar metaplasia may simulate mucinous adenocarcinoma. In difficult cases p63 may be useful: a complete row of retained p63-positive basal cells strongly favors bronchiolar adenoma or peribronchiolar metaplasia, whereas their absence in a significant number of glands tends to exclude the latter and strongly favors adenocarcinoma.
- The morphologic distinction between a primary mucinous adenocarcinoma of the lung and a metastasis, particularly from pancreas/biliary tract, may be impossible and clinical correlation is generally required.

Goran Elmberger: My case! No further information on follow-up. Since we are a referral center here in Linköping this does not mean much.

Franco Fedeli: An interesting discussion about this rare entity.

Masaharu Fukunaga: Pulmonary invasive mucinous adenocarcinoma (IMA) with CD74-NRG1 fusion. This is the best opportunity to study comprehensively of IMA. Thank you very much for the beautiful case and detailed discussion.

Anais Malpica: Invasive mucinous adenocarcinoma. I found interesting the fact that the CD74-NRG fusion was detected in a cohort of women affected by this disease who were non-smokers.

Thomas Mentzel: Many thanks for this wonderful teaching case. Great discussion!

Jesse McKenney: Agree, Nice example.

Markku Miettinen: Mucinous adenocarcinoma.

Vania Nose: Mucinous carcinoma involving lung (?primary, ?metastases).

Fredrik Petersson: Well differentiated mucinous adenocarcinoma. Agree.

Kyle Perry: Thank you for this very comprehensive overview of invasive mucinous adenocarcinoma (including those with NRG1 fusions).

Preetha Ramalingam: Invasive mucinous adenocarcinoma of the lung. Another group of pulmonary tumors that has undergone nomenclature change. I learnt that the CD74-NRG fusion was initially detected in Asian patients with further studies showing its presence in about a third of Caucasian patients.

Tiziana Salviato: Really very interesting case. Peculiar the genetic abnormality.

David Suster: This looks like a classic invasive mucinous adenocarcinoma of the lung; the really cool part is you sequenced it and actually found an NRG fusion. Most have KRAS but I haven't seen many cases with an actual NRG1 fusion (probably because most of these do not get RNA-sequenced).

Saul Suster: Agree, invasive mucinous adenocarcinoma of lung.

Daniel Wong: Thank you Dr Elmberger for sharing this very interesting case.

CASE NO. 15 – LUCA DiTOMMASSO:

Reza Alaghehbandan: Thanks for sharing!

Phil Allen: I'm not sure what this is. I doubt that Harry Evans would have included it in his original series, if he could have had that opportunity, but it could well behave as a low grade fibromyxoid sarcoma and metastasize after many years. I wonder if the thymus was identified by the surgeon or in the excised tissue.

Ira Bleiweiss: Agree.

Alberto Cavazza: A well documented example of LGFMS in a rare location.

Goran Elmberger: LGFMS. Good fit with IHC and molecular. Wolf in sheep clothes. High mortality on long time follow-up. How is he doing?

Franco Fedeli: Low grade fibromyxoid sarcoma. In the differential diagnosis I would also put solitary fibrous tumor. Did you perform STAT6?

Masaharu Fukunaga: LGFMS of the mediastinum. Thank you for the great case with molecular analysis. I have never seen LGFMS in the mediastinum. My impression was smooth muscle tumor. I feel there is some morphological difference between that in soft tissue and mediastinum.

Anais Malpica: This example of low grade fibromyxoid sarcoma shows no myxoid areas with the typical curvilinear thin vessels; however, the fibrous appearance with thin vessels, the positive expression of MUC4 and the EWSR1 rearrangement are in keeping with the above diagnosis.

Thomas Mentzel: This seems to be an unusual example of LGFMS almost lacking myxoid stromal changes.

Jesse McKenney: Agree, Nice example.

Markku Miettinen: Low-grade mesenchymal neoplasm, consistent with low-grade fibromyxoid sarcoma. Not an easy diagnosis, staining was pale.

Vania Nose: Myxoid sarcoma (for definitive dx these lesions need molecular).

Fredrik Petersson: Low-grade (cytologically bland) spindle cell/fibroblastic neoplasm with pushing border. Not much in terms of mucin on my slide. According to my soft tissue colleagues, they have seen cases of LGFMS (molecularly confirmed) with "myxoma- and fibromatosis-like morphology", respectively. The clue was MUC4 (which is thus used a lot!). LGFMS occurring in the mediastinum, I was not aware of. Thank you for educating me. Is there myxoid medial degeneration in the large vessels?

Kyle Perry: This is an interesting case. I've seen LGFMS in some unusual places such as the small bowel mesentery and breast but not yet in the mediastinum.

Preetha Ramalingam: The presented case of low grade fibromyxoid sarcoma does not show typical myxoid features and has a more fibromatous and hyalinized appearance in the provided section. In my reading it appears that MUC4 expression can be seen in other sarcomas, though initially thought to be fairly specific for LGFMS. Since the morphology is quite different from typical low grade fibromyxoid sarcoma and has the less common EWSR1 fusion, should this be an unclassified sarcoma in true Dr. Evan's style?

Tiziana Salviato: Interesting and unusual case. Perfectly identified by IHC for MUC4.

David Suster: Very interesting case; the morphology did not make me immediately think of LGFMS given that it is predominantly fibroblastic with no myxoid component (at least on the provided slide). It actually looks more on this slide like a solitary fibrous tumor or one of those *YAP1::KMT2A* rearranged tumors (first described as MUC4 negative LFGMS/SEF); but those are MUC4 negative. I wonder what the fusion partner for EWSR1 was in this case.

Saul Suster: This case highlights the fact that in 2024, it is difficult to make a diagnosis of spindle cell lesions or soft tissue tumors without the input of molecular studies. This is the first time I see this in the mediastinum. Thank you, Luca for sharing this case with us.

Daniel Wong: Thank you Dr. de Tommasso for sharing this nice example of LGFMS, which was quite challenging just on morphology as it seems diffusely fibrous in this section, rather than the more classical alternating fibrous and myxoid areas.

CASE NO. 16 – DANIEL WONG:

Reza Alaghehbandan: Very rhabdoid – thanks for sharing!

Phil Allen: I agree that this is the same tumor described by the three Yoshidas and associates (Am J Surg Pathol 2015;39:1102-1113). It seems to me to be a genuine pathological entity with no relationship to the members of the myoepithelioma nation nor to the rhabdoid tumors and proximal epithelioid sarcomas tribes. I would be reluctant to commit myself to an unfavorable metastatic prognosis when none of the Yoshidas' cases did so, despite considerable mitotic activity. Goodness knows what I called any previous cases that I may, or even must have seen. S100 negative metastatic melanoma and secondary anaplastic tumor of unknown primary suggest themselves. I have now been saved from

future error thanks to Daniel, the AMR club and Saul, who cared for the endangered club during COVID and breathed new life into us after he retired.

Ira Bleiweiss: Agree.

Alberto Cavazza: Very unusual and interesting case. I agree: the epithelioid component looks fine for a malignant myoepithelioma, and there is clearly a high-grade small cell component. I ignored the existence of the entity you mentioned in the vulva.

Goran Elmberger: Very interesting and rare case. Handful of MELTVR described and unique HGT pattern. Spectrum of SMRCB1 deficient vulvar tumors. I cannot come up with a reason why there should be any myoepithelial cells proper in soft tissue, but I guess tumor named by phenotype rather than by histogenesis.
ChatGPT list various plausible explanations:

a. Ectopic myoepithelial cells
b. Multipotent stem cells
c. Genetic and molecular factors
d. Prior injuries.

Franco Fedeli: Proximal type epithelioid sarcoma with rhabdoid appearance was my first impression.

Masaharu Fukunaga: Malignant myoepithelioma with transformation to high grade round cell malignancy. This is a very beautiful case, thank you for the detailed comment and discussion, Daniel. This type of tumor is often discussed about its relationship with proximal epithelioid sarcoma.

Anais Malpica: The slide received shows no low grade areas. This is a tumor with a predominant epithelioid/rhabdoid component where the cells are arranged in confluent nests or have a distinct alveolar pattern, the mitotic index is > 10 mitoses per 10 HPFs. The smaller component shows small blue cells with an even higher mitotic index and rosette formation reminiscent of a primitive neuroectodermal tumor. This combination is similar to the one seen in atypical teratoid/rhabdoid tumor of the central nervous system. In addition, the IHC results are similar to the profile described in the latter entity.

Thomas Mentzel: Many thanks for the outstanding case and the discussion of the relationship of myoepithelioma and MELVR with high-grade transformation (or dedifferentiation).

Jesse McKenney: This is an unusual case. One component looks like a "malignant neurectodermal tumor" and one looks like a SWI/SNF complex-deficient malignancy with rhabdoid morphology. Not sure exactly where this fits in classification but given the location "malignant myoepithelioma-like tumor of the vulvar region (MELTVR), with transformation to high-grade round cell malignancy" may be best fit?

Michael Michal: Myoepithelioma-like tumors of the vulvar region are very interesting topic. I have seen 2 cases so far, but none had such a nicely prominent rhabdoid morphology, neither a HG transformation. Great case!

Markku Miettinen: Rhabdoid tumor/ Genital region myoepithelioma.

Vania Nose: Basaloid-like myoepithelial cell tumor (need IHC and molecular).

Fredrik Petersson: High-grade biphasic malignant epithelioid mesenchymal tumor with small round blue and large rhabdoid cells. I have yet to fully understand/grasp the concept of myoepithelial tumors in soft tissue. Well worked up.

Kyle Perry: Thank for this interesting discussion. From this case, I am wondering if there could perhaps be a relationship between this entity and malignant rhabdoid tumor of the vulva?

Preetha Ramalingam: The combination of rhabdoid morphology and tumor with neuroectodermal differentiation/PNET like morphology is reminiscent of CNS atypical teratoid/rhabdoid tumor. The slide provided does not have a low-grade component but image B in the case write up shows a more differentiated tumor component i.e. myoepithelial tumor (presumably also showed INI loss) and hence could suggest a form of dedifferentiation?

Saul Suster: Welcome Daniel to the Club and thank you for this impressive and exotic case. I am truly at a loss of words on this case – can only say…..its time to retire!

Tiziana Salviato: Difficult case. I couldn't come up with any other better conclusion.

CASE NO. 17 – ISRAA LAKLOUK:

Reza Alaghehbandan: Very nice case – Jesse and I just published a series of PTEN-related RCCs (PMID: 37357918).

Phil Allen: I think there are smooth muscle fibers in the fibrous capsule, suggesting that the tumor has invaded a dilated vein. I wonder if there are any metastases in bone. Thanks for the PTEN update. I fear I am getting further and further behind with every passing AMR club circulation.

Alberto Cavazza: A beautiful case, reminding us that as pathologists a limited but important piece of our job is to help to recognize syndromic cases. I agree that the lesion is unusual for "banal" goiter and suggests the possibility of PTEN hamartoma tumor syndrome (considering also the age of the patient). I see the main nodule is different from the others and has some worrisome features, but honestly, I have some difficulties in considering it malignant.

Goran Elmberger: Good case. Need sampling and sharp eyes. Mural nodules with anaplastic carcinoma. I guess this case represent the rhabdoid subtype. Good outcome in this patient! Low stage. Just thinking about definition of anaplasia in broader terms. Loss of specialized features exhibiting a more undifferentiated status seems OK here. Key characteristics of anaplasia however not seen.
Absence of: A) Cellular pleomorphism, B) Increased N:C ratio, C) Hyperchromasia, and D) Abnormal mitoses.

Franco Fedeli: I am not sure about the diagnosis of IEFVPTC in this patient with PTEN loss.

Masaharu Fukunaga: IEFVPTC and numerous adenomatous nodules with PTEN loss. Making this diagnosis is very difficult for me. My impression was multiple adenomatous nodules. Thank you very much for sharing a precious case.

Anais Malpica: I agree with the diagnosis of adenomatous nodules, however, I think the carcinoma is a follicular carcinoma rather than a follicular variant of papillary thyroid carcinoma. I do not see the nuclear features of the latter.

Thomas Mentzel: Great case and nice discussion. Can I use this PTEN antibody also in cases of questioned Cowden syndrome?

Jesse McKenney: Very interesting case… I do not get to see very much thyroid these days.

Markku Miettinen: Follicular adenoma.

Vania Nose: Good case of PTEN-HTS/Cowden thyroid findings with ANs and carcinoma.

Fredrik Petersson: MNG in a young patient – always exclude PTEN-syndrome. Thank you for the reminder! The thickly encapsulated tumor does not reach my threshold for PTC, rather Follicular tumor UMP.

Kyle Perry: Thanks for the case. Nice reminder to be vigilant for PTEN hamartoma syndrome.

Preetha Ramalingam: The lack of typical nuclear features of papillary thyroid carcinoma and focal intrusion of the capsule in my opinion favors a minimally invasive follicular carcinoma.

Tiziana Salviato: Very interesting case: this shows how important it is to evaluate PTEN in patients with multiple thyroid nodules.

Saul Suster: Welcome Israa to the Club. Nice case to highlight the importance of thinking of PTEN syndrome when evaluating thyroid nodules. This case, however, also highlights the difficulties and lack of consensus that we still have regarding the diagnosis of papillary thyroid carcinoma. When I looked at the slide blind I though I was dealing with a multinodular hyperplastic process, and when I read the comments, I came back to the slide and struggled to make the large central nodule into a PTC. The tumor is well-circumscribed and encapsulated and I was unable to appreciate any convincing extracapsular invasion in my slide. The nuclei are small, round, uniform, and contain small centrally placed nucleoli and scattered heterochromatin. Granted that everyone has a different threshold for what constitutes "nuclear clearing" in the thyroid, but I'm afraid according to the way I was trained by Dr. Rosai in thyroid pathology this would not qualify for PTC.

Daniel Wong: Thank you Dr Laklouk for sharing this very interesting case.

CASE NO. 18 – ANAIS MALPICA:

Reza Alaghehbandan: Great case – thanks for sharing!

Phil Allen: Some of the mucin looks like hydatid membrane. A positive PAS stain would probably have confirmed my error. Such is the danger of special stains.

Ira Bleiweiss: Agree.

Alberto Cavazza: An interesting, updated comment on an unusual entity.

Franco Fedeli: How is the Ki67 in solid tumor? Doesn't look too anaplastic.

Masaharu Fukunaga: Anaplastic carcinoma in mucinous borderline tumor. I think it is a kind of mucinous tumor with mural nodule (anaplastic carcinoma). Loss of SWI/SNF protein is very interesting.

Thomas Mentzel: It's interesting indeed that rhabdoid cytomorphology is associated with loss of SWI/SNF protein as seen also in the proximal variant of epithelioid sarcoma.

Jesse McKenney: Agree, Great example!!

Markku Miettinen: Mucinous carcinoma in a borderline mucinous tumor.

Vania Nose: Mucinous carcinoma with ?focal high grade features? (Difficult to interpret this component).

Fredrik Petersson: Mucinous borderline tumor with a nodule of anaplastic carcinoma. Great case. Based on the morphology, I am not surprised that the AC component often shows loss of SWI/SWF proteins. Gracias!

Kyle Perry: This is a nice reminder for vigilant histologic sampling in these mucinous tumors of the ovary.

Preetha Ramalingam: This case of mucinous borderline tumor with anaplastic carcinoma highlights the need for extensive sampling as it can be a focal finding. Cases with spindle rather than rhabdoid morphology can be easily mistaken for reactive stromal cells. While FIGO stage IA tumors are reported to have a favorable prognosis, we have encountered early recurrences in a subset of patients. Therefore, its recognition and documentation in the pathology report is imperative.

Tiziana Salviato: Very interesting case. It reiterates the concept of the 'importance of broad sampling" of lesions in order to increase the probability of finding it.

David Suster: Very nice example of this entity! I was not aware of the existence of these until Dr. Malpica made me aware about these and, to my surprise, we even had a few in the files here.

Saul Suster: Thank you Anais for this rare case. Do you also use the term "dedifferentiated" in GYN pathology or are GYN pathologists more illuminated than the rest of us?

Daniel Wong: Thank you Dr Malpica for sharing this very interesting case.

CASE NO. 19 – PREETHA RAMALINGAM:

Reza Alaghehbandan: First time I saw one of these tumors was in Julei's (Irving) archives in Victoria, BC.

Phil Allen: I don't think I have seen one of these before. Thanks for the contribution.

Ira Bleiweiss: Can't recall seeing anything like this. Thanks.

Alberto Cavazza: Useful comments (including the association with FAP) on an uncommon but distinctive entity. In areas the bizarre nuclei are striking but, overall, the tumor is quite bland.

Goran Elmberger: MCST of ovary. Interesting variant of stromal tumors with pathogenic activation of Wnt/beta-catenin pathway and important association with FAP.

Franco Fedeli: Very rare case. I have never seen this tumor. Thank you Preetha for presenting it.

Masaharu Fukunaga: Welcome, Preetha. Thank you very much for the beautiful case and discussion of microcystic stromal tumor of the ovary.

Anais Malpica: This example of microcystic stromal tumor shows some cells with bizarre nuclei and nuclear enlargement, an uncommon feature in this type of tumor. As mentioned already two cases have recurred and interestingly, these two cases were treated with cystectomies. Regarding the single case that presented with omental involvement, this consisted of a microscopic focus of tumor that measured 2.0 mm.

Thomas Mentzel: Another exciting neoplasm of the group of neoplasms with activation of the Wnt/ß-catenin pathway!

Jesse McKenney: Agree… I am always surprised how much these resemble juvenile granulosa cell tumor.

Markku Miettinen: Spindle cell carcinoma, low-grade (never seen microcystic stromal tumor of ovary).

Vania Nose: Unusual ovarian tumor (?IHC; ?Molecular - are needed).

Fredrik Petersson: Stunning case! Low-power, I initially considered metastasis, but cytologically too bland. Could not get it to fit with YST. Superb. Thank you!

Kyle Perry: Thanks for sharing this case. It is interesting to see just how variable the morphology can be in one of these tumors (yet another tumor with CTNNB1 mutation!).

Tiziana Salviato: Very interesting case. Never seen it. However, it needs to be taken into consideration in patients with FAP.

Saul Suster: Welcome Preetha! And thank you for sharing this beautiful example of this rare tumor.

Daniel Wong: Thank you Dr Ramalingam for sharing this very interesting case.