

COMMENTS TO AMR SEMINAR #65

CASE NO. 1 – CONTRIBUTED BY ABBAS AGAIMY, M.D.

Phil Allen - Recurrence in small-bowel of sporadic, microsatellite unstable, colorectal carcinoma of the CIPM methylated phenotype with extensive rhabdoid features six months after right hemicolectomy. The tumor in the circulated section is completely undifferentiated, as viewed in the H&E stain. I think tumors should best be classified by both phenotype and genotype,

Carlos Bacchi - It is amazing how the morphologic findings give us a clue about the possible genotype and vice-versa. In this case, I initially thought this case could represent some sort of epithelioid sarcoma in an unusual anatomic location and because of this I was suspecting this tumor would be SMARCB1/INI1 defective by IHC. Great case and comprehensive discussion.

David Ben-Dor - This is certainly not your "grandfather's" typical colon adenocarcinoma! This shows how far pathology has been progressing in the recent past. The question posed as to what the implications of this knowledge are for traditional methods of classification based on organ/histology was echoed at the meeting in Tokyo where several cases with this genetic alteration were shown. My reptile brain would have led me down the lymphoma path first.

Michele Bisceglia - Sporadic microsatellite unstable colorectal carcinoma of the colon, with rhabdoid features. Approximately 10-15% of sporadic colorectal carcinomas exhibit microsatellite instability, the genetic basis of which being represented most frequently by the somatic methylation of the promoter region in *MLH1* gene and only occasionally (as in your case) in *MSH2*. Sporadic microsatellite instability is more often seen in early-onset colorectal carcinoma rather than in the adult-onset type. Very interesting case and discussion, particularly the part of it concerning the tumor rhabdoid phenotype.

Alberto Cavazza - From the paper in press in Am J Surg Pathol and from your stimulating comments I learned a lot on this controversial topic. I agree with the diagnosis, and I am curious to read the opinions of the experts.

Thomas Colby - Agree with diagnosis following full evaluation. I got as far as undifferentiated malignant tumor, probably carcinoma, with lots of neutrophils. I also noted the rhabdoid features.

Kum Cooper - Thank you for this educative case, Abbas. I was unaware that the "rhabdoid carcinoma" has now entered the MSI-H cecal carcinomas. It is not clear to me whether SMARCB1 gene loss was tested for these cases. I think that classification should be based on both phenotype and genotype. Was good to catch up with you in Japan.

Otto Dietz - I can only remember one case from the retroperitoneum, most probably arising from the pancreas; this tumor was only treated with chemotherapy and was fatal within several weeks.

Hugo Dominguez Malagon - Rhabdoid morphology is rather ubiquitous, is associated with aggressive behavior and frequently express loss of INI1, the exception seems to be melanoma and rhabdoid (epithelioid) rhabdomyosarcoma that does not have INI1 loss and responds well to the chemotherapy regimens for alveolar RMS. Regarding the question if the classification should be molecular or morphologic, I believe it is going to be molecular (or immunohistochemical) because not all the rhabdoid tumors have the same molecular alteration and not all behave uniformly ominous; more studies need to be done.

Giovanni Falconieri - High-grade tumor with remarkable cell discohesion, scattered inflammatory cells, glassy stained cytoplasm imparting distinct rhabdoid qualities. I may not add a single word to your excellent description, and cannot contribute further to the issue you are focusing on, Abbas. I have seen something (not exactly) comparable to this either in the lung or the anterior mediastinum, and reported as rhabdoid carcinoma although in these particular cases CK stain was often focal or completely negative. It was a pleasure to see you again in Japan.

Franco Fedeli - Based on HE only my initial (as well as final) diagnosis was that of undifferentiated large cell malignant tumor with rhabdoid features involving the colon. However after taking into account both your immunohistochemical and molecular results, your diagnosis of sporadic microsatellite unstable colorectal rhabdoid carcinoma of the CIPM methylator phenotype (BRAF+) seems completely right. Agree that SMARCB1/INI1 loss is

secondary as well as responsible for the rhabdoid features of the tumor. Concerning with your question: I vote for the denomination of rhabdoid carcinoma rather than visceral epithelioid sarcoma, in your case. Nice case, fully studied and beautifully discussed.

Cyril Fisher - Very interesting case. The spectrum of epithelioid/rhabdoid tumors with INI1 loss is enlarging. Molecular findings will become more relevant in the differential.

Andrew Folpe - Fascinating case. I think you are entirely correct- the presence of the V600E mutation and the MSI-H definitely suggest this is fundamentally a carcinoma, with secondary SMARCB1 loss. It would be very interesting to look at the cause of the SMARCB1 loss - deletion vs mutation etc. I have seen other examples of true "composite" rhabdoid tumors as well - a very interesting area.

Jeronimo Forteza - This is an interesting case of pleomorphic giant cell carcinoma. The morphology points to a need for further molecular studies to complete the diagnosis.

Maria Pia Foschini - Poorly differentiated carcinoma with rhabdoid features. Thank you for the nice discussion on the association between genotype and phenotype in this neoplasm.

Ondrej Hes - This is very nice case. I have seen a similar phenomenon from clear cell RCCs with "granulomatous differentiation", where one can see "rhabdoid-like" morphology. Mostly in such cases it is not possible to demonstrate real rhabdoid differentiation. Mostly the cytoplasm is packed by rich organelles....but still keeps its epithelial nature (proven by ultrastructure).

Thomas Krausz - Excellent, thought-provoking case with superb discussion/publication. I am currently struggling with a phenotypically rhabdoid neoplasm co-expressing cytokeratin/vimentin and demonstrating loss of SMARCB1 (needle core biopsies from a 5 cm left axillary mass; negative for ER, PR, Her2, Gata3, p63; no portion of lymph node in the biopsy tissue) but occurring in a confusing clinical setting: 63-year old woman, multiple small (0.5 – 1.0cm) nodules in both breasts (clinical impression multiple metastases in breasts), multiple bone, lung, and brain metastases. I do not find it easy to determine whether the axillary mass is a primary proximal-type epithelioid sarcoma or part of the widespread metastatic process from an unknown primary (no tumor in the GI tract or kidney).

Janez Lamovec - Most interesting case. Of interest is the information that such tumors often show »redifferentiation« in metastases. We have seen this in a different context in a case of fibromatosis-like metaplastic carcinoma of the breast that was completely devoid of glandular component but showed it in some of the subsequent local recurrences and also in axillary lymph node metastasis. Recently, it has been demonstrated that small cell carcinoma of the ovary, hypercalcemic type, a tumor that often shows rhabdoid morphology, is characterized by SMARCA4 germline and somatic mutation (Witkowski L, et al. Nature Genetics, May 2014) while the submitted cecal rhabdoid tumor shows a loss of SMARCB1 – two tumors of rhabdoid morphology with different types of mutation!

Thomas Mentzel - A very interesting case indeed. How do you differentiate it from the proximal variant of epithelioid sarcoma?

Michal Michal – Nice case and nice paper about the topic in Am J Surg Pathol (2014;38:910-920)

Markku Miettinen - Agree on poorly differentiated carcinoma with a solid pattern. Has some rhabdoid differentiation. I checked my records; there is one MLH- colon Ca with a solid pattern and p63 expression. Have not tested INI1 on these.

Fredrik Petersson – On low-power, very tempted to a tentative diagnosis of high-grade lymphoma. However, when picking up the obvious rhabdoid features on high-power, then back to square one. "Everything can be rhabdoid", carcinoma, melanoma etc. (although I have never come across a rhabdoid high-grade/aggressive/large cell lymphoma). Convincing work-up and educational references. Regarding terminology, let me paraphrase the eminent physicist Richard Feynman; just because you can assign a name to a thing/phenomenon does not mean that you know the nature of it. Debates on terminology are more often reflections/manifestations of the self-fulfilling urge of colleagues, than not. We should have a productively infidel relationship to the (historically extremely useful) Virchowian histogenetic approach to tumor classification.

Murray Resnick - Interesting case especially given the aggressive nature of the tumor. Do you think that similar colorectal tumors may have been classified in the past as undifferentiated or medullary carcinomas? Undifferentiated/medullary carcinomas of the colon are frequently MLH1 negative. There are some reports

suggesting that undifferentiated/medullary carcinomas behave less aggressively. Would be interesting to go back and look at this group to see if a subset have rhabdoid features and behave more aggressively than the rest of the group, although given the rarity of these tumors it may be difficult to prove. The p63 positivity is also quite interesting.

Juan Rosai - Great demonstration of the increasingly recognized relationship between morphology and phenotype (immunohistochemistry and molecular genetics) in human tumors. Regarding the terminology issue posed by the contributor, I prefer calling malignant tumors with extensive rhabdoid features whatever they are (carcinomas, sarcomas, melanomas, or simply undifferentiated malignant tumors) followed by the qualifier "with rhabdoid features" or "of rhabdoid type", rather than calling them rhabdoid tumors, thus suggesting a distinct entity. The only exception may be the kidney, and I am not sure of that either. As to whether to base the tumor diagnosis on morphologic or genotypic features, this is an evolving area in which it would be prudent to let the dust settle down before taking a definite position. For the time being, I would rely more on the morphology, partly because of tradition, partly because of all the clinically important information that has been gathered over the decades on them, and partly because there is probably not a gene worth its name whose alteration does not result in a morphologic change. Perhaps the most important thing to remember in relation to the present case is that the rhabdoid change is bad news (except perhaps for the benign mixed tumor with hyaline cells of the palate described by Azzopardi many years ago. (Lomax-Smith JD, Azzopardi JG. The hyaline cell: a distinctive feature of "mixed" salivary tumors. *Histopathology*. 1978;2:77-92)

Brian Rubin - Not a very definitive histological pattern to me. The differential for this lesion would include poorly differentiated carcinoma, melanoma, epithelioid sarcoma, epithelioid angiosarcoma, etc. Since it has a BRAF mutation could it possibly be a weird melanoma. I didn't see that S100 or other melanoma antigens were tested. Is MSI-H and CIMP specific for carcinoma? I note the lesion is negative for CK7 and CK20 with only focal EMA and p63 staining and there was no apparent well-differentiated component, either in-situ or invasive was identified. I'm left wondering about the classification although I understand Abbas' rationale for the diagnosis and I'm not sure it makes any difference from a treatment standpoint. I like the question posed at the end of Abbas' comment. Should we classify such lesions based on genetics? The fact that there is a BRAFV600E mutation is a "home run" since BRAF inhibitors are clinically available. It probably won't cure the patient but it will likely stabilize the cancer for a while.

Dominic Spagnolo - A great case of undifferentiated carcinoma with rhabdoid features arising in the cecum (occasioning quite a list of differential diagnoses). I am pretty sure I may have seen a similar case in the late '70s or early '80s, also a cecal case. I recall it because of a publication at that time by Gibbs (*Histopathology* 1977; 1:77-84). But there were differences in those cases, and the behavior was not aggressive. Whether the case I saw had rhabdoid features or not I don't recall, but it certainly was undifferentiated. Whether it may have had MSI features such as increased TIL's I don't recall. I have been unable to find it in our archival database. Reading your ePub paper and your case submission here, I would think that nosologically these are best regarded as undifferentiated carcinomas having rhabdoid features. Thanks for this stunning case.

James Strauchen - Fabulous diagnosis!

Saul Suster - Undifferentiated malignant neoplasm with rhabdoid features. My first impression on H&E would have been a malignant, poorly-differentiated GIST. Regarding the terminology for this tumor and the question posed about whether diagnosis should be dependent on genetics or phenotype, I will quote Dr. Rosai who commented in an editorial that "the more we study molecular alterations in neoplasms the more we're going to find that they are like protein expression by immunoperoxidase, not quite as specific as we would like them" (obviously this quote is not verbatim but my take on the comment). We commented on this in our paper on gastrointestinal neuroectodermal tumors of the GI tract (GNET) that was published in *AJSP* (36:857-868, 2012) in which we postulated that the morphologic phenotype of the various tumors sharing the same genetic alteration but with different histology may be dependent on the stage of differentiation or maturation of the precursor cell at the time the genetic alteration takes place. Thus, if the mutation or translocation affects a tumor cell in a primitive stage, it may end up having a completely different morphology than if it affects the same cells when it's further along its differentiation pathway. Only time will tell, but we keep findings similar and even identical genetic translocations and fusion products in clinically and histologically disparate tumors every day. We still need to study this more; as with the early years of immunoperoxidase, we've only begun to scratch the surface.

Bruce Wenig - Alveolar pattern and cell type reminiscent of alveolar soft part sarcoma but obviously not. Abbas, thank you for educating me on this entity.

Ady Yosepovich - thank you for this very interesting case, personally I think if there is no glandular element it is difficult to call this a carcinoma. but rather a sarcoma with rhabdoid differentiation.

CASE #2 – CONTRIBUTED BY: PHIL ALLEN, M.D.

Abbas Agaimy – Very unusual and tricky case. Diffuse deciduosis in a non-uterine pelvic mass is quite misleading but endometrioid atrophic glands are a good clue. Very mimicking adenofibromas. Never seen similar case of polypoid endometriosis but comparable lesions in the appendix. I assume that necrosis is rather very uncommon under physiological hormone effect but might be in this particular case related to the "perimenopausal" age and exogenous progesterone effect in a manner similar to what we observe in leiomyomas under hormone therapy leading to necrosis and atypical features. Thanks for this nice case.

Carlos Bacchi - I agree with the diagnosis of endometriosis and I don't see why the features of necrosis and adenosarcoma-like appearance could not be present in endometriosis, especially with this polypoid type of growth.

David Ben-Dor - It was great finally having had the chance to meet you in person. I was glad to be able to leisurely revisit this case which had been shown in Tokyo. At first glance the stroma looks myoid to me and the glands don't show typical endometrioid features so this would be an endometriotic nodule with extensive metaplasia. I even found a few small foci which I thought looked granulomatous. Your analysis is intelligent and certainly better than anything I would have been able to come up with on my own. Any necrosis seen on the slide I received seems superficial and I would have assumed it was trophic in nature. In any case I don't see anything remotely malignant here.

Michele Bisceglia - Polypoid endometriosis clinically as well as histologically simulating a sarcoma in the pouch of Douglas after hysterectomy and salpingo-oophorectomy. Yes, I agree on your comments concerning the histological pseudosarcomatous appearance as well as on the pathogenetic role and effect by exogenous hormonal treatment. Am not sure, but probably have seen a case like this in the past.

Alberto Cavazza - Highly educational case. I have seen a couple of peritoneal decidual nodules (without glands) clinically simulating malignancies, but never a polypoid endometriosis with this degree of similarity to adenosarcoma. I agree with the diagnosis, and I think it is very reasonable to suspect a role for the hormonal therapy in the morphology of this lesion.

Thomas Colby - Polypoid endometriosis is a new one to me but I like that possibility. I had somewhat reluctantly gotten to a peculiar adenosarcoma. Was the patient still on hormones to explain the decidual reaction or is this a persistent decidual reaction. Was the necrosis related to prior surgery or hormones?

Kum Cooper - Thank you Allen. I agree that this is polypoid endometriosis (similar to the case you presented in Japan). My question is why is there still progestogenic influence a year following the pre-operative hormonal manipulation? Good to chat with you in open museum in Hakone.

Otto Dietz - I have not seen a case of polypoid endometriosis but remember a case of low grade stromal sarcoma with endometrioid glands, which in areas of regression showed some resemblance to this tumor.

Hugo Dominguez Malagon - Excellent example of polypoid endometriosis, resembles the endometrium curetted after exogenous hormonal therapy.

Giovanni Falconieri - Another lesson from endometriosis, I agree with your assessment Phil. I did not know the entity you are describing, and I am afraid that I would certainly mislabel it should I have come across it. I was happy to meet you again in Tokyo after so long.

Franco Fedeli - Polypoid endometriosis with stromal progestogen effect, foci of necrosis, and adenosarcoma-like appearances. Never seen a case like this, but entirely agree with you.

Cyril Fisher - The absence of atypia helps to exclude adenosarcoma.

Andrew Folpe - Agree with endometriosis. Nice case.

Jeronimo Forteza - Nevertheless the macroscopic appearance suggests it is a benign lesion.

Ondrej Hes - I have seen just 2 cases, both without necrosis.....

Thomas Krausz - In this particular case I find the distinction between polypoid endometriosis and low grade adenosarcoma problematic. Progestogenic effect makes interpretation even more difficult. I am concerned about adenosarcoma rather than polypoid endometriosis for the following reasons: apart from the adenosarcoma-like pattern you mention in the comments, the periglandular "stroma" exhibits mitotic activity (despite progestogenic effect) in contrast to the glandular epithelium which is inactive. In such a case I would review the slides from the previous hysterectomy specimen. If on review, the cervical "endometriosis" and the "adenomyosis" in the hysterectomy specimens does not show any adenosarcoma-like features, than I would accept polypoid endometriosis as the correct diagnosis.

Janez Lamovec -. I would think that all these stromal changes, including necrosis, are the results of hormonal treatment.

Thomas Mentzel - Unfortunately, I`ve never seen an example of polypoid endometriosis simulating a sarcoma before (or I`ve missed it).

Markku Mietten - Agree on endometriosis with prominent decidual change (presumably progesterone effect). Could not find adenosarcoma here.

Fredrik Petersson – Nice case. Somewhat adenosarcoma-like, but with no mitotic activity, rather with features that are very suggestive (even without the provided clinical information) of progesterone effect, as we regularly see in the endometrium of progesterone treated patients, often with (stromal) necrosis. We have seen a few cases of (non-progesterone treated) ovarian polypoid endometriosis. Not easy on frozen section.

Maria Pia Foschini - The polypoid lesion is constituted by glands with "benign epithelium" and stroma showing pleomorphic cells. To me the lesion looks more like adenosarcoma.

Juan Rosai - Phil made a very convincing argument for his proposal of interpreting this intra-abdominal lesion as the variant of endometriosis that Bob Scully called "polypoid" (Mostoufizadeh M, Scully RE. Malignant tumors arising in endometriosis. *Clin Obstet Gynecol.* 1980,23:951-63). Yet, it seems to me that the stroma is too prominent, too atypical focally, and too closely related topographically to the cleft-like glands for this not to be a Mullerian adenosarcoma.

Brian Rubin - I agree with this diagnosis although absolute distinction from adenosarcoma might be impossible. I personally haven't seen an adenosarcoma-like appearance in polypoid endometriosis probably because I haven't seen hormonal changes in a case. I haven't seen many but the ones I've seen just looked like typical endometriosis. However, I agree that decidualization could be seen in a polypoid endometriosis and I think that's what's happening here and this is what causes one to bring up the differential diagnosis of adenosarcoma. It's a fascinating case with an interesting differential diagnosis.

Dominic Spagnolo - While the features of polypoid endometriosis are there, I am disquieted by the periglandular stromal cuffing, and the large "atypical" stromal cells with macronucleoli. I did find rare mitoses in my section, but they don't help either way, nor does the necrosis. I think this is atypical but whether it equates to adenosarcoma on this one section I don't know. I am certainly very worried about it. I have also shared the case with several of my respected Gyn path colleagues. All agree the differential diagnosis is between a polypoid endometriosis and an adenosarcoma with progesterone effect. Similar concern was expressed about the periglandular stromal cuffing, atypia and isolated mitoses, though the necrosis was not considered unduly worrying in this patient's context. No-one could make a definite diagnosis of adenosarcoma. I was told that pseudo-sarcomatous change with hormones, especially tamoxifen may occur, including periglandular stromal cuffing and condensation, so it would be interesting to know specifically what hormones the patient is on. We all look forward to others' opinions in due course. Thanks for the wonderful case.

James Strauchen - Polypoid endometriosis. Great example.

Saul Suster – Never heard of polypoid endometriosis before – thank you for the education. I don't have sufficient experience with GYN to venture an opinion, but the cellular stroma is quite concerning to me. I have never seen a case of endometriosis elsewhere that contained such a cellular periglandular overgrowth that does *not* resemble endometrial stroma. Likewise, I have never seen club-like (adenofibromatous) papillae in endometriosis. Provided that this will behave in a benign fashion, the name we give it is probably irrelevant.

Bruce Wenig - I thought for sure given foci of plexiform capillary vascular pattern this would be a (low-grade) sarcoma. Another educational case. Thank you, Phil. I have no significant experience with this type of lesion so cannot comment on your question.

CASE #3 CONTRIBUTED BY: MICHELE BISCEGLIA, M.D.

Abbas Agaimy – Thanks Michele for this very unusual case which I think was presented in Tokyo. I never have seen similar tumors in the liver. Adult cases might be genetically heterogeneous. Nice and illustrative case with likely better prognosis, thanks.

Phil Allen - Undifferentiated embryonal sarcoma of the left lobe of the liver, male aged 11 years and 8 months, treated by resection of the left lobe and post operative chemoradiotherapy with no residual tumor at age 14. This case says a lot for the modern oncologists.

Carlos Bacchi - Good example of undifferentiated embryonal sarcoma. It is amazing that this patient is still alive after 3 years of surgery with the tumor being very large (22 x 19 x 9.5 cm) and with infiltration of several adjacent organs. As usual, nice discussion.

David Ben-Dor - Can't go much farther then say it looks primitive and highly malignant. The immunohistochemical findings at least for this particular case are likewise mostly uninformative so the name at this point is fitting. Maybe in the future more positive identifying features will be described. The discussion as usual is masterful and complete.

Alberto Cavazza - Agree. Very nice case and discussion.

Thomas Colby - Agree with diagnosis. Very nice discussion. It occurs to me that undifferentiated embryonal sarcoma of the liver is something that the soft tissue pathologists would have pounced on. This remains one of those peculiar tumors that is diagnosed by its site rather than its soft tissue features, somewhat analogous to pulmonary artery sarcoma.

Kum Cooper - Thank you Michele for this classic example of embryonal sarcoma of the liver. As you alluded to in your presentation in Japan, we described an angiosarcoma arising in a mesenchymal hamartoma in an adult woman. I recall consulting Thomas Krausz on that case and he agreed with the interpretation.

Otto Dietz - I agree with the diagnosis; however my first impression of the entrapped and cytological suspicious bile ducts was that of a biphasic differentiated tumor.

Hugo Dominguez Malagon - I agree with the diagnosis of hepatic undifferentiated sarcoma, nice case.

Giovanni Falconieri - This is the second case of embryonal sarcoma of liver, the first being that contributed by Janez to the Istanbul AMR meeting. We do not receive (fortunately) so many pediatric specimens, hence our experience with these lesions is nearly close to zero. Thank you for contributing this exotic case, Michele. We still share great memories from the Japan trip.

Franco Fedeli - Michele, this should be the same case you recently presented in Tokyo. Yes, I do agree on the fact that this tumor may also occur in adults, where it may represent a real pitfall especially on FNAB or small biopsy. In fact, in our files we have a case of adult-onset undifferentiated embryonal sarcoma of liver, which underwent cytology aspiration and was diagnosed as pleomorphic sarcoma, NOS.

Cyril Fisher - Embryonal sarcoma of liver. The importance of the essentially negative immunophenotype is nicely emphasized.

Andrew Folpe - Entirely agree with embryonal sarcoma of the liver. Thanks for submitting this nice example.

Jerónimo Forteza - It is remarkable the amount of blood vessels and hemophagocytosis.

Thomas Krausz - Agree with diagnosis. Very nice example.

Janez Lamovec - My colleagues and I published 3 cases of undifferentiated liver sarcoma in Ann Diagn Pathol 2011; 15: 250-56. Two cases were in children, one in an adult woman. In two cases, the tumor was associated with other metachronous neoplasms, i.e. embryonal rhabdomyosarcoma of the vagina and acute B-cell lymphoblastic leukemia, respectively.

Thomas Mentzel - Many thanks for sharing this rare case!

Markku Miettinen - Agree on undifferentiated embryonal sarcoma of liver.

Fredrik Petersson – Never seen such a case before.

Maria Pia Foschini - Undifferentiated pleomorphic sarcoma of the liver. Thank you Michele, never seen before.

Murray Resnick - Nice example. The degree of atypia in the entrapped biliary epithelium is striking.

Juan Rosai - Very demonstrative case of embryonal sarcoma of liver. By the way, this is one the best papers that Pepper Dehner wrote, done during his short but extremely productive stay at the A.F.I.P.

Brian Rubin - Very interesting case. I saw a similar case about 10 years ago. It's not a very specific histological or immunohistochemical pattern but the case I saw was identical histologically and immunohistochemically. I find the potential relationship between UES-L and MH tantalizing. It has to be more than a coincidence.

Dominic Spagnolo - Nice example of undifferentiated embryonal sarcoma Michele. We recently encountered a case in a 43 yo female with a 22 cm mass.

James Strauchen - Undifferentiated embryonal sarcoma of the liver. Wow!

Bruce Wenig - High-grade undifferentiated malignant neoplasm. Intracytoplasmic globules rather impressive. Nice case and another educational one.

Ady Yosepovich - - Thank you for this fascinating case

CASE #4 CONTRIBUTED BY: IRA BLEWISS, M.D.

Abbas Agaimy – Pretty lesion that "has a larger family but obviously no clear-cut own name". I feel it deviating from myofibroblastoma and "too organoid" for fibroadenoma and phyllodes. Would be interesting to know Rb1-status. Anyway, agree fully benign. Thanks Ira.

Phil Allen - Undiagnosed, histologically bland, biphasic breast tumor with a villoglandular columnar epithelial component and a spindle cell component resembling ovarian stroma. This tumor is so distinctive that it ought to have been described somewhere but I can't find it. I don't think it is a myofibroblastoma.

Carlos Bacchi - I favor myofibroblastoma over phyllodes due the involvement of the adjacent fat (somewhat away from the fibroepithelial lesion). In this area of spindle cells in the fat there is no epithelial or fibroepithelial elements associated with the neoplastic spindle cell population.

David Ben-Dor - To me this looks like a biphasic tumor but there seems to be too much "patterning" for phyllodes tumor (i.e. the epithelium looks too sophisticated for what is usually seen in the latter). I can certainly accept your analysis. I don't see any signs of malignancy in this.

Michele Bisceglia - Myofibroblastoma of the breast with peculiar interstitial and periductal pattern. Ira, may the fibroadenomatous or phyllodes-like appearances be just an induction effect on the side of myofibroblastoma?

Alberto Cavazza - Great case, I have never seen anything like this. To me this looks more like a myofibroblastoma with a peculiar involvement of benign glands, creating a phyllodes-like configuration, but I think your interpretation (myofibroblastoma involving a fibroadenoma) is also perfectly reasonable. I have no clues to be sure. In practice, I think I would consider this lesion a peculiar myofibroblastoma.

Thomas Colby - I like myofibroblastoma as the main lesion and whether the epithelial proliferation is secondary to interstitial infiltration of the spindle or whether there is a pre-existing lesion like a fibroadenoma I am not sure. This would make a very unusual phyllodes tumor (but I did think of that).

Kum Cooper - Ira I was wondering about adenomyoepithelioma. Did you do baso-myoe epithelial stains on the spindle cells?

Otto Dietz - Myofibroblastoma in association with a benign glandular lesion. ("Adenomyofibroblastoma"? , resembles cellular and stroma rich variants of pleomorphic adenoma).

Hugo Dominguez Malagon - Phyllodes tumor with specialized CD34+ breast stroma (so called myofibroblastoma), I have seen a nasal polyp with stroma of solitary fibrous tumor CD34 +, as you say, why not?

Giovanni Falconieri - Quite remarkable complex fibroepithelial lesion of breast, Ira. I agree with you, it looks myofibroblastomatous (despite desmin negativity, which is not an obligate feature) within a fibroadenoma. Never seen it before. I imagine it is worth a brief report. It was a pleasure to see again you and your family in Tokyo.

Franco Fedeli - Agree on your diagnosis of myofibroblastoma, possibly involving a preexisting fibroadenoma.

Cyril Fisher - Lacking desmin, might favor stromal hyperplasia in fibroadenoma.

Andrew Folpe - That's a peculiar lesion, Ira. At the risk of free associating, I am reminded a bit of DFSP, involving a fibroadenoma. Maybe it would be interesting to look for PDGFB amplification?

Jeronimo Forteza - The architectural features of the lesion made me think that, as a first diagnosis, it is a phyllodes tumour.

Ondrej Hes - For me, this is a very nice case! Just a question from an ignorant in breast pathology: stromal component resembles Mullerian type of stroma...was there any ER/PR positivity?

Thomas Krausz - Not easy to classify, however, I favor solitary fibrous tumor entrapping mammary epithelial structures in a fashion similar to pulmonary SFTs entrapping bronchiolar epithelium. Suggest checking for NAB2/STAT6 fusion gene.

Janez Lamovec - I would have the same dilemma how to call this lesion; partly it looks like a fibroadenoma, partly as a phyllodes tumor and peripherally, also beyond the limits of more defined tumor, as myofibroblastoma. Strange combination, indeed.

Thomas Mentzel - Given the morphological features and the lack of desmin expression I would prefer an unusual example of a fibroadenoma (a benign epithelial/mesenchymal biphasic tumour) instead of a myofibroblastoma.

Michal Michal - Benign phyllodes tumor with myofibroblastic stroma. Beautiful case.

Markku Miettinen - It is definitely benign and thus equal to myofibroblastoma. Unusual in the trapped epithelial component.

Fredrik Petersson - The stromal component very suggestive of mammary myofibroblastoma. Intuitively, collision tumor. Nothing much else to offer.

Maria Pia Foschini - This is really an unusual case of benign, well circumscribed fibroepithelial tumour, taking into account the age, the polypoid features and the myofibroblastoid proliferation, I would call (for what it means) the lesion a benign phyllodes tumor with spindle myofibroblastic stroma.

Murray Resnick - Difficult case. Would favor weird phyllodes.

Juan Rosai - Bizarre-looking mammary fibroepithelial lesion that shares some features of fibroadenoma/ phyllodes tumor and of myofibroblastoma/solitary fibrous tumor (the latter supported by the positivity for CD34), but which is not entirely typical of any of them. I have the impression that the stromal component is the neoplastic one and that

the lesion falls into the complex category of spindle cell stromal tumors of the breast described by Tavassoli and Vincenzo Eusebi in the 4th series of the AFIP fascicle. It just happens that Vincenzo visited our place recently, and I used the opportunity to show the case to him. He was also more impressed by the stromal than by the epithelial component.

Brian Rubin - I think this is a very weird case. I see your point about the stroma looking like myofibroblastoma – it does but I think the epithelial component is part of the lesion. There is a small satellite on my slide with the same unusual stroma and epithelioid component. Could it be a weird fibroadenoma? I think that true collision tumors are very rare – I don't have a lot of experience with them, perhaps a couple of convincing cases over my entire career.

Dominic Spagnolo - This is weird. It does not strike me as being a single biphasic lesion. The spindly element certainly looks like myofibroblastoma to me. I also think that the adipose tissue at one pole of the cellular nodule, where there are some large vessels and multiple tiny foci of the spindly cells between fat cells, is part of it (i.e. lipomatous myofibroblastoma). What to do with the epithelial element is more problematic. It certainly has a phyllodes/fibroadenomatous look. At the end of much gnashing of teeth, I agree that it is probably a fat-containing myofibroblastoma involving a pre-existing benign epithelial proliferation, resulting in a phyllodes-like appearance. Have never seen anything like it. Nor could I find anything written about this, other than for bland statements that myofibroblastoma rarely incorporates parenchymal elements. Any opportunity to do FISH for 13q abnormality?

James Strauchen - ? Weird phyllodes (or a new breast tumor!).

Saul Suster – Certainly looks like some hybrid tumor of sorts. You probably should report it! Maybe other people will start noticing it.

Bruce Wenig - Histologically busy but cytologically benign. I thought this could be a myofibroblastoma with areas of fibroadenomatous change. I have no experience with this specific breast lesion and look forward to comments from others with more experience than me.

Ady Yosepovich - A very peculiar lesion, never saw such a case, maybe this can be called a hamartoma with predominantly myofibroblastic proliferation, the cystic structures in the lesion are suggestive or reminiscent of a hamartoma

CASE #5 CONTRIBUTED BY: THOMAS COLBY, M.D.

Abbas Agaimy – Beautiful and very peculiar case, I think the main difference from the angioendotheliomatosis reported by Mcmenamin and Fletcher is the striking intravascular confinement of the lesions and regular association with thrombotic material in this very unusual case. I have observed earlier two colonic cases but none showed the strict intravascular proliferations as seen in your case. I too would support the hypothesis of some angiogenic or "thrombangitic" factor related to his underlying CVD. The mucosal changes likely reflect chronic ischemic changes secondary to these vascular abnormalities. Will be glad to read the comments of Dr. Fletcher and members of the club. Thank you for sharing this impressive case.

Phil Allen - . Reactive angioendotheliomatosis-like process in colon removed for ulcerative colitis in a 32-year-old male with congenital tricuspid atresia, hypoplastic right ventricle and pulmonary atresia treated by Blalock-Taussig shunt and atrial septectomy. I agree that the vascular proliferation is too excessive to be secondary to venous hypertension. It seems highly likely that the pathogenesis is similar to that of reactive angioendotheliomatosis of the skin. What's wrong with the interest of the Mayo clinicians?

Carlos Bacchi - There is a dramatic angiomatous-type of proliferation in this fragment of colon. No question that the some kind of angiogenic factor is very active. I wonder if this complex and intense vascular proliferation was collaborating with the refractory ulcerative colitis.

David Ben-Dor - This patient is certainly a fascinating "experiment in (or of?) nature". Maybe over the years he has developed multiple AV shunts in the microcirculation an example of which we're seeing here? The epithelium to me looks pretty well preserved for ulcerative colitis- there are crypt abscesses and goblet cell depletion but the gland

architecture looks well preserved. There are superficial erosions. I would be more in favor more of a trophic phenomenon than of an immunological process at this point but I would be very interested in the opinion of a card carrying GI pathologist.

Michele Bisceglia - Agree with your interpretation. I believe that in this case ulcerative colitis is primary and that the vascular changes are reactive. The latter changes remind me the vascular changes I had the opportunity to see once in a case of axillary lymphadenopathy in an adult patient with multiple previous episodes of severe heart failure, which I signed out as nodal angiomatosis. Nodal angiomatosis is a pathological condition closely related to vascular transformation of lymph node sinuses, and vascular transformation of sinuses in lymph nodes draining cancers in the absence of lymphovascular obstruction has been also attributed to the effect of circulating angiogenic factors (Chan JK, Warnke RA, Dorfman R. Vascular transformation of sinuses in lymph nodes. A study of its morphological spectrum and distinction from Kaposi's sarcoma. Am J Surg Pathol. 1991;15:732-43).

Alberto Cavazza - Spectacular case. I shared this case with my GI colleague, and our humble opinion is the patient probably has two separate diseases, ulcerative colitis and a dramatic vascular proliferation due to the mechanisms you suggest.

Kum Cooper - Striking vascular lobules with eosinophilic material and associated necrotic detritus. Mild nuclear pleomorphism of the endothelial cells. This reminds me of Bacillary Angiomatosis (cat-scratch bacillus/Bartonella).

Otto Dietz - I believe that the term reactive angioendotheliomatosis is the best diagnosis for that what we can see in this slide. Personally I have never seen something similar in the gut, but there are some cases following TUR of bladder tumors with vascular proliferations of a similar degree.

Hugo Dominguez Malagon - I see the typical changes of ulcerative colitis and the dramatic vascular proliferation with organizing thrombosis, it could be called angiomatosis. Regarding pathogenesis, angiogenic factors should play a role but I ignore the triggering cause.

Giovanni Falconieri -My first (totally wrong) impression was that of extensive colonic ulcer due to a vascular malformation, although changes are objectively too much for the trivial arteriovenous dysplasia we are accustomed to. Unfortunately, I don't have better ideas to contribute. Nice to meet you again at the AMR seminars, Tom.

Cyril Fisher - I guess this represents collaterals also.

Franco Fedeli - Agree on the fact that the section from your case shows both (primary) features of active chronic ulcerative colitis as well as a dramatic vascular proliferation of the colonic wall, extending to the subserosal fat. Also impressive are the numerous intravascular fibrin deposits in the context of that vascular proliferative reaction. The idea of circulating angiogenic factors implicated in the pathogenesis of this reactive vascular changes is really appealing.

Andrew Folpe - That's a really wild case. I don't think there is a whole lot of vascular proliferation, just thrombosis and recanalization of essentially every vessel in the entire section. Coagulopathy? Factor deficiency? Drug effect? There are UC-like changes as well. Such a complex medical history- it's really hard to say what is going on. He needs a serious Coag workup.

Jeronimo Forteza - This is an interesting case. I wonder if angioendotheliomatosis can be present in other organs such as the kidney.

Ondrej Hes - I have never ever seen such lesion....despite 5 years spent in routine autopsy service.... Great. I would consider it also as secondary vascular proliferation (recanalization??). I know similar (not identical) picture from "iatrogenic embolization" of renal vessels feeding renal tumors.

Thomas Krausz - Dramatic reactive vascular proliferation, probably related with collateral circulation in response to the congenital heart/pulmonary artery anomaly. Associated organizing thrombi in the vessels. I am not sure whether the ulcerative colitis genuine or mimicked by ischemic colitis in response to the vascular/circulatory problem.

Janez Lamovec - I agree with you that in this case there are two different pathologic processes present – ulcerative colitis and vascular proliferation. Whether the latter is due to underlying heart disease is definitely worthwhile exploring.

Thomas Mentzel - Histologically, an angiomatous vascular proliferation is seen, and in some dilated vascular spaces an intravascular endothelial proliferation and fibrin thrombi are evident, features that are consistent with reactive angioendotheliomatosis.

Markku Miettinen - Agree on reactive vascular proliferation with microthrombosis. Not sure where the line with angioendotheliomatosis and generic reactive vascular proliferation goes (synonymous?).

Fredrik Petersson – Enigmatic benign vasoproliferative lesion that does not neatly fit into any known (by me) entity. As always in such instances I started to retreat to the bastion of “vascular malformation”. Looked in vain for vasculitis changes. Could the colitis be on an ischemic basis,? “steal” phenomenon + micro-thrombotic events?? Superimposed infection?? Fascinating possible/likely pathogenesis.

Maria Pia Foschini - Ulcerative colitis with vascular proliferation and thrombosis. Reactive angioendotheliomatosis seems a reasonable genesis.

Murray Resnick - Fascinating case. Not really seeing good evidence of chronicity in the surrounding colonic mucosa. The numerous thrombi are intriguing.

Juan Rosai - Very impressive vascular proliferation which looks reactive rather than neoplastic. The size of the involved vessels and the extent of thrombotic changes in various stages within their lumina are particularly noteworthy. I suppose one could place this pattern into the category of reactive angioendotheliomatosis. I like Tom's suggestion of a systemic angiogenic factor inducing those widespread vascular changes. I cannot tell whether those changes are unrelated to the ulcerative colitis that this patient is known to have.

Brian Rubin - I agree that this is a “reactive” vascular proliferation. I'm not sure of the etiology although I've seen cases of bowel lesions with similar histological findings since we have a lot of GI pathology at my institution and everyone brings their weird vascular things to me.

Dominic Spagnolo - Spectacular case. Descriptively, reactive angioendotheliomatosis seems very apt. I suspect this is secondary to the cardiopulmonary issues, rather than a consequence of the ulcerative colitis. Was there evidence of similar vascular changes elsewhere??

James Strauchen - Impressive vascular proliferation and congestion. Was there evidence of venous obstruction?

Bruce Wenig - In my slide there is ulceration with prominent neutrophilic infiltrate but no specific histologic evidence of UC although focal crypt abscess formation is present perhaps secondarily extending into the crypts from the ulcerated mucosa. However, the mural vascular proliferation including fibrin thrombi is quite impressive.

CASE #6 CONTRIBUTED BY: KUM COOPER, M.D.

Abbas Agaimy – A beautiful and teaching case with nice description of pertinent diagnostic criteria of rare and difficult overlapping renal rare entities. Thanks Kum.

Phil Allen - Metanephric stromal tumor, left kidney in a two-year-old female with situs inversus and polysplenia. I thought some of the stromal cells exhibited chondroid or even osteoid features, particularly in the radiating columns around some of the entrapped renal tubules. We do not handle any childhood renal tumors, Kum, so I appreciate this contribution and discussion.

Carlos Bacchi - Slide not received.

David Ben-Dor - I certainly can't argue with your clear exposition of this entity and your conclusions which are entirely reasonable though I can't talk from personal experience with these entities. It was a welcome opportunity to brush up on the topic.

Michele Bisceglia - An interesting and rare case of metanephric stromal tumor, with cystic component. Thank you, Kum. Cystic component I think is a very rare feature in this stromal tumor of the kidney. Another interesting feature

have seen in a case I had the opportunity to look at in a case from Turkey was juxtaglomerular cell hyperplasia in entrapped glomeruli (as also described by Argani and Beckwith in AJSP 2000).

Alberto Cavazza - My experience in pediatric pathology is very limited, and this case is beyond my possibilities. Thanks for sharing it and for the nice discussion.

Thomas Colby - Agree with diagnosis and realize that I am falling further and further behind in trying to keep up with kidney tumors.

Otto Dietz - I would probably have missed the right diagnosis and considered it as a well differentiated variant of Wilms tumor.

Hugo Dominguez Malagon - Beautiful case of metanephric stromal tumor, my experience is very limited since I do not see pediatric pathology.

Giovanni Falconieri - Thank you Kum for contributing this case and the excellent discussion thereof. I may not comment properly due to total lack of experience regarding pediatric pathology. Great to see again you and your family in Japan.

Franco Fedeli - Metanephric stromal tumor. Nice case of the subspecialty pediatric surgical pathology. I think this is a classic example, although angiodysplasia as well as heterologous elements were absent. Just for the sake of completeness, still remaining in the spectrum of stromal tumors of the kidney, would like to quote a case of a pediatric stromal tumor with features overlapping with metanephric stromal tumor and solitary fibrous tumor which was published a few years ago (Brancato F, Gurrera A, Bisceglia M, Alaggio R, Di Cataldo A, Di Benedetto V, Magro G. Unclassified pediatric renal stromal tumor overlapping with metanephric stromal tumor and solitary fibrous tumor with diffuse S-100 protein expression. Pathol Res Pract. 2011;207:707-11).

Cyril Fisher - Metanephric stromal tumor, very rare. Thanks Kum for useful guide to differential diagnosis.

Andrew Folpe - Great case, Kum. Thanks for sharing. I will have to study this more so as not to miss the next one.

Jeronimo Forteza - I agree with the diagnosis.

Ondrej Hes - Very nice case, I haven't any nice example of metanephric stromal tumor (we haven't pediatric cases at all in our institution).

Thomas Krausz - Before reading the diagnosis/discussion I was considering a peculiar variant of Wilms tumor with a predominantly mature spindle cell differentiation as I thought that the mitotically active peritubular epithelioid cells were blastematosus. However, reading the excellent discussion (thanks Kum), I hope I will recognize MST next time.

Janez Lamovec - I have never seen one of these; thank you for your in depth discussion.

Thomas Mentzel - Thanks a lot for the nice discussion and differential diagnosis of stromal renal tumours in childhood.

Markku Miettinen - Thank you- never saw this before. Looks like a good example of epithelio-mesenchymal transition resembling one seen in some metaplastic carcinomas and myoepitheliomas.

Fredrik Petersson - Never seen before. The primitive appearing epithelioid cells should have steered the diagnosis towards a metanephric type of neoplasm (it didn't). Very convincing discussion. Thanks.

Maria Pia Foschini - Metanephric stromal tumor of the kidney. Thank you for presenting this rare and interesting case and for the nice discussion.

Murray Resnick - Very nice example.

Juan Rosai - Great case, with a lucid discussion. So, we have yet another type of renal tumor. While I am impressed by the never-ending description of "new" tumor entities, I have some nostalgic feeling for my residency

years, when there were only 2 types of malignant epithelial renal tumors: renal cell carcinoma in the adult and Wilms tumor in the child.

Brian Rubin – Enjoyed this case since I never get a chance to see pediatric renal tumors. Thanks for emphasizing the perivascular and peritubular collarettes. That seems like a helpful feature.

Dominic Spagnolo - Beautiful example of a metanephric stromal tumour, and informative discussion. We don't see these pediatric cases here. Thanks Kum.

James Strauchen - Metanephric stromal tumor. Thank you for the informative discussion!

Saul Suster - Thank you Kum for contributing this collector's item. Never seen this before. It has been an education.

Bruce Wenig - I have no experience with this lesion, but other than for the absence angioplasia and glial-epithelial complexes it more or less looks like the pictures in the textbook. Thanks, Kum.

CASE #7 CONTRIBUTED BY: IVAN DAMJANOV, M.D.

Abbas Agaimy – Very impressive clinical history and dramatic presentation highlighting unusual presentation of a fatal rare disease. This case nicely underscores the importance of biopsy diagnosis in apparently non-neoplastic serious systemic illnesses and the pivotal role and value of autopsy in our "NGS-era".

Phil Allen - . Midline NK/T cell extra-nodal lymphoma involving heart, lungs, pancreas, and stomach but not the nose. A very convincing case. Thanks for the contribution.

Carlos Bacchi - : Extensive involvement of the heart by high-grade lymphoma. First time I see Nasal NK/T-cell type of lymphoma infiltrating the heart like this case. Nice case.

David Ben-Dor - One conclusion to be drawn from this case is that autopsies still have a role to play in modern medicine. From what I understood from the submitted history the tumor formed diffuse interstitial but not mass-like infiltrates. On looking at the slide without benefit of history the initial "knee-jerk" reaction was myocarditis, but on careful examination the mononuclear infiltrates look completely atypical- the variety of inflammatory cells expected in an inflammatory process is absent.

Michele Bisceglia - Midline NK/T cell extranodal lymphoma, nasal type, involving the heart. Thank you Ivan for this case. Never seen one. Nice contribution. Very nice references.

Alberto Cavazza - Thanks, unusual lesion in an unusual location. I shared this case with my hematopathologist colleague, and none of us has seen a cardiac involvement in NK/T cell lymphoma before.

Thomas Colby - Agree with diagnosis. Beautiful case. I got as far as lymphoreticular malignancy and IPOX and ISH saved the day.

Kum Cooper - NK/T cell lymphoma. Great morphology and EBV positive. The other sites that I have encountered (in Africa) includes the GIT and testis.

Otto Dietz - The pleomorphic lymphoid infiltrate is suggestive for a malignant T-cell infiltrate, even without immunostaining!

Hugo Dominguez Malagon - Spectacular case of T-NK lymphoma involving myocardium, the only possible clue is the pleomorphism of lymphoid cells and nuclear dust immersed in necrotic material. It must be a very rare phenomenon, in Mexico we see T-NK lymphomas with relative frequency and I am not aware of a case like this.

Giovanni Falconieri - A remarkable case of autopsy pathology, Ivan. I could not recognize the entity although I have memories of several post mortem examinations in Trieste where myocardial involvement by lymphoma was

more than occasionally seen due to the high autopsy rate pursued at time of my residency so long ago. Definitely a paper worth reporting.

Franco Fedeli - Midline NK/T cell extranodal lymphoma, nasal type, involving the heart and other visceral organs. Good case.

Cyril Fisher - NK/T cell lymphoma involving myocardium, nice slide to have.

Andrew Folpe - Cardiac NK/T lymphoma- very interesting case.

Jeronimo Forteza - The differential diagnosis is with Giant cell myocarditis.

Thomas Krausz - Agree with diagnosis. Highly educational discussion, thank you very much. We see lots of cardiac biopsies in a variety of clinical settings (mostly transplants). On small biopsies lymphoma involving the heart may cause diagnostic challenge in distinguishing it from myocarditis. In the submitted case, the neoplastic lymphoid cells are markedly atypical and mitotically active, so recognition of their neoplastic nature would not be too difficult.

Janez Lamovec - In the past, when we performed a large number of autopsies, the finding of heart infiltration in disseminated lymphoma was not at all unusual, perhaps in some cases unidentified NK/T cell extranodal (and extranasal!) lymphomas were also present among them.

Thomas Mentzel - A very nice case showing a diffuse infiltration of the heart muscle by enlarged and atypical lymphoid cells – an unusual presentation of an extranasal variant of nasal NK/T-cell lymphoma.

Markku Miettinen - Thank you – certainly looks large cell lymphoma in most areas but also has areas of heterogeneous cellular infiltration simulating myocarditis.

Fredrik Petersson – Cytologically malignant lymphoid/lymphomatous infiltration of the heart. Convincing work up. We do see a fair bit of extranodal NK-T-cell lymphomas in Singapore. One classical diagnostic pitfall in the sinonasal tract is that the lymphomatous infiltrate (which can be quite bland and associated with large areas of necrosis) may give rise to a striking pseudoepitheliomatous hyperplasia of the squamous epithelium that can be mistaken for SCC. Regarding another pitfall, we have seen a patient with NK/T-L who had had a prior Burkitt lymphoma and after 2 years in remission developed muscle pain where a biopsy showed features consistent with polymyositis (small “benign-looking” lymphocytes). She failed to respond to treatment and further work-up showed that the patient had developed a metachronous NK/T-L with predominant involvement of soft tissue. Later on the patient developed a hematophagocytic syndrome and passed away. Unusual case of metachronous EBV-associated B-cell and NK/T-cell lymphoma mimicking polymyositis-diagnostic challenges and pitfalls. Chan EH, Lu SJ, Petersson F, Tan KB, Chng WJ, Ng SB. *Am J Hematol.* 2014 Jan;89(1):110-3.

Maria Pia Foschini - Malignant lymphoma with pleomorphic cells, some of which look plasmacytoid. Difficult case.

Juan Rosai - Another very instructive case, which shows that it is dangerous to name entities on the basis of a single parameter, whether topographic, such as location: leg-type lymphoma, dorsum lymphoma (Berti E, Alessi E, Caputo R. Reticulohistiocytoma of the dorsum (Crosti's disease) and other B-cell mm. *Semin Diagn Pathol.* 1991;8:82-90); cell size: large cell variant of small cell carcinoma of ovary; immunomarker (Ki-1 lymphoma; and others.

Brian Rubin - Interesting case. I'll keep this in mind since I occasionally see hematopoietic neoplasms in my soft tissue pathology practice.

Dominic Spagnolo - The stunning thing is that a post-mortem was actually done! And it is laudable that it was done. In our institution we have gone from doing (from memory) about 800 non-coronial autopsies annually in the late 70's early 80's, to fewer than 20 per annum now. A sad state of affairs. At any rate, this is a good example of cardiac involvement by NK/T-cell involvement. We have had some cases where the disease presents outside the nasal/nasopharyngeal region, but PET avidity is found even if CT etc. do not show obvious disease. Of course this does not prove that there is involvement, but it may be subtle. Thank you for the case.

James Strauchen - NK/T cell lymphoma. The cardiac involvement is impressive!

Saul Suster – Spectacular case! Thank you for contributing it. Goes to prove that autopsies still have a lot to teach us – a pity our clinical colleagues do not appreciate the best quality-assurance tool they have at their hands – and for free!

Bruce Wenig - What an interesting case. I have had the opportunity to review a number of nasal-type NK/T cell lymphomas but none involving the heart. Atypical cytomorphology would have engendered a detailed work-up that eventually may have allowed for a correct diagnosis. Thank you.

Ady Yosepovich - - Wow!!!

CASE #8 CONTRIBUTED BY: HUGO DOMINGUEZ MALAGON, M.D.

Abbas Agaimy – Very nice case illustrating a rare lesion at this site. I would be interested in perineurial cell markers (claudin-1 & GLUT1) and in SSTR2 and progesterone receptor. The scattered hyperchromatic nuclei make a neurogenic tumor (perineurioma or hybrid perineuriomas-schwannoma) the second differential. I have never seen it before at this location. Meningioma and perineurioma are very closely related embryologically and hence also phenotypically. In a recent paper, Thomas Mentzel, Brian Rubin and I published a comparative study on the two entities and found SSTR2 and progesterone receptor (both uniformly expressed in meningiomas and almost lacking in perineurioma) most helpful than classical perineurial markers in head and neck lesions (EMA is uniformly expressed in both entities). Thank you for sharing this case.

Phil Allen - Extra-axial fibroblastic meningioma, left maxillary sinus. I'm afraid I did not even think of meningioma. No doubt I will continue to make the same mistake in the future.

Carlos Bacchi - Would progesterone receptor be helpful in confirming the diagnosis in this case?

David Ben-Dor - Hats off for this diagnosis!- I can't say that I would have thought of it. I once had a frontal sinus biopsy showing glial cells. The patient was summarily sent to a neurosurgical unit for further investigation. I assume that the submitted case was totally ectopic.

Michele Bisceglia - Nasal meningioma, fibrous type, with some atypical features. Speaking of extraneuraxial meningiomas we already had the opportunity to see two other unquestionable primarily heterotopic cases: the one of otic meningioma by Giovanni Falconieri (sem. #38) and the case of intraosseous primary meningioma by Vincenzo Eusebi (sem. # 41).

Alberto Cavazza - My first impression was a schwannoma, but in retrospect I think meningioma is perfectly reasonable (and confirmed by your stains). An unusual possibility to be considered in this location, thanks!

Thomas Colby - Agree with diagnosis. I just wish I had thought of it prior to reading the discussion but I was having difficulty putting this lesion into any category that I felt comfortable with.

Kum Cooper - Sino-nasal schwannoma with ancient change. Nice intact example. These usually are removed piece meal making recognition more difficult.

Otto Dietz - Due to desmoplastic growth and mitotic activity I have the impression of an aggressive growing tumor (grade 3?).

Giovanni Falconieri - Great case, Hugo. I have memories of a couple of similar cases which fooled me, learning that meningioma should go on the top of the differential when dealing with spindle cell tumors of paranasal sinuses. I usually add a ki67/MIB1 since our clinicians like to have an assessment of the proliferative lesion fraction even in the absence of frank mitotic activity. Mexico deserved better fortune with the Netherlands last Sunday.

Franco Fedeli - Heterotopic nasal meningioma. Thank you for the electron micrographic picture. A very convincing case.

Cyril Fisher - Nasal meningioma. Good to see electron micrographs, thanks Hugo.

Andrew Folpe - Since I don't see many meningiomas, my first thought was "perineurioma". But your EM's are very convincing, and of course meningioma makes more sense in this location. Thanks for this nice case.

Jeronimo Forteza - This is an amazing case.

Ondrej Hes - Wow, I have seen only 2 cases (Pilsen Tumor Registry) + 1 from AMR.....very nice.

Thomas Krausz - Agree with diagnosis (though GFAP positivity is somewhat unusual). Before reading the discussion and immuno results I was considering cellular schwannoma (of course negative S100 excludes this possibility).

Janez Lamovec - Very difficult case to diagnose in such a location and with this morphology. As usual, Hugo presents superb EM images!

Thomas Mentzel - I was thinking on extraneural spindle cell perineurioma. How can we distinguish spindle cell perineurioma and spindle cell meningioma? I'm not sure if the antibody desmoplakin, that should be positive in meningiomas but negative in perineuriomas, is available.

Michal Michal - Meningeal proliferation and it seem to me that I see glial component as well.

Markku Miettinen - Favor low-grade sarcoma, difficult to specify type.

Fredrik Petersson - Ectopic meningioma was initially high on my diagnostic list, but as you correctly say - it is a difficult one when the tumor does not show typical meningotheomatous features. The quality of the cytoplasm in some of the cells and the patchy "degenerative" nuclear atypia made me consider a PEComa (also some larger vessels, albeit not "dysplastic" were there). Great learning case.

Maria Pia Foschini - Nice case. I agree with the interpretation.

Juan Rosai - Nice case, with a decisive and welcomed contribution of electron microscopy (which is not quite dead yet).

Brian Rubin - Cool case. I've seen a couple sinonasal meningiomas but they were a lot easier than this one as they had typical histology.

Dominic Spagnolo - Agree with the diagnosis of meningioma, fibrous variant. My main differential was a cellular schwannoma but the negative S100 excludes that. I found it difficult to assess the GFAP image. I have seen focal GFAP expression in bona fide intra-cranial meningiomas but rarely (this may be more common in rhabdoid and papillary forms). The ultrastructure shows condensation of abundant extracellular matrix (basement membrane-like) rather than banded collagen; this happens more frequently in fibrous variants of meningiomas. Was extension from an intracranial meningioma reliably excluded?

James Strauchen - Nasal meningioma. Very nice case!

Saul Suster - Beautiful and nicely documented case, Hugo. I have been collecting nasal meningiomas for a few years and have set aside more than a dozen cases that are ready for publication. Perhaps it's time now to start working on that project. Some of these tumors, particularly the unusual variants, can be quite difficult to recognize in this location. Would the members who have cases like this in their files like to join me and Hugo in putting together a series for publication? If you do, please send me your cases with full information, blocks and slides to my attention so we can start working on them.

Bruce Wenig - I recently saw a somewhat similar appearing sinonasal meningioma albeit less fibroblastic appearing as this one. Sinonasal meningiomas (primary or secondary) are uncommon but not so rare and I believe there are more than 40 cases in the world literature. Thank you, Hugo.

Ady Yosepovich - Amazing case.

CASE #9 CONTRIBUTED BY: OTTO DIETZ, M.D.

Abbas Agaimy – Very interesting and quite rare entity. Could be easily missed on limited biopsy. Again reminiscent of the apparently non-neoplastic serious neoplasm as the case submitted by Dr. Damjanov in this seminar.

Phil Allen - Intravascular large B-cell lymphoma, punch biopsy, skin of breast. There are numbers of mast cells in the interstitium of the upper dermis which differ from the intravascular lymphoma cells. I wonder what they are doing there.

Carlos Bacchi - Nice example of intravascular lymphoma.

David Ben-Dor - The presence of intravascular lymphoid cells is subtle (at least in the slide I received) and seems to be overshadowed by the perivascular infiltrates which looked reactive to me. If this represents the finding then it's a very clever pick-up. I had a case of this entity diagnosed on a biopsy of a bluish-red nodule on the toe. Why a systemic condition would present as a focal cutaneous lesion is curious.

Michele Bisceglia - Intravascular large B-cell lymphoma in the skin. Good case. Good slide. Had the opportunity to see some cases of this peculiar form of NHL in routine diagnostic biopsies. Among these: one in the skin, one in the bone marrow, one in lung, and another one in the prostate.

Alberto Cavazza - Very nice example of intravascular large B-cell lymphoma. This tumor can really be seen anywhere: in the first case I saw the diagnosis was made in a cholecystectomy performed in a patient with abdominal pain and systemic symptoms. Sometimes it is subtle and can be missed (I remember some terrible cases in the lung presented by Tom Colby).

Thomas Colby - Agree with diagnosis. What a peculiar tumor IVLBCL is!

Kum Cooper - Thank you for this great example of intra-vascular lymphoma. I have seen this previously in the adrenal gland and CNS. Andrew Folpe showed one in the esophagus.

Otto Dietz - My case, the patient received CHOP and ofatumumab and was seen last in the oncology department 4 weeks ago in a stable course, the ofatumumab therapy is continued with an increased dosage.

Hugo Dominguez Malagon - Intravascular lymphoma, I agree.

Giovanni Falconieri - Agree, although I have little experience with intravascular lymphoma.

Franco Fedeli - Intravascular large B-cell lymphoma in the skin. A rare and beautiful case.

Cyril Fisher - Intravascular B cell lymphoma, nice slide.

Andrew Folpe - IV lymphoma- nice case.

Jeronimo Forteza - This disease is usually systemic and sometimes involves bone marrow.

Thomas Krausz - Very nice example.

Janez Lamovec - Intravascular large B cell lymphoma; very typical case.

Thomas Mentzel -Many thanks for this example of rare intravascular B-cell lymphoma. Do you have follow-up information?

Markku Miettinen - Fully consistent with intravascular lymphoma.

Fredrik Petersson – Good case. If one is aware of the entity, the H&E is very suggestive. One important ddx is *intralymphatic histiocytosis* (primary or secondary).

Maria Pia Foschini - Interesting case of aggressive lesions, especially when it involves the CNS.

Juan Rosai - Another spectacular lesion. I will never forget a case of this lymphoma type in the breast that was misdiagnosed as intraductal carcinoma, comedo type.

Brian Rubin - Nice case. I like these cases since every time I've seen one in my practice I've thought it was metastatic breast cancer or melanoma, only to figure it out on IHC.

Dominic Spagnolo - Thanks for this nice example of intravascular B-cell lymphoma. Have also seen rarer examples of intravascular T-cell lymphoma, including an intravascular anaplastic large T-cell lymphoma, confined to skin.

James Strauchen -. Intravascular large B-cell lymphoma. Beautiful case!

Saul Suster - Beautiful example of intravascular B-cell lymphoma. This condition was formerly known as "Malignant angioendotheliomatosis proliferans" and it was believed to be a form of angiosarcoma. In fact, Dr. Rywlin was the first to recognize the lymphomatous nature of the tumor in a case report published in Am J Dermatol, in which he showed for the first time positivity with LCA in the tumor cells. Unfortunately, he cautiously interpreted the process as biphenotypic differentiation showing mixed endothelial/lymphoid lineage. This was followed by Dr. Mark Wick's paper in AJCP declaring this to be an intravascular B-cell lymphoma unrelated to endothelial proliferation. Life has been changing under our feet only recently and our generation is still creating history!

Bruce Wenig - I have nothing to add; thank you.

Ady Yosepovich - - Thank you for this case

CASE #10 CONTRIBUTED BY: VINCENZO EUSEBI, MD.

Abbas Agaimy – Fascinating case, I agree with low-grade adenosquamous and find the term "syringoid" very fine. On the day of writing these comments, I have seen (this week) a case of metaplastic carcinoma "fibromatosis-like type in the submammary skin of a young female. It showed a prominent peritumoral panniculitis with lymphoid follicles which I stressed as a clue to diagnosis in some cases of metaplastic or spindle cell carcinoma and some desmoplastic melanoma. I have seen several similar findings but almost always in such "metaplastic" or deceptively low-grade lesions. I wonder if the breast colleagues share this experience in non-medullary cases. I could hardly appreciate the ACC-like features low power but these are evident at higher magnification.

Phil Allen - Low-grade adenoid cystic carcinoma with syringoid foci associated with lymphocytic lobulitis, left breast. I can't see many normal breast ducts in my section. I wonder if the lymphocytes are reacting directly to the tumor.

Carlos Bacchi - Vincenzo, I am happy you are showing this case as I have faced exact this situation before where there was a low-grade carcinoma with areas favoring adenosquamous and others more akin to adenoid cystic carcinoma. Maybe just invasive low-grade carcinoma with features of adenosquamous and adenoid cystic carcinoma would be a more appropriate designation at least for now for these neoplasm.

David Ben-Dor - Certainly there are foci with the classical cribriform architecture of adenoid cystic carcinoma. But though there are small ducts with a teardrop shape I couldn't say that the cells which form them show squamous morphology. Should immunohistochemistry show evidence of myoepithelial and/or squamous differentiation in the syringoid component, and would this be helpful in delineating it from the adenoid cystic component? According to the latest AFIP fascicle there is something called a "syringomatous tumor" of the breast for which there is not definite evidence of myoepithelial differentiation and whose demarcation from low grade adenosquamous carcinoma is not clear. The tumor looks low grade/invasive.

Michele Bisceglia - Syringoid (low grade adenosquamous) carcinoma merging with adenoid cystic carcinoma. Concerning (sclerosing) lymphocytic lobulitis, if the patient is not diabetic, it would be worth studying expression of HLA class II DR by breast epithelium (i.e., DRB1*03 allele. see: Lee AH, Bateman AC, Turner SJ, Theaker JM, Howell WM. HLA class II DRB1 and DQB1 allelic polymorphism and sclerosing lymphocytic lobulitis of the breast. J Clin Pathol 1999;52:445-49.)

Alberto Cavazza - Thanks for sharing this peculiar tumor, highlighting the blurred limits among these lesions. No clues about lobulitis: maybe it could be a peculiar non-specific reaction to tumor, particularly if it is absent far from the tumor and if the patient has no autoimmune diseases.

Thomas Colby - Agree with diagnosis. I too noted the prominent lobulitis but have no explanation for it.

Kum Cooper - Vincenzo, thank you for this challenging case. My differential diagnosis was also between an infiltrating "nipple" adenoma and adenoid cystic carcinoma.

Otto Dietz - Adenoid cystic carcinoma in association with syringoid carcinoma seems the best explanation to me. However I cannot explain the lymphocytic lobulitis.

Hugo Dominguez Malagon - Another tumor analogous to salivary gland (and to skin adnexa) neoplasm. It certainly looks adenoid-cystic in some areas and syringomatous in others, I wonder if some cases of so-called adenomyoepithelioma of breast are equivalent to epithelial-myoepithelial carcinoma of salivary gland.

Giovanni Falconieri - Difficult case, Vincenzo. I would not be able to go further than invasive ductal carcinoma inasmuch as there are clear cut features of malignancy, yet classification appears problematic. Looking twice, I could notice both the syringoid and ACC-like pattern. Agree with you, we seen more often than expected "lymphocytic lobulitis" in clinical setting different from diabetes.

Franco Fedeli - Syringoid (low grade adenosquamous) carcinoma merging with adenoid cystic carcinoma. Lymphocytic lobulitis of the female breast has been reported both in association with autoimmune diseases (insulin dependent diabetes mellitus, Hashimoto's thyroiditis, rheumatoid arthritis, Graves disease) and in association with carcinoma of the breast (Coyne JD, Baidam AD, Asbury D. Lymphocytic mastopathy associated with ductal carcinoma in situ of the breast. Histopathology. 1995;26:579-80.; and Lee AH, Millis RR, Bobrow LG. Lymphocytic lobulitis and carcinoma of the breast. Histopathology. 1996;28:94-5.). Furthermore, lymphocytic lobulitis has been reported also in male breast (Lee AH, Zafrani B, Kafiri G, Rozan S, Millis RR. Sclerosing lymphocytic lobulitis in the male breast. J Clin Pathol. 1996;49:609-11.

Cyril Fisher - Adenoid cystic carcinoma with variant patterns, and lymphocytic lobulitis. Very unusual.

Andrew Folpe - Low-grade carcinoma with syringomatous features.

Jeronimo Forteza - I have nothing to add. Thank you for this case.

Ondrej Hes - I have never seen a similar case. I've seen dense lymphocytic infiltration in the stroma of some clear cell renal cell carcinomas.... just by coincidence or from unknown reasons. We have tested such carcinomas for Lynch syndrome-there was no association.

Thomas Krausz - I am not sure either, but at least focally it would qualify to be regarded as adenoid cystic carcinoma. Elsewhere it exhibits syringomatous/adenosquamous features without cribriforming. In view of the two cell types in many of the architecturally less complex structures I cannot exclude a precursor adenomyoepithelial lesion. I am also not sure whether the sclerosis/desmoplasia is primarily tumor induced or related with burnt out lobulitis.

Janez Lamovec - I think you are right to call this tumor a combined ACC and I.g. adenosquamous carcinoma. We have seen small foci of ACC associated with predominant adenosquamous carcinoma and, on the other hand foci of adenosquamous carcinoma in association with predominant ACC. In addition, squamous cell metaplasia in ACC was also observed in some of our ACC cases. I also believe that there is a whole spectrum of morphological appearances in the family of adenomyoepithelial tumors. The nature of lobulitis in your case is not clear to me.

Thomas Mentzel - The neoplasm nicely shows features similar to adenoid cystic carcinoma.

Michal Michal - In one part of the lesion I would call the tumor as mammary adenoid cystic carcinoma.

Markku Miettinen - Agree on invasive carcinoma (low-grade?, adenoid cystic-like).

Fredrik Petersson - Clearly cribriform adenoid cystic ca-component. Initially I thought that the tubular structures were part of the Adcca, but the absence of expression of myoepithelial markers in a significant component argues against that. It would be interesting to know whether the syringoid carcinomatous component was positive for the t(6;9) (q22-23;p23-24); MYB-NFIB gene fusion. MYB-IHC?? Syringoid sclerosing sweat duct- microcystic adnexal carcinoma-like neoplasms may also rarely occur in the tongue. Sclerosing sweat duct-like carcinoma of the tongue-a

case report and a review of the literature. Petersson F, Skogvall I, Elmberger G. Am J Dermatopathol. 2009 Oct;31(7):691-4.

Maria Pia Foschini – As a follow-up, IgG4 was negative in the inflammatory changes of lobulitis (case came from our department).

Murray Resnick - Great case. Intriguing there are no intratumoral lymphocytes and that the tumor stroma has only a mild immune response as opposed to the lymphocytic lobulitis.

Juan Rosai - I have nothing to add to Vincenzo's thorough and thoughtful discussion of this confusing subject.

Brian Rubin - I recognized this as adenoid cystic carcinoma but didn't really appreciate the low-grade adenosquamous component. It does seem rather low-grade morphologically. There is a lot of hyalinization in the region with the lymphs. I prefer to unify things so I would guess the lymphocytic lobulitis is secondary to the neoplasm.

Dominic Spagnolo - I have nothing to add Vincenzo. This carcinoma has striking syringoid and adenoid cystic patterns. The lobulitis is impressive but I have no idea why it is there. I surmise that, in the absence of any other explanation, it is a response to the carcinoma. The tumor itself at low power seems to exhibit a vague lobulocentric architecture, at least focally.

James Strauchen - Syringoid/adenoid cystic carcinoma.

Saul Suster - I agree this is malignant and I believe this is adenoid cystic carcinoma with a tubular component (tubular pattern of ACC). The "syringomatous" areas in this tumor are quite reminiscent of a condition we reported many years ago as "syringomatous squamous tumors of the breast" (Cancer 67:2350-2355, 1991). Those tumors showed features that clearly overlap with "low-grade adenosquamous carcinoma", except on long-term follow-up they all behaved benign. Clearly not everything that looks syringomatous and squamous in the breast is necessarily carcinoma. But this case definitely has an adenoid cystic carcinoma component, and rather than invoke a collision between two different tumor types I would rather invoke Ockham's razor's rule and consider this as two different morphologic manifestations of the same process.

Wenig, Bruce - Agree with low-grade infiltrative adenocarcinoma with focal areas of adenoid cystic carcinoma-like features. Not sure what to make of the lymphocytic lobulitis and while IgG4-related type changes crossed my mind the overall features were not quite right for such a diagnostic consideration.

Ady Yosepovich - A very nice case, agree with the diagnosis thank you for this very unique example of two rare breast carcinoma subtypes in one slide.....

CASE #11 CONTRIBUTED BY: GIOVANNI FALCONIERI, M.D.

Abbas Agaimy – Thank you for sharing this interesting case Falco, I am aware of this rare finding but never seen a case like this myself.

Phil Allen - Compound melanocytic nevus with granular cell changes, skin of back of female aged 20. I agree with the diagnosis. I've never seen it before. I found one other probable relevant reference. Is K Colby Tom's brother, Son or only a remote relative?. Jakobiec FA; Colby K; Bajart AM; Saragas SJ; Moulin A. Immunohistochemical studies of atypical conjunctival melanocytic nevi. Arch Ophthalmol (United States), Aug 2009, 127(8) p970-80.

Carlos Bacchi - Nice example of a compound nevus with peculiar histology with convincing EM documentation.

David Ben-Dor - The more I look at melanocytic lesions the less I feel I understand them. I would have thought of a balloon cell nevus since in the slide I have the cytoplasm looks more clear than granular but that may be due to fading of the stain. What bothers me is that the larger granular cells (per description) seem to form a confluent discrete nodule well demarcated from the surrounding nevus component with a "traditional appearance" coming to an abrupt stop with a sharp demarcation from the underlying dermis. Could this be considered a "pushing" border? One of the key properties in deciding whether a melanocytic lesion is benign or malignant is the presence of

maturation which is not operative in this case (maybe arguably at the edges but not in the central portion). I know that the appearance of a discrete nodule in a congenital nevus is cause for concern. I agree that in of themselves these cells look innocuous cytologically without mitotic activity and it's comforting for the patient that the melanoma experts concluded that the lesion is benign.

Michele Bisceglia - Compound melanocytic nevus with granular cell changes, and congenital features. From a constructive critical point, Giovanni, I have the following questions: are you sure that these granular cell changes can confidently be distinguished from balloon cell changes? Are you sure that the lysosomal quality of the EM findings does not reflect in some way the melanosomal quality of these HMB-45 positive cells? Notice: in Ann Diagn Pathol, there's a case report of a cutaneous compound cell nevus with balloon cell changes of the back, immunohistochemically similar to yours, which was also studied with EM. (Cagnano E, Benharroch D, Sion-Vardy N. Compound nevus with congenital features and balloon cell changes--an immunohistochemical study. Ann Diagn Pathol. 2008;12:362-64).

Alberto Cavazza - A peculiar finding, and I do not remember having seen it before. My first impression was a balloon cell nevus, but in retrospect I agree, the cells are more granular.

Thomas Colby - Agree with diagnosis; a new one for me. I have no experience with this sort of nevus and nowadays see very few nevi at all.

Kum Cooper - Falco I am impressed that you still look at melanocytic skin lesions. My low power view was one of balloon cell nevus. But then again I have not signed out skin in over 20years!

Otto Dietz - I did not know about this entity before and thought of a balloon cell nevus.

Hugo Dominguez Malagon - . The granular cell transformation in nevi agrees with the concept that "granular" like "oncocyctic" and "rhabdoid" changes only mean a phenotype.

Franco Fedeli - Compound melanocytic nevus with granular cell changes. Have seen a few cases of common melanocytic nevi with a few isolated scattered melanocytes exhibiting granular cell changes. Even in your case there are a few isolated melanocytic cells with granular clear cytoplasm scattered in the usual melanocytic component. However, I did not see a case with such extensive granular cell changes as in your case.

Cyril Fisher - Compound melanocytic nevus with granular/balloon cell changes

Andrew Folpe - I have never seen a nevus quite like this one.

Jeronimo Forteza - The cellular granular component is very remarkable. I agree with the diagnosis.

Thomas Krausz - Agree with diagnosis. On low power I thought this is going to be a balloon cell nevus, but the tumor cells do have a granular rather than a vacuolated cytoplasm. After careful study I could identify an occasional cell with both granular and vacuolated cytoplasm. I am speculating that the lysosomal cytoplasmic granularity is a "clearing" event (the tumor cells getting rid of abnormal melanosomes). Strong HMB45 immunoreactivity would go along with this idea (still many "antigenically but not morphologically preserved" melanosomes in the cytoplasm).

Janez Lamovec - I haven't heard of this change in nevi but in the skin there are a number of lesions that they may exhibit it: leiomyoma, leiomyosarcoma, basal cell carcinoma, dermatofibroma, atypical fibroxanthoma, etc. Thank you, Falco, for submitting this case.

Thomas Mentzel - Many thanks for this interesting case of a compound melanocytic nevus showing prominent granular cell changes. Given the mentioned ultrastructural findings, the granular cell changes could represent a degenerative phenomenon.

Michal Michal - Granular balloon cell melanocytic nevus.

Markku Miettinen - Agree on granular cell change in benign nevocellular nevus. This could be analogous to balloon cell change sometimes seen in melanoma.

Fredrik Petersson – Agree. Both the nevoid and granular cell features are distinct. HMB-45 is directed towards a melanosome associated protein. Maybe a component the pathologic cytoplasmic equipment/organelle(s) is partly melanosomes and not only lysosomes? Pathologically processed melanosome associated proteins ??

Maria Pia Foschini - Unusual case. Perhaps I have diagnosed similar lesions as balloon cell nevi. Lysosomes would be “natural” organelles in the granular cells of nevi as granular cell schwannian tumors are loaded with lysosomes. The EM provided of the lesion shows some lysosomes in the lesional cells, which certainly are not “lysosome rich” cells. This would be the result of sampling artifacts or the granularity is due to something else. The likely candidate would be mitochondria, that are difficult to see in formalin fixed tissue. If this is the case, the granular cells would be mitochondrion loaded, and the lesion would fall into the large family of oncocytomas (oncocytic intradermal nevus).

Murray Resnick - Curious case. For what it's worth my level had a mitotic figure in one of the granular cells.....

Juan Rosai - Sorry, but I cannot buy this as a nevus with granular cell changes. I think it is instead a pretty good example of balloon cell nevus (which is not quite the same thing).

Brian Rubin - Really strange case but believable diagnosis. I've never seen a nevus with granular cell change. I guess we can just add this to the list of neoplasms that can have granular cell change. It's a very long list indeed.

Dominic Spagnolo - Agree with benign compound nevus showing granular cell change (PAS would be interesting), and agree this is very uncommon. Some of the cells also contain multiple clear vacuoles sometimes accompanied by nuclear scalloping (more sebocyte-like)? The EM micrograph is difficult to interpret because of the prior paraffin processing. Some of the structures may very well be lysosomal in nature but many of the spaces are largely empty or contain finely flocculent material of uncertain nature in my view. At least some of the denser granules might be true melanosomes. Thanks for the case Giovanni.

James Strauchen - ? Balloon cell nevus

Bruce Wenig - Agree with compound melanocytic nevus and my initial thought was the other cells were of histiocytic or sebaceous origin. Granular cells not quite as granular as I am used to seeing. I do not recall seeing anything similar previously. Thanks, Falco.

CASE #12 CONTRIBUTED BY: CYRIL FISHER, M.D.

Abbas Agaimy – Nice rare variant of ESS. What about the bland CD10+/ER+ spindle component, do these tumors arise by dedifferentiation from conventional low-grade ESS? Thank you Cyril for sharing this rare case.

Phil Allen - Endometrial stromal sarcoma with *YWHAE-FAM22A/B* (*NUTM2A/Bn* rearrangement). This is the first case I have been shown and I have certainly never recognized one before.

Carlos Bacchi - Thank you Cyril for updating me about these genetic alterations in cases of endometrial stromal sarcoma.

David Ben-Dor - Did the component described as bland CD-10 positive spindle cell component show the typical genetic changes associated with traditional endometrial stromal sarcoma, or did it also show the translocation described in aggressive tumors?

Michele Bisceglia - Biphasic low grade and high grade endometrial stromal sarcoma with *YWHAE-FAM22A/B* (*NUTM2A/B*) rearrangement. What can I say? Thank you, Cyril, for this educational session.

Alberto Cavazza - Thanks, this is the first example of this entity I have ever seen. Very nice case and discussion.

Thomas Colby - Agree with diagnosis. Very nice discussion. In addition to the high-grade endometrial stromal sarcoma there is also a somewhat more epithelioid proliferation and I had wondered about co-existing leiomyosarcoma but I think it is all consistent with stromal-type differentiation.

Kum Cooper - Thank you Cyril. Now I have a glass slide of this Y-FAM tumor (as Marisa Nucci calls it). Yes the low grade areas are fairly distinctive from the high grade round cell component.

Otto Dietz - H&E is suggestive of high grade stromal sarcoma but I did not know of the more aggressive subtype. Thank you.

Hugo Dominguez Malagon - Nice case of endometrial stromal sarcoma and discussion. I had no idea.

Giovanni Falconieri - Very difficult and challenging for me; the low-grade ESS is nearly obscured by the high-grade component, in fact my first impression was that of a poorly differentiated carcinoma rather than ESS of which I ignored the complex segregation based on molecular profile. Thank you for contributing this instructive case.

Franco Fedeli - Endometrial stromal sarcoma with *YWHAE-FAM22A/B* (*NUTM2A/B*). This case nicely illustrates the impact on tumor morphology and immunophenotype deriving from certain molecular events.

Andrew Folpe - Entirely agree with "high-grade" ESS. Really interesting to have the molecular findings alongside the morphology.

Jeronimo Forteza - This is a case of endometrial stromal tumor with both well differentiated and undifferentiated areas. This is unusual.

Thomas Krausz - Highly educational case. I knew about this aggressive, morphologically and molecularly distinct variant of endometrial stromal sarcoma, but this is the first case I have had the opportunity to analyze microscopically (thanks Cyril for submitting it). I am wondering whether the *YWHAE-FAM22* rearrangement was present in both the small/bland and larger/polygonal cell components.

Janez Lamovec - I didn't know of this variant of endometrial stromal sarcoma before. Thank you

Thomas Mentzel - A difficult case given the tumour areas are composed of enlarged polygonal cells.

Markku Miettinen - Agree on variant of stromal sarcoma, this is easily confused with some type of undifferentiated or neuroendocrine carcinoma.

Fredrik Petersson – Educational. I was not aware of this. Thank you for enlightenment.

Maria Pia Foschini - I am happy with the diagnosis of endometrial stromal sarcoma. Thank you for providing the molecular pathology.

Juan Rosai - Another good demonstration of the marriage of morphology and molecular genetics that is taking place at the very moment we are typing these notes. We pathologists are in the lucky position of playing an essential role in this matter, but we should seize the opportunity (and is not going to be easy)

Brian Rubin - Awesome case. I've never seen one of these. The histology is too high-grade for typical low-grade ESS.

Dominic Spagnolo - Nice example of a YWHAЕ/ FAM22A/B high grade undifferentiated endometrial stromal sarcoma. My GYN path colleague Dr. Colin Stewart has shown me several of these cases, and he recently published a population-based review of monomorphic endometrial stromal tumors, 5 of which were monomorphic undifferentiated stromal sarcomas similar to this one (Histopathology 2014 early online April 17). I have since had a case sent to me which I suspect may be primary in the retroperitoneum. Thanks for the great example Cyril.

James Strauchen - Stromal sarcoma. Thank you for the molecular discussion!

Saul Suster - Very educational! Thanks for the contribution!

Bruce Wenig - I have nothing to add but yet another learning case especially relative to the associated rearrangement. Thank you, Cyril.

CASE #13 CONTRIBUTED BY: CHRISTOPHER FLETCHER, M.D.

Abbas Agaimy – Very interesting case. Recent papers (i think one by Fredrik & Michal´group) showed absence of clonality of the smooth muscle component. At least focally I feel there some similarity to MEST with hobnail nuclei in cysts. It might be of interest to stain for ER/PR and WT1 to test for any similarity to "Müllerian-like" smooth muscle cells seen in MEST. The clear cell RCC component was very scarce in my slide which could happen on core needle biopsy resulting in confusion with a smooth muscle lesion. Thank you for contributing this very nice slide.

Phil Allen - Renal cell carcinoma, clear cell type with very prominent smooth muscle proliferation. There is a single glomerulus as well as a few renal tubules and plenty of smooth muscle in my slide but the clear cell renal carcinoma seems to have cut out. Having previously seen hundreds of renal cell carcinomas, the absence of that part of this tumor in the circulated section does not really matter for me. I have never recognized smooth muscle change and renal cell carcinomas before.

Carlos Bacchi - This case of renal cell clear cell carcinoma does show prominence of smooth proliferation. It is nice to be aware of this in order not to miss the diagnosis of carcinoma when the carcinoma component is very scarce like in this case. There is a paper by members of AMR group (Ondra Hes and Michal Michal) favoring the fact that the leiomyomatous stroma in renal cell carcinoma is polyclonal and not part of the neoplastic process (Virchows Arch 2014, May 18).

David Ben-Dor - The slide I received shows a perfectly bland smooth muscle stroma. There are scattered pigment deposits. In my cursory examination I didn't pick up carcinoma- maybe immuno would have been helpful. At the edge of the section there is an epithelial lining which I assume is urothelial. Dr Ondra Hes showed a case of RCC with leiomyomatous stroma recently in Tokyo- the slide I have of that case shows predominantly epithelial tumor with relatively little smooth muscle. So we're getting both ends of the spectrum!

Michele Bisceglia - Renal cell carcinoma, clear cell type, with very prominent smooth muscle cell proliferation. In my slide I could hardly trace and see just one tiny focus of epithelial-looking clear cells consistent with renal cell carcinoma. Additionally in my section one can see also a few peripheral cystic cavities, lined by variously layered epithelium with both bland and (focally) atypical features. Given these cysts and the fact that in the original paper by Khun et al those authors emphasized also a marked angiogenic proliferation which accompanied the smooth muscle

cell proliferation, it might be worth investigating *VHL* gene status to exclude genetic abnormalities involving *VHL* gene (on a mosaic basis).

Alberto Cavazza - Thanks, I have never seen a similar case and I am curious to read the comments of the experts.

Thomas Colby - Cannot really add to the discussion. It took me awhile to convince myself that there are nests of clear cells but I agree that they are present and that there is a component of clear cell carcinoma here. I was impressed by the smooth muscle proliferation. I don't think it is related to AML and chalk it up to one of the many faces of renal cell carcinoma.

Kum Cooper - Thank you Chris. Yes there is a focus of glands with clear cells, along with the smooth muscle. However, the larger epithelial structures resemble MEST (multilocular cystic nephroma). What did the ER and PR show in the stroma? Ondra showed a low grade clear cell carcinoma with smooth muscle in Japan. I am curious to read his comments on your case.

Otto Dietz - I have never seen something similar.

Hugo Dominguez Malagon - RCC with prominent smooth muscle proliferation, at least in my slide there are also adipose tissue and thick walled vessels, HMB45 is mandatory to rule out angiomyolipoma.

Giovanni Falconieri - What a case, Chris! This looks deceitfully bland suggesting a benign stromal tumor. I shall look forward to the kidney experts' opinion as well to learn more on this

Franco Fedeli - Renal cell carcinoma, clear cell type, with very prominent smooth muscle cell proliferation. Never seen a similar case. Indeed the leiomyomatous bulk of the tumor is overwhelming, and the embedded minute groups of tumor cells can easily escape routine examination.

Cyril Fisher - What a difficult case. I would need immunohistochemistry for the epithelial component.

Andrew Folpe - I'm not sure if my section still has clear cell carcinoma on it.

Jeronimo Forteza - I have never seen before this muscular proliferation associated with renal cell carcinoma.

Ondrej Hes - This is very interesting case, unfortunately, in my slide I have just minute and very few foci (up to 10 cells) with clear cell morphology. There are cysts lined by hobnail cells. The rare existence of renal cell carcinomas with a prominent smooth muscle rich stroma was first described by Canzonieri et al. in 1993 and then Kuhn in 2006 and subsequently by other authors. These tumors have been descriptively referred to as "renal cell carcinoma with smooth muscle stroma", "mixed renal tumor with carcinomatous and fibroleiomyomatous components", "renal cell carcinoma associated with prominent angioleiomyoma-like proliferation" or "clear cell renal cell carcinoma with smooth muscle stroma". Possible relationship of this type of tumor and clear cell papillary RCC/renal angiomyomatous tumor (RAT) has been discussed recently. I personally believe there are "conventional" clear cell RCCs with prominent stroma (we have demonstrated its reactive nature recently: *Virchows Arch* 2014) and something else © (without *VHL* gene abnormalities). My opinion, there is no relation between this type of tumor and clear cell papillary RCC/renal angiomyomatous tumor (RAT).

Thomas Krausz - Focally there is mingling of the smooth muscle with the adipose tissue, so I would explore immunohistochemically an angiomyolipomatous component (despite the rather differentiated appearance of the smooth muscle) adjacent to the renal cell carcinoma.

Janez Lamovec - In my slides, there is very little of the clear cell carcinoma left, a vast majority of the lesion is represented by smooth muscle proliferation; such lesions may presumably be misdiagnosed in a needle biopsy.

Thomas Mentzel - What a case! I was thinking of a benign smooth muscle lesion of the kidney, and only tiny areas of atypical epithelial elements are present that represent well-differentiated clear cell renal cell carcinoma.

Markku Miettinen - Agree on renal clear cell carcinoma with a prominent smooth muscle component. In my slide epithelial elements were scant so that you can imagine this diagnosis could be missed in needle biopsy. Would suspect that smooth muscle is of vascular origin here.

Fredrik Petersson –Very few cells with clear cell/vacuolated features on my slide. Would have had to do IHC to confirm the epithelial nature. Regarding the nature of the leiomyomatous stroma, we (me, Michal and Ondrej Hes) have established the polyclonal/reactive nature of it by HUMARA in a series that has been accepted in Virchows Archiv.

Maria Pia Foschini - Very strange case. Never seen before. Pathologically this case can be equated to the metaplastic carcinoma that show, adjacent to malignant epithelioid cells, monstrous cartilage.

Juan Rosai - Great example of the lesion that Kuhn and I reported several years ago (Kuhn E, De Anda J, Manoni S, et al. Renal cell carcinoma associated with prominent angioleiomyoma-like proliferation. Report of 5 cases and review of the literature. *Am J Surg Pathol.* 2006,30:1372-81). We interpret it as a renal cell carcinoma with a secondary smooth muscle proliferation, much of it vessel-related. The epithelial component, however, does not look like a conventional renal cell carcinoma. It looks rather like the one present in tumors associated with the Lindau-von Hippel syndrome, i.e.it is composed of medium-sized clear cells with very little atypia. It has been suggested that this is yet another distinct type of epithelial renal tumor, and one not necessarily malignant. (USCAP Meeting of 2012 or 2013, Abstract in Lab Invest and Mod Pathol)

Brian Rubin - Very weird case. I see the nests of RCC but I'm not sure I would have recognized it. I guess they are EMA and Cam5.2 positive.

Dominic Spagnolo - There is a solitary focus of clear cell carcinoma in this sea of smooth muscle. I have not seen this to this extent before. Thanks for the case.

James Strauchen - Remarkable degree of smooth muscle proliferation!

Saul Suster – Thank you for this great and exotic case, Chris. Ondra Hes and Michal Michal are probably the ones who've seen the largest number of rare renal tumors in the planet and they have published previously on RCC with smooth muscle components. I'm sorry and feel a sense of loss that this is the last case you will be contributing to the Club given that you've chosen to step down and let one of your colleagues take your place. We will miss you, your cases, your comments and experience!

Bruce Wenig - Lesional clear cell identifiable in my slide but I have never seen an associated exuberant smooth muscle component. I too will be interested in the comments from the GU experts. Thanks, Chris.

Ady Yosepovich - Oh - I would have probably missed the tumor cells, thank you, I was not acquainted with this RCC variant.

CASE #14 CONTRIBUTED BY: ANDREW FOLPE, M.D.

Abbas Agaimy – Very interesting pitfall case, I learned from your previous works on CK in RMS while writing on frequent expression of Islet-1 and neuroendocrine markers in RMS. The likelihood of confusion is rather greater in such a case of very old age and unusual location that is rather typical of Merkel cell carcinoma. Thank you Dr. Folpe

Phil Allen - Merkel cell carcinoma with heterologous rhabdomyoblastic differentiation, left upper eyelid. Thanks for the discussion, Andrew. It has prompted me to request Merkel cell polyoma virus large T antigen for our lab.

Carlos Bacchi - In the slide that I received, there are areas showing Homer-Wright rosettes. I think this may be a good clue, in morphological grounds, that this neoplasm is more likely to be a neuroendocrine carcinoma rather than rhabdomyosarcoma.

David Ben-Dor - It seems odd that the pathologist of record for the biopsy went straight to a very unusual diagnosis (cutaneous rhabdomyosarcoma) overlooking an entity that would be suggested by the histology and more probable given the age group (Merkel cell tumor) which could be easily proven or at least suggested with a simple keratin stain, even given the proviso of keratin positive rhabdomyosarcomas. Did he not try to do it?

Michele Bisceglia - Merkel cell carcinoma showing heterologous rhabdomyoblastic differentiation. Nice case. We also observed a few years ago a case of MCC showing rhabdomyoblastic differentiation with positivity for several skeletal muscle markers (this case was not circulated in the club, but was shared with Dominic Spagnolo and Allen Gown, who concurred with the diagnosis). In our case the rhabdomyoblastic differentiation was documented at immunohistochemical level only and was prompted just by chance. This tumor arose from the gluteal skin in a 45 year old woman. The case was presented in form of an abstract at the national Italian congress of anatomic pathologists in 2008, and is still waiting to see the light of a full publication somewhere in a journal. Furthermore, I would like to say that in the AMR club another case of metastatic MCC with rhabdomyoblastic differentiation was contributed by JK Chan in Seminar # 53 (metastasis occurred in the parotid region). Additionally, one more case of sarcomatous MCC, metastatic in an inguinal lymph node, was contributed by TV Colby in seminar #44: this latter sarcomatous MCC exhibited "sarcomatous" differentiation, NOS, as per definition of the contributor. Thomas did not tell us which kind of sarcomatous differentiation was implicated in his case (which parenthetically also showed glandular differentiation). The sarcomatous differentiation in Colby's case was probably of smooth muscle type, since at that time, in his list of references, he quoted also the case of MCC with leiomyosarcomatous differentiation reported by Cooper L et al (Histopathology 2000;36:540-43).

Alberto Cavazza - Very intriguing case. I have seen a few Merkel cell carcinomas combined with squamous cell carcinoma, but never with other histotypes. In routine, I would probably call this Merkel cell carcinoma without performing desmin and myogenin. Are there data on the frequency of rhabdomyoblastic differentiation detected by these antibodies in Merkel cell carcinomas without a rhabdomyoblastic component evident in Hematoxylin-Eosin?

Thomas Colby - Small blue cell tumor and I had been thinking lymphoreticular and Merkel cell. I would not have thought about rhabdo (but I suspect I should have) but the workup of this case again impresses me with the many faces of Merkel cell carcinoma.

Kum Cooper - What an instructive case Andrew. My differential included carcinoma, sarcoma and lymphoma; but Merkel? No sir! Your Mod Pathol paper of AR showing epithelial and neuroendocrine IHC is very instructive.

Otto Dietz - My diagnosis would have been Merkel cell carcinoma; I don't believe that I had found the heterologous differentiation. Thank you for this educational contribution.

Hugo Dominguez Malagon - Merkel cell carcinoma, aberrant expression can be expected, rhabdomyoblastic must be a rare phenomenon.

Giovanni Falconieri - Never seen before as well, yet I am now tempted to retrieve Merkel carcinoma I have on file and have them stained for an extended IHC panel. I think that this might be more frequent than we actually believe. Thank you for this excellent contribution and discussion.

Franco Fedeli - Merkel cell carcinoma showing heterologous rhabdomyoblastic differentiation and MCPV expression. Indeed, MCC is a small cell tumor which is capable of various types of morphologic and immunohistochemical polymorphism, due to different events, such as: collision phenomenon with squamous cell carcinoma and melanoma; bi- or tri-ectodermal partition phenomenon, such as eccrine differentiation and/or squamous differentiation and/or melanocytic differentiation; and heterologous differentiation, such as rhabdomyoblastic differentiation (as the magnificent case herein illustrated), leiomyosarcomatous differentiation (Cooper L, et al. Histopathology 2000), and fibrosarcomatous differentiation (Tan et al, Pathology, 2008;40:314-6). The case presented herein does well describe the diagnostic pitfall with rhabdomyosarcoma (MCC vs alveolar rhabdomyosarcoma and viceversa). Another pitfall is the one which may occur with blastic hematological malignancies due to the possible expression of PAX5 and TdT markers on the side of MCC (Kolhe R, et al. Immunohistochemical expression of PAX5 and TdT by Merkel cell carcinoma and pulmonary small cell carcinoma: a potential diagnostic pitfall but useful discriminatory marker. Int J Clin Exp Pathol. 2013;6(2):142-7).

Cyril Fisher - Merkel cell carcinoma with rhabdomyoblastic differentiation. The morphology is that of Merkel cell. Good discussion.

Jeronimo Forteza - I agree with your diagnosis. Thank you for the case.

Thomas Krausz - I was surprised to read about the desmin and myogenin immunoreactivity, as looking at the slides I thought this was a Merkel cell carcinoma. On H&E I could not identify myogenic cells. I haven't seen

heterologous rhabdomyoblastic differentiation in neuroendocrine carcinomas before, but both the immuno-evidence and literature data are convincing. Intriguing and highly educational case.

Janez Lamovec - . On H&E, this tumor appears to me like Merkel cell carcinoma and I wonder how many of these tumors were tested for specific rhabdomyosarcoma antigens in the past.

Thomas Mentzel - A nice case of a Merkel cell carcinoma. In addition a heterologous rhabdomyoblastic differentiation has been detected by immunohistochemical staining.

Markku Miettinen - Agree that this looks like small cell carcinoma-like variant of Merkel cell carcinoma. Histologically cannot see rhabdomyoblastic differentiation but this must be true by immunostains.

Fredrik Petersson – My initial impression was Merkel cell carcinoma and the CK20 and Merkel cell polyoma virus nails it. I would not have gone for muscle markers, at least not initially. Performing “excessive” IHC is a double edge sword, you may run into difficulties on interpretation, but one may also miss unexpected (and publishable) findings. An example of this is: Thymoma with nuclear expression of thyroid transcription factor-1: a potential diagnostic pitfall on core biopsy. Yan B, Seng SC, Petersson F. *Appl Immunohistochem Mol Morphol*. 2011 Jan;19(1):76-81.

Maria Pia Foschini - This is a beautiful small round blue cell neuroendocrine (Merkel cell) carcinoma with rhabdomyoblastic differentiation. As reported in the handout this is very similar to the case that we have published with Dr. Rosai some years ago. I will try to restore the block for MCPV stain that was done 14 years ago,

Juan Rosai - Nice case, similar to the one we reported in 2000 (Eusebi V, Damiani S, Pasquinelli G, et al. Small cell neuroendocrine carcinoma with skeletal muscle differentiation: report of three cases. *Am J Surg Pathol*. 2000;24:223-30) We interpreted at the time as a Merkel cell carcinoma showing rhabdomyoblastic differentiation, but somebody asked me recently “Why isn’t this a rhabdomyosarcoma with neuroendocrine differentiation?”. I have to admit he had a point.

Brian Rubin - Interesting case. Based on the H&E I would have thought Merkel cell CA. Surprising that it had rhabdomyoblastic differentiation, which is very rare in carcinoma.

Dominic Spagnolo - Thought-provoking differential diagnostic problem – agree with the diagnosis of Merkel cell carcinoma with heterologous rhabdomyoblastic differentiation. Thanks Andrew.

James Strauchen - Merkel cell. Shows that immuno can be misleading.

Saul Suster - This has been quite an education, Andrew! I would have never thought of searching for myogenic differentiation in a case like this and would have stopped at the keratin and chromogranin stage. The sections I got look like typical poorly-differentiated neuroendocrine carcinoma. Wow!

Bruce Wenig - Cool case. By morphology alone and without reading the information I did think this lesion had a more neuroendocrine “look” to me within the broad differential spectrum of small round cell malignant neoplasms although Merkel cell carcinoma did not leap to the forefront. If I knew Merkel cell carcinoma could have heterologous rhabdomyoblastic differentiation then that information completely escaped my ever increasing forgetful mind. Andrew, thank you.

Ady Yosepovich - - Thank you for this very well presented interesting case

CASE #15 CONTRIBUTED BY: ONDRA HES, M.D.

Abbas Agaimy – As per my email, I thought when looking at this peculiar tumor “one more case for Ondra’s series” but found out that it is your own case. This confirmed for me that I can now recognize this entity as well. Very clear and teaching example of an exceptionally rare entity.

Phil Allen - Biphasic alveolo-squamous renal carcinoma, right kidney found incidentally on ultrasonography after a traffic accident and treated by partial nephrectomy. This has got to be a “new” entity. I have never seen one like it before. Thanks very much for the contribution.

Carlos Bacchi - This is just a spectacular case of renal cell carcinoma with incredible morphology! Thank you for this beautiful example of RCC with alveo-squamoid features.

David Ben-Dor - Fascinating case. I agree that in places the morphology brings to mind papillary tumor.

Michele Bisceglia - Biphasec alveolo-squamoid renal carcinoma. A new tumor entity: never seen one. Thank you, Ondra.

Alberto Cavazza - I vaguely remember having seen a similar case in the past, and my interpretation (not very convinced!) was a peculiar variant of papillary carcinoma (I have not been able to find out the case, but I will try again). Thanks for sharing this very peculiar case, I hope the next time I will not miss it!

Thomas Colby - Very nice descriptive diagnosis for this lesion which is new to me but I somehow knew it was one of these new peculiar renal cell carcinomas that I can't quite keep up with.

Kum Cooper - Another fascinoma Ondra! Look forward to the definitive paper. Good to catch up with you in Japan.

Otto Dietz - I have read about this unusual biphasic differentiation in RCC, but have never seen a case before.

Hugo Dominguez Malagon - A unique case, I have never seen anything like this, thank you Ondra.

Giovanni Falconieri - An impossible case, Ondra. Looking at the glass slide without knowing the history my first, incorrect impression was that of a pseudo- or perhaps true papillary carcinoma due to the optical clear spaces and retractions which may be seen all the way thru around the tumor nests. Follow up in this case seems uneventful. If comparable survival is seen in other cases, I wonder whether the appellation of "tumor", rather than carcinoma, might be adopted as to reflect a benign or quasi-benign course. Great case. It was nice to meet you again in Japan.

Franco Fedeli - Biphasec alveolo-squamoid renal carcinoma. Look forward to your new paper.

Cyril Fisher - Rare variant of renal cell carcinoma I have not seen before; many thanks Dr Hes.

Andrew Folpe - Exceedingly strange renal cell carcinoma with squamous differentiation. I'll look forward to your paper, Ondra.

Jeronimo Forteza - Thank you for showing me this entity. I didn't know it.

Thomas Krausz - I haven't seen this type of kidney tumor before. Intriguing morphology, the squamoid groups remind me squamous morules in endometrioid carcinoma. The peripheral smaller cells focally have clear cytoplasm. Just for my interest, do they express hormone receptors ER, PR?

Janez Lamovec - Very strange tumor, indeed. However, in some areas it really has a sort of micropapillary appearance.

Thomas Mentzel - Many thanks for sharing this spectacular case – what an interesting morphology!

Markku Miettinen - Thanks – nice new entity, have not seen it before. Has some remote resemblance to metanephric adenoma.

Fredrik Petersson – See reference 10.

Maria Pia Foschini - Never seen an alveolo-squamoid renal cell carcinoma, Thank you.

Juan Rosai - Still another variant of renal epithelial tumor ? I give up!

Brian Rubin - This is a unique case for me – never seen one before. Thanks.

Dominic Spagnolo - Thank you for this gem Ondra! Had seen your paper on this unique alveolosquamoid renal neoplasm. In the expanded series, have any behaved in a malignant fashion? Looking forward to the publication.

James Strauchen - New one to me! Thank you.

Saul Suster - Thank you, Ondra, for contributing such a nice example of this new entity described by you. At this pace, renal tumor pathology is going to rival lymphoma morphology in variety and complexity!

Bruce Wenig - The best I could do was neoplasm with dual cell population and foci of emperipolesis beyond that I had no clue so thank you for allowing me to be a bit less clueless.

Ady Yosepovich - - Thank you for this unusual case

CASE #16 CONTRIBUTED BY: JANEZ LAMOVEC, M.D.

Abbas Agaimy – Pretty and rare case, Janez, thanks for sharing with us.

Phil Allen - Myxoinflammatory fibroblastic sarcoma with scattered hemosiderin deposits, dorsum of right foot. To my eye, the histological resemblance between both this tumor and the hybrid tumor published in Am J Surg Pathol 2010;34:1723-1727, on the one hand, and a good going hemosiderotic fibrolipomatous tumor is not very convincing. It smacks of surgical pathologists being led by rings of chromosomes through their noses to a conclusion that may not be as simple and straightforward as it seems at first. The current proposal is that myxoinflammatory fibroblastic sarcoma and hemosiderotic fibrolipomatous tumor feature the same or very similar genetic abnormalities so hybrid forms must exist. It's not too dissimilar from the old-fashioned and widely accepted "synovial" sarcoma story that was built on tissue culture work that "established" carcinosarcoma of soft parts as a synovial sarcoma. That belief has been debunked but "synovial" sarcoma still lives on in name form. Such are the dangers of easy credulity.

Carlos Bacchi - Janez, I am convinced of this diagnosis (hybrid hemosiderotic fibrolipomatous tumor/myxoinflammatory fibroblastic sarcoma) but I have no experience with this hybrid type of tumor. This seems to be a very nice example of this unique tumor.

David Ben-Dor - It would be complicated enough to understand each one of these entities on its own but both together!- certainly mind stimulating.

Michele Bisceglia - When I looked blind to this case I missed the correct diagnosis. After reading your description of "hybrid hemosiderotic fibrolipomatous tumor/myxoinflammatory fibroblastic sarcoma", then everything was clear and plausible. Thank you, Janez: instructive case, showing two rare tumors in one.

Alberto Cavazza - I recognized the myxoinflammatory myofibroblastic sarcoma component but I missed the hemosiderotic fibrolipomatous tumor component. Obviously I am happy to buy your interpretation.

Thomas Colby - Agree with diagnosis. This case is more florid than the few of these lesions that I have seen in the past.

Kum Cooper - Amazingly I have an identical case Janez with hybrid HFLT and MIFS. My case too was on the dorsum of the foot and was resected with amputation of the great toe. The diagnosis of MIFS was made on an outside biopsy that was confirmed with Chris Fletcher. But the biopsy did not have the HFLT elements. The latter was only present in the resection specimen.

Otto Dietz - I have seen a few cases of HFLT and MIFS but never a hybrid like this.

Hugo Dominguez Malagon - Nice case of myxoinflammatory fibroblastic tumor combined (as should be expected) with HFLT, thank you Janez.

Giovanni Falconieri - Very difficult for me, Janez. Shall look to learn further from the soft tissue experts. I cannot contribute any idea or opinion, I apologize. It was nice to meet once again at the AMR symposium.

Franco Fedeli - Thank you, Janez. Agree with your diagnosis. Of course, never seen one before.

Cyril Fisher - Hybrid HFL and MIFS, nice case. These and some PHATs have now been shown to have similar genetic changes. Undoubtedly such cases will be increasingly identified.

Andrew Folpe - I still agree that this is what has been called hybrid HFLT/MIFS, but I am uncertain that these lesions are strictly related to conventional MIFS. Will be curious what others think.

Jerónimo Forteza - If the entity is not known it is difficult to identify the malignancy in this lesion.

Thomas Krausz - Agree with diagnosis. The central “fibrolipomatous” component is more cellular/solid and “fat-poor” compared to other examples I have seen before.

Thomas Mentzel - An interesting and difficult case, and I think I would go in the direction of a myxoinflammatory fibroblastic sarcoma.

Michal Michal - It seems to me that the whole lesion is myxoinflammatory myofibroblastic tumor with posttraumatic changes (traumatization of a 3 cm big lump on the dorsum of a foot is to be expected).

Markku Miettinen - Looks also like pleomorphic hyaline angiectatic tumor which also may have the same genetic basis. The slide I reviewed had no lipomatous elements.

Fredrik Petersson – I was wondering what the solid component was doing in this inflammatory myofibroblastic sarcoma... Despite having read about the association between IMFS and hemosiderotic fibrolipomatous tumor. Great case.

Maria Pia Foschini - I have been convinced on the myxoid-inflammatory-fibroblastic sarcoma part.

Juan Rosai - Pretty convincing arguments in favor of these two entities being closely related, if not variations of the same theme.

Brian Rubin - Fantastic case – agree with the diagnosis. I've seen a similar case although I think the hybrid cases are really rare. HHFLT are pretty rare too so I wonder if these cases rapidly evolve to myxoinflammatory fibroblastic sarcoma, which are more common in my experience.

Dominic Spagnolo - This looks like the real deal. Agree with hybrid acral myxoinflammatory fibroblastic sarcoma/hemosiderotic fibrolipomatous tumor. Great case – thank you.

James Strauchen -. Interesting combination!

Saul Suster - Life just keeps getting harder!

Bruce Wenig - I have nothing to add other than I agree with the diagnosis. If it was not for the AMR seminars I would have little opportunity to see such cases. Thank you.

Ady Yosepovich - Very unusual, thank you.

CASE #17 CONTRIBUTED BY: MICHAL MICHAL, M.D.

Abbas Agaimy – Thanks you Michal for this fascinating case, Very interesting to note that histology of this peculiar metastatic neoplasm suggests the site of origin. Yet another argument for the site-specific lines of differentiation in head and neck teratoid malignancies.

Phil Allen - Metastatic teratocarcinoma of the nasal cavity to the subcutis of the right side of the neck. Yet another amazing case. I don't think I would ever have worked it out.

Carlos Bacchi - I thought this case was a metastatic teratoma with areas of transformed carcinoma. However, the age would be a little odd for this diagnosis. Metastatic teratocarcinoma makes much more sense. Thank you for this unique case.

David Ben-Dor - The epithelial component looked rather bland to me but there are more primitive looking elements

Michele Bisceglia - Neck metastasis of teratocarcinoma of the nasal cavity. This tumor seems classically composed of variably benign or malignant epithelial, neuroepithelial, and mesenchymal elements. In my slide, in addition to the malignant glandular component, the benign looking squamous component, and the undifferentiated (probable) neuroendocrine component, one can recognize also a few small scattered foci of glial tissue as well as a tiny focus of spindle cell sarcoma and a small focus of (? olfactory) neuroblastoma-like tissue.

Alberto Cavazza - Thanks for this case, and particularly for the useful practical point you raised.

Thomas Colby - Agree with diagnosis. I had figured that this was teratomatous but was wondering how it got in the neck and I suspect this may represent a replaced lymph node.

Kum Cooper - I have never heard of this entity before Michal. Thank you for the education. My slide does have a focus of glial element.

Otto Dietz - Convincing case! I did not know that the abrupt change of the epithelium points to the diagnosis of an extragonadal germ cell tumor.

Hugo Dominguez Malagon - Beautiful case of teratocarcinoma of nasal cavity, in my slide there is glial component.

Giovanni Falconieri - Unfortunately, can't say much. This looks an outstanding rarity. Thank you Michal for contributing another collectible item.

Franco Fedeli - Teratocarcinoma of the nasal cavity, metastatic to soft tissue of the neck. Very interesting case. Occasionally this polymorphic tumor can lack any mesenchymal component and even some epithelial component, exhibiting only neuroectodermal and oral ectodermal-like differentiation ("mixed olfactory neuroblastoma-craniopharyngioma"). In a case ectopic hormone secretion by tumor was also demonstrated ([Clin Neuropathol.](#) 2000;19:63-9).

Cyril Fisher - Incredible case of metastasizing teratocarcinoma of nasal cavity

Andrew Folpe - I'm not really clear why this isn't an immature teratoma with carcinomatous overgrowth.

Jeronimo Forteza - A surprising case.

Thomas Krausz - Agree with diagnosis. I have seen a couple of examples of teratocarcinoma before.

Thomas Mentzel - Again, a very unusual clinical situation and a very unusual neoplasm, many thanks,

Markku Miettinen - Very strange case, certainly has teratoma-like features. Definitely need clinical correlation for diagnosing as a metastatic nasal tumor.

Fredrik Petersson - Light microscopy is virtually diagnostic ! Typical fetal appearing squamous epithelium. One oral cavity case published. Crazzolaro R, Puelacher W, Ninkovic M, et al. Teratocarcinoma of the oral cavity. *Pediatr Blood Cancer* 2004;43:687-91. In addition, the seminal paper on this entity was actually published in **1983** by Prof. Shanmugaratnam who is still coming to work every day (>90 years old) and sees second opinion cases. (His office is just a few meters from mine. Teratoid carcinosarcoma of the paranasal sinuses. Shanmugaratnam K, Kunaratnam N, Chia KB, Chiang GS, Sinniah R. *Pathology.* 1983 Oct;15(4):413-9.

Maria Pia Foschini - Thank you for showing this rarely seen tumor.

Juan Rosai - Nice example of a somewhat obscure entity.

Brian Rubin - I haven't seen one of these before. Thanks!

Dominic Spagnolo - A spectacular example of teratocarcinoma. Thanks Michal.

James Strauchen - Was not aware of this entity. Thank you for the informative discussion!

Saul Suster - Thank you for the education – was not even aware of the existence of this entity!

Bruce Wenig - The presence of "classic" fetal type or immature squamous epithelium in conjunction with the glandular and immature neuroectodermal cell components (even in the absence of clear cut mesenchymal component) is diagnostic for sinonasal teratocarcinoma (malignant teratoma) although I do not recall seeing a metastatic case to soft tissues of the neck. Great case, Michal.

CASE #18 CONTRIBUTED BY: MARKKU MIETTINEN, M.D.

Abbas Agaimy – Nice case of "epithelioid" pleomorphic rhabdomyosarcoma in the retroperitoneum, never seen a sporadic somatic case but a recent similarly pleomorphic retroperitoneal case as somatic malignancy after testicular germ cell tumor. The DDx is nicely pointed out underscoring the vanishingly rare occurrence of true pure pleomorphic RMS in the retroperitoneum in adults. Thanks Markku.

Phil Allen - Poorly differentiated, desmin, myogenin and MyoD1 positive high-grade sarcoma, retroperitoneum, male aged 56. Thirty years ago, everyone thought that pleomorphic rhabdomyosarcoma had joined synovial sarcoma in the grave, but it was dragged from its tomb by a bunch of immunohistochemical stains. I am pleased to see that Markku is preparing the ground work for a re-internment.

Carlos Bacchi - Hard case to diagnose based on morphology features only.

David Ben-Dor - Once the skeletal muscle differentiation is proven with immuno the diagnosis becomes one of exclusion (i.e. ruling out other possible components)

Michele Bisceglia - Rhabdomyosarcoma (pleomorphic), high-grade. I liked very nice the practical concept of sub classifying adult rhabdomyosarcoma into bona fide RMS and "other tumors" with RMS overgrowth/differentiation.

Alberto Cavazza - Thanks for this case and for the useful comments on pure rhabdomyosarcoma versus rhabdomyosarcoma component in other tumors (to keep in mind also when dealing with small biopsies).

Thomas Colby - Agree with diagnosis.

Kum Cooper - Thank you Markku. Good to catch up with you in Japan.

Otto Dietz - High grade sarcoma, consistent with pleomorphic RMS. To my opinion in H&E morphology not to distinguish from rhabdoid tumor and proximal type ES.

Hugo Dominguez Malagon - RMS epithelioid, monotypic, very good case, I completely agree.

Giovanni Falconieri - Epithelioid malignant tumor arranged in solid sheaths exhibiting remarkable glassy cytoplasm. Excellent case Markku. I would add also to the differential diagnosis epithelioid angiosarcoma (although uncommon in the retroperitoneum) and synovial sarcoma since these tumors may occasionally exhibit glassy stainable cytoplasm and less vacuolization. My pleasure to see you again in Tokyo.

Franco Fedeli - Pleomorphic/epithelioid rhabdomyosarcoma. Helpful discussion

Cyril Fisher - Pleomorphic rhabdomyosarcoma in abdomen, in one of the contexts described by Markku. MDM2 amplification in such cases can be regarded as confirmatory of dedifferentiated liposarcoma with divergent element.

Andrew Folpe - Agree with PRMS.

Jeronimo Forteza - I agree with the diagnosis.

Thomas Krausz - I was also wondering about dedifferentiated liposarcoma with rhabdomyosarcomatous differentiation in this clinicopathologic setting. I assume MDM2 and CDK4 were negative.

Janez Lamovec -. In a few cases of pleomorphic rhabdomyosarcoma we saw here, most were more mixed as this case, with epithelioid, spindle cell and areas of more pleomorphic rhabdoid cells. This one is predominantly epithelioid.

Thomas Mentzel - A wonderful example of pleomorphic epithelioid rhabdomyosarcoma arising in an adult patient. Have you done staining for MDM2 and CDK4?

Fredrik Petersson – I saw cross striations on my sections. However, it has happened to me that I have seen them when they were not there!

Maria Pia Foschini - Pleomorphic rhabdomyosarcoma.

Juan Rosai - So, pleomorphic rhabdomyosarcoma is back! It was a relatively common diagnosis in the 40's and 50es (because of Stout), then it became very unpopular (mainly because of the doubts expressed by Enzinger), and now has been resuscitated by Miettinen and Fletcher. It is good to remember, though, that skeletal muscle differentiation can be seen in a large variety of tumors (Snover DC, Levine GD, Rosai J. Thymic carcinoma. Five distinctive histological variants. *Am J Surg Pathol.* 1982;6:451-70). I once asked Enzinger how many cases of pleomorphic rhabdomyosarcoma he had seen, and he said "One, which was in the mediastinum". I told him: "I bet that was a rhabdomyosarcomatous thymoma".

Brian Rubin - Cool case. I agree with the classification but this pattern of RMS is very unusual. Based on H&E I thought melanoma. I think the discussion is very pertinent here since while it is impossible to prove, I wonder if this is a rhabdomyoblastic component of something else that overgrew the original component and thus, has an unusual morphologic appearance. Obviously this is just conjecture.

Dominic Spagnolo - Epithelioid rhabdomyosarcoma with prominent rhabdoid cytologic features. Very nice example. I have not encountered one of these. Thanks.

James Strauchen -. Pleomorphic rhabdomyosarcoma. Thank you for the discussion.

Bruce Wenig - Undifferentiated epithelioid/pleomorphic malignancy that could be many entities depending on adjunct findings so I am not surprised it is a rhabdomyosarcoma.

CASE #19 CONTRIBUTED BY: KYLE PERRY, M.D.

Abbas Agaimy – Thanks Kyle for sharing this pretty case of Kimura disease.

Phil Allen - Kimura /Kimm's disease, soft tissues and lymph nodes, right side of neck in a Canadian, presumably a Caucasian. A very typical case. I have only ever seen one case in a Caucasian but it is a comparatively common disease in Hong Kong, where it is occasionally diagnosed by fine needle aspiration cytology. The recurrence rate is approximately 25%. According to Ignatius Kung, who now lives in Victoria, Australia, (reference 1 in Kyle's submission), this disease was originally described by HT Kimm and C Szeto in a Chinese Journal in 1937, just before the war. Dr Kim was a surgeon (deceased 1990) who was formerly the director of Tianjin Municipal Hospital in China. Its confusion with angiolymphoid hyperplasia with eosinophilia dates from Wells and Whimster's 1969 paper (*Br J Dermatol* 81:1, 1969). They concluded, apparently without having studied any sections of Kimura's, that it probably represented older lesions of angiolymphoid hyperplasia with eosinophilia. This assertion was supported in several of the earlier editions of Enzinger's textbook although Juan Rosai and associates were convinced, on the basis of one personally studied case supplied to them from Japan, that the two diseases were unrelated (*Hum Pathol* 10:707, 1979). In my experience, Kimura / Kimm's disease shares eosinophils with angiolymphoid hyperplasia but

not much else. It certainly bears no resemblance to epithelioid angiomatous nodule. The Kimura / Kimm saga shows how hard it can be to get rid of previously accepted textbook assertions.

Carlos Bacchi - Very good example of Kimura's disease. The presence of germinal centers show an extensive amount of central apoptosis with associated proteinaceous debris is especially typical in this case.

David Ben-Dor - Very nicely worked up and presented case. I was very impressed by the very vigorous apoptosis seen in some germinal centers; this can be confounded with leukocytoclasia with different implications. I wonder if the morbidity in general of "First Nations" (I presume the Canadian homologue for Native Americans) is that of the general population in North America or more closely resembles people from the Far East (where Kimura disease is more common as stated). I enjoyed meeting you and wish you lots of luck in the club and in your career.

Michele Bisceglia - Kimura disease (in both soft tissue and regional lymph nodes). Nice case. Agree with you completely. Had a personal case of Kimura disease in a 31 year old non-Oriental (Caucasian) male patient, who presented bilateral enlargement of the parotid region (more pronounced on the left side) for 10 years, involving parotid gland, periparotid soft tissue, and periparotid lymph nodes. The patient showed both peripheral blood eosinophilia and hyper-IgE. We published that case here in a national journal, *G Ital Dermatol Venereol* 2002;137 (Suppl. 2 to n.1): 141-144. Furthermore, relatively quite recently an interesting case report was published also in other two Caucasian patients from Australia, one of whom presented in association with IgG4 production (McKelvie PA, Lyons B, Barnett G, Allen PW. Kimura's disease in two Caucasians, one with multiple recurrences associated with prominent IgG4 production. *Pathology*. 2012;44:275-8). Maybe Phil Allen will tell us something about those 2 patients, especially on the one with hyper-IgG4.

Alberto Cavazza - The histology seems classical of Kimura's disease, nevertheless this is one of those entities I have seen mostly in books and very rarely on slides. Thanks! By the way, a quite difficult situation may occasionally occur in temporal artery biopsies, because the so-called juvenile temporal arteritis (the main entity to consider in inflamed temporal arteries in patients under 40 years) can be histologically very similar to Kimura's disease: the distinction is based on the fact that in juvenile temporal arteritis the lesion tends to be restricted to the arterial wall, whereas in Kimura's affecting the temporal artery it involves more extensively the peri-arterial tissues, but the limits can be blurred. To complicate matters, angiolymphoid hyperplasia with eosinophilia/epithelioid hemangioma can rarely involve the temporal artery. All these lesions need to be recognized and separated from classical giant cell arteritis, because excision is generally curative and the patients do not need steroids.

Thomas Colby - Agree with diagnosis. This case is identical to one I submitted for AMR #56 (Case 6). The case that I submitted was grossly even more dramatic than the x-ray shown by Kyle. My case had removal of large amounts of tissue for cosmetic purposes.

Kum Cooper - The eosinophil microabscesses, peripheral eosinophilia and sclerosis are very useful to rule out ALHE (epithelioid hemangioma). In fact I saw a case in Vermont, Caucasian as I recall. Thank you Kyle. Good to meet you in Japan.

Otto Dietz - Very good example of Kimura's disease.

Hugo Dominguez Malagon - Beautiful Kimura disease, in México as the native population is of oriental descent the entity is not so rare.

Giovanni Falconieri - Very difficult case, Kyle. Although I suspected a reactive disorder, Kimura was not on top of the differential since I could not catch the diagnostic clues. Nice to meet you in Japan

Franco Fedeli - Agree. Nice case of Kimura disease. Really impressive are here the follicular hyperplasia and the prominence of germinal centers, which are the two features prompting the early designation by Japanese authors under the term of "eosinophilic lymphfolliculosis" (of the skin) for this disease. All the remainder positive signs of the disease are also visible in this case (marked tissue eosinophilic infiltrations, polykaryocytes of Warthin-Finkeldey type). In the differential diagnosis versus angiolymphoid hyperplasia the absence of endothelial changes (tombstone appearance and vacuolization) are discerning. However I think peripheral blood eosinophilia is the most helpful clinical aid in doubtful cases.

Cyril Fisher - Kimura's disease, very difficult case, many thanks.

Andrew Folpe - Agree with Kimura's disease. Actually I'm kind of stunned that I remembered what that was supposed to look like...

Jeronimo Forteza - Very nice case.

Thomas Krausz - Agree with diagnosis. Nice example.

Janez Lamovec - . A very characteristic example of Kimura disease. The absence of epithelioid vascular structures is quite obvious which shouldn't be the case with angiolymphoid hyperplasia (epithelioid hemangioma).

Thomas Mentzel - A very nice and convincing case!

Markku Miettinen - Agree on Kimura disease, the presence of amorphous debris with apoptotic bodies in germinal centers seems to be a common feature. Dr. Suster, please determine where this belongs.

Fredrik Petersson – Classic case. We see them quite frequently here in Asia. The main issue is to r/o Hodgkin.

Maria Pia Foschini - The only two cases I have seen of Kimura's disease displayed more necrosis. Thank you for showing this case.

Juan Rosai - Good case of Kimura's disease. I am glad to see that our belief that Kimura disease and angiolymphoid hyperplasia with eosinophilia are two different diseases (Rosai J, Gold J, Landy R. The histiocytoid hemangiomas. A unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone, and heart. *Hum Pathol.* 1979,10:707-30) has been substantiated by subsequent studies.

Brian Rubin - Neat case. I've considered Kimura disease in my differential diagnosis many times but I've never seen a case before. At least I have a slide to show my fellow and the residents now.

Saul Suster - Beautiful example of a very rare condition (at least here in America). I have been collecting these cases for years and now have about 5 or 6 cases in Caucasian patients from here in the USA. Welcome to the Club, Kyle!

Dominic Spagnolo - Very good example of Kimura disease – thank you. Phil Allen will remember the authors cited in the 1984 Pathology publication from the Hong Kong University. I remember the senior author Pat Bannatyne (an Aussie), but not the first 2 authors.

James Strauchen - Kimura disease. Very nice example!

Bruce Wenig - My differential included ALHE versus Kimura disease so not surprised with the diagnosis. Nice case. Thank you

CASE #20 CONTRIBUTED BY: FREDRIK PETERSSON, M.D.

Abbas Agaimy – Very rare and unusual neoplasm at this location. Most older cases were classified as Wilms. I have a single case in my files. It seems much more rare than renal synovials. Thanks Fredrik.

Phil Allen - Primary renal Ewing's sarcoma. If this had occurred in bone or soft tissues, I don't think anyone would have considered a Wilms' tumor.

Carlos Bacchi - Agree with the diagnosis

David Ben-Dor - in other words we all need "re-education"!

Michele Bisceglia - Primary renal Ewing sarcoma/PNET. Unusual and interesting case in that location and at that patient's age. Fully studied case. Helpful comments. Thank you, Frederik. In a pediatric patient, renal EWS/PNET may

well enter the differential diagnosis also with DSRCT of the kidney, also taking into account that among the cases of DSRCT of the kidney so far reported (around a dozen of cases), the majority were non-desmoplastic, and therefore even more similar to EWS/PNET.

Alberto Cavazza - Beautiful example. I am certainly not an expert, but to me the diagnosis is convincing.

Thomas Colby - Agree with diagnosis. PNET was my first thought as well and it is nice to see that that panned out.

Kum Cooper - Fred I agree with your diagnosis of Ewing Sarcoma. My differential was synovial sarcoma. Was good to chat with you in Japan.

Otto Dietz - I agree, based on your findings EWS / PNET is the most convincing diagnosis.

Hugo Dominguez Malagon - I also though in EWS/PNET but no geographic necrosis is present in my slide, nice case.

Giovanni Falconieri - Very difficult case, Fredrik. No experience with Wilms whatsoever, yet I totally agree with your last considerations. Great to see you in Japan again.

Franco Fedeli - Primary Ewing sarcoma/PNET of the kidney. Nice case, that I like to intend as a casual and timely (and unconscious) complement to the case of desmoplastic small round cell tumor of the kidney that Michele presented in Tokyo at the 7th Int'l AMR symposium.

Cyril Fisher - Ewing sarcoma of kidney with genetic confirmation, clinically important to distinguish from other similar tumors in this age group that are increasingly recognized in the kidney.

Andrew Folpe - Agree with ES/PNET. Good discussion.

Jeronimo Forteza - In this case the molecular study is very important.

Ondrej Hes - Interesting case. I agree with Fred that at least part of "Wilms tumors" from adult patients diagnosed in the past were not Wilms tumors at all. Even pathologists specialized in pediatric pathology can see up to 5 cases of WT a year (as was estimated in Great Britain), the situation among "general" pathologists and even among "non-pediatric" GU pathologists should be even worse. Therefore, the prognosis of "adult Wilms tumors" could be slightly different than it is generally believed. Also I believe, that all "small blue cell" renal tumors (particularly in adult patients) should be also considered as possible EWS/PNET or synovial sarcoma. From the broader differential diagnosis I would consider "solid" papillary renal cell carcinoma, metanephric adenoma and small cell variant of oncocyoma.

Thomas Krausz - I agree with both the final diagnosis and the preceding differential diagnostic considerations. Yes, molecular ancillary studies are becoming part of routine diagnostic workout

Janez Lamovec - I agree that one should be very much in doubt of the diagnosis of adult purely blastematos variant of nephroblastoma. Good points in the discussion.

Thomas Mentzel - A very nice example of Ewings sarcoma/MPNET arising in the kidney and probably these neoplasms are more common in this location than previously believed.

Markku Miettinen - Agree on Ewing sarcoma involving kidney. My slide had a focus of ballooned cells with organism-like elements, could be well a meaningless artifact or possibly specimen focally infected prior to fixation.

Maria Pia Foschini - I agree with the diagnosis of Ewing sarcoma \ PNET of the kidney. The discussion on the impact of modern techniques in histological diagnoses is interesting.

Juan Rosai - Good case of Ewing sarcoma/PNET of kidney

Brian Rubin - I agree with this diagnosis. I also agree that monophasic blastemal Wilms tumor probably doesn't exist in adults. I had a core needle biopsy of a renal tumor several years ago that had extensive dot-like keratin immunoreactivity that I called neuroendocrine carcinoma only later to realize that it was a renal Ewing sarcoma, confirmed by *EWSR1* FISH.

Dominic Spagnolo - Agree with renal Ewing/PNET – it is a very good example, thank you. And nice discussion of the issue of the disappearing adult blastemal Wilms tumor.

James Strauchen - Renal PNET versus adult Wilms. Thank you for the excellent discussion!

Saul Suster – Beautiful case – agree with the diagnosis and discussion. Welcome to the Club, Fredrik.

Bruce Wenig - Small round cell malignant neoplasm given findings I agree with your diagnosis, Fred. Thanks.

CASE #21 CONTRIBUTED BY: JAMES STRAUCHEN, M.D.

Abbas Agaimy – Indeed, a pretty and quite tricky case, represents a real pitfall. Particularly the CK+ axillary cases when primarily seen by breast pathologists might closely mimic metastatic carcinoma within lymph node sinuses. thanks.

Phil Allen - ALK-1 positive anaplastic large cell lymphoma, right axillary lymph node. No wonder the classification of lymphomas was in an uproar before the advent of immunohistochemistry.

Carlos Bacchi - Nice example of ALCL.

David Ben-Dor - I hope I was able to identify the hallmark cells correctly.

Michele Bisceglia - Anaplastic large cell lymphoma, classical morphology. CD45 negative, CK positive, and ALK positive at immuno. Thank you. Nice case.

Alberto Cavazza - Thanks, particularly for the useful comments highlighting some important pitfalls.

Thomas Colby - Agree with diagnosis. Obviously malignant and the issue is one of IPOX.

Kum Cooper - Differential of melanoma, carcinoma and lymphoma. However, after reading the IHC I went back and found the sinus involvement as was seen in Carlos' case in the last seminar!

Otto Dietz - Like case 7, a very suggestive diagnosis from the H&E aspect .

Hugo Dominguez Malagon - Anaplastic lymphoma, hallmark cells are prominent.

Giovanni Falconieri - Very challenging, “blind” considerations were seminoma within an odd site because of the intimate mix of neoplastic cells with small lymphocytes, and melanoma due to the larger cell size and abundant glassy cytoplasm. I can imagine how an “out of context” keratin-positive stain may divert us from the right diagnostic path.

Franco Fedeli - Anaplastic large cell lymphoma, ALK positive. Morphology as well as your immunos do explain why these tumors were easily misunderstood as anaplastic carcinoma in the past.

Cyril Fisher - ALCL with cytokeratin expression, can be easily misdiagnosed.

Andrew Folpe - ALCL. Thanks for the good case.

Jeronimo Forteza - The differential diagnosis would be metastatic seminoma and melanoma. I agree with the anaplastic large cell lymphoma diagnosis.

Thomas Krausz - Agree with diagnosis, provided INI1 is retained and SALL4 is negative.

Janez Lamovec - . Anaplastic large cell lymphoma; I don't remember seeing one that was keratin positive.

Thomas Mentzel - Many thanks for the nice case and the interesting discussion.

Markku Mietten - Certainly a well-documented anaplastic large cell lymphoma.

Fredrik Petersson – Got that one. How extensive was the expression of cytokeratins ??? In a woman (or in a cervical LN) one has to also consider metastatic breast carcinoma and undifferentiated, "NPC-type", which nowadays may be associated not only with EBV, but also HPV – in oropharyngeal sites ! (Lymphoepithelial-like carcinoma of the oropharynx: a morphologic variant of HPV-related head and neck carcinoma. Singhi AD, Stelow EB, Mills SE, Westra WH. Am J Surg Pathol. 2010 Jun;34(6):800-5).

Maria Pia Foschini - I agree with the diagnosis of anaplastic large cell lymphoma.

Juan Rosai - Good example of anaplastic large cell lymphoma, a good simulator of other lesions, as well shown in the literature, including non-medical publications, such as the venerable New York Times of January 4, 1983, in which an article by June Brody appeared entitled "Strange, cancer-like ailment turns out to be new disease; Minneapolis."

Brian Rubin - Interesting case and discussion. The cytokeratin immunoreactivity might have caused problems in my hands. Luckily the H&E does suggest a hematolymphoid neoplasm so I would have hoped that I would recognize that I at least needed to check for CD30 and other hematolymphoid markers. Thankfully I didn't get an opportunity to screw this one up.

Dominic Spagnolo - Very nice case of ALK+ (var) ALCL and good discussion of some of the pitfalls – thank you. The new kid on the block for therapy is the recently FDA-approved anti-CD30 therapy with Brentuximab vedotin for patients with refractory disease (also being used in Hodgkin lymphoma).

Saul Suster – Great case! A real pitfall if one goes by results of immunohistochemistry alone and doesn't think of the entity!

Bruce Wenig - Has features of an undifferentiated carcinoma and given cytokeratin (and EMA) staining with absence of CD45 I might have gone down the diagnostic tubes on this case. Thanks for reminding me about CK reactivity in ALK+ anaplastic large cell lymphomas.

CASE #22 CONTRIBUTED BY: ADY YOSEPOVICH, M.D.

Abbas Agaimy – Back to the Ira's case, a group of heterogeneous lesions unified by presence of stromal, lipogenic and epithelial elements, the microglandular adenosis is highly tricky on CNB and explains the initial misinterpretation well. Very nice teaching case, thanks Ady.

Phil Allen - Undiagnosed breast lesion resembling microglandular adenosis. I agree that the appearances are not characteristic of an infiltrating ductal carcinoma of the breast. The features might be those of microglandular adenosis but I am unable to make a definite diagnosis. I would be very cautious in this case because microglandular adenosis is sometimes associated with invasive carcinoma.

Carlos Bacchi - I would favor adenosis.

David Ben-Dor - It's so widely infiltrative that unless it would be microglandular adenosis (which it doesn't seem to look like) I can't think of any entity other than invasive carcinoma but I may be betraying my ignorance. Can an adenomyoepithelioma be so haphazardly scattered around?- since I don't see these I wouldn't know. I also from time to time get cases thrown at me brought from the ex- Soviet Union (yes I grew up in the sixties). The material consists of slides made on window pane glass, the blocks are small cubes of a brownish resin, and the information can consist of a few words scribbled in Russian on a piece of scrap paper. Fortunately they're often very straightforward and can make a diagnosis on the H and E (after the blocks are remade and recut). But if it gets too complicated I plead ignorance and tell the patient or contact person to bring it to a large academic hospital (like Tel-Hashomer Hospital in Tel-Aviv) which is one of the prerogatives of working in the "periphery".

Michele Bisceglia - Ady, I do not have a name for this lesion. Indeed your case seems to overlap a few entities that you cited. However, based on HE slide only, I think this is a benign tumor-like breast lesion, with adenosis-like features.

Alberto Cavazza - The lesion looks benign also to me. I favour a sort of adenosis, or alternatively an adenosis arising in hamartoma.

Thomas Colby - I would favor microglandular adenosis or perhaps adenosis tumor.

Kum Cooper - I agree with you Ady that this is benign. I would have signed it out as "sclerosing adenosis tumor".

Otto Dietz - A diffuse pattern of partially sclerosing adenosis, in every case a benign lesion.

Hugo Dominguez Malagon - Sclerosing or tubular adenosis.

Giovanni Falconieri - Scary case! I agree that this is a complex breast proliferation. I also share your thought that it is benign, yet further classification may be somewhat arbitrary and above all impractical once malignancy is reasonably excluded. For the purpose of the lesion's designation, I would merely go with "tumor forming adenosis". I do not feel at ease with microglandular adenosis, since MGA as far as I may recall features distinct tubules with open lumina containing dense eosinophilic secretion.

Franco Fedeli - Favour a proliferative myoepithelial and epithelial benign breast lesion.

Andrew Folpe - Benign breast lesion, in part MGA.

Jeronimo Forteza - It has been difficult for me to discard malignancy in this lesion.

Ondrej Hes - I am not sure how to call this challenging case. In my opinion this is a benign lesion-adenosis tumor?

Thomas Krausz - I favor sclerosing adenosis.

Janez Lamovec - This appears to me as an unusual variant of sclerosing adenosis with partial apocrine metaplasia of epithelium, and myoid metaplasia. There is an unusual infiltrating pattern seen here (not the nodular configuration of typical sclerosing adenosis) which is more alike to microglandular adenosis but the glands don't have characteristic open lumina, intraluminal secretion, etc. Anyway, the lesion is benign.

Thomas Mentzel - I'm not sure how to exclude well-differentiated tubular carcinoma.

Michal Michal - Microglandular adenosis

Markku Miettinen - Could be combination of microglandular adenosis and myolipoma of breast (benign anyway).

Fredrik Petersson - Agree with benign diagnosis, likely some sort of adenosis.

Maria Pia Foschini - Difficult case. The invasive part of the lesion is formed by small glands that have one single layer of cuboidal cells, with clear cytoplasm showing basal lamina. These features would be in keeping with microglandular adenosis. Nevertheless 5 blocks were taken from this breast. It would be nice to know what was seen in these. In addition smooth muscle actin is mandatory to exclude myoepithelial cells as well as stains for apocrine elements are necessary in case the lesion is the peripheral part of adenomyoepithelioma (so called apocrine adenosis). Furthermore the presence of a thin layer of myoepithelial cells at the periphery of the glands should also suggest the diagnosis of tubular adenosis of the breast (Lee K, Chan JKC, Gwi E. Tubular adenosis of the breast: a distinctive lesion mimicking invasive carcinoma. Am J Surg Pathol 1996;20(1):46-54).

Murray Resnick - Agree that this is benign. Would also favor adenosis.

Juan Rosai - It looks like a benign process to me, with a predominance of foci of microglandular adenosis. Your complaint about having often to work without clinical data, radiologic data, etc. etc., will be echoed by any pathologist who does consultation work. There is no easy answer that would apply to all situations. One needs to exercise good judgment, tending to be very cautious in what to say and what to recommend, especially in terms of therapeutic advice.

Brian Rubin - Agree that it looks benign - seems like what I've seen described as microglandular adenosis. This case does highlight the problem of getting referrals from countries with sub-standard fixation. I'm starting to see

more of this type of material over time and honestly, I think you just have to do the best you can. I can remember Chris Fletcher shouting that the specimen must have been fixed in goat's milk (or worse)!

Dominic Spagnolo - I agree this is a benign lesion. I would consider it in the spectrum of atrophic sclerosing adenosis or tubular adenosis. The presence of myoepithelial cells I guess is inconsistent with microglandular adenosis (and I agree they are there).

James Strauchen – Benign, favor microglandular adenosis.

Bruce Wenig - Understandably, the histologic preparation leaves a lot to be desired. I would favor a diagnosis of microglandular adenosis

QUIZ CASE #1 CONTRIBUTED BY: THOMAS COLBY, M.D.

Abbas Agaimy – Epithelioid angiosarcoma, I think most likely (from irradiated breast?).

Phil Allen - Malignant tumor, ?angiosarcoma, associated with plentiful pigment, presumably iron, subcutis, right buttock. I don't suppose this tumor arose at the site of a previous iron injection. I seem to remember that I had a buttock angiosarcoma post iron injection therapy once before.

David Ben-Dor - Angiosarcoma? Was there a previous injection at the site?

Michele Bisceglia - I think this is a malignant endothelial tumor with epithelioid-like features. Maybe an epithelioid hemangioendothelioma (of the skin) transforming into high grade angiosarcoma.

Alberto Cavazza - I think this is an angiosarcoma with epithelioid/high grade features (and maybe with a lower grade component?). The long history is quite unusual, and probably I am missing something.

Kum Cooper - Malignant epithelioid hemangioendothelioma.

Otto Dietz - Epithelioid hemangioendothelioma.

Hugo Dominguez Malagon -Vascular lesion, epithelioid cells with lumens containing erythrocytes, I first thought of epithelioid hemangioendothelioma, malignant, because of the nuclear enlargement, prominent nucleoli and atypical mitosis. But the evolution is not aggressive, it also has slits and hemosiderin. It could be a kind of reactive hemangioendotheliosis.

Giovanni Falconieri - Recurrent angiosarcoma, perhaps epithelioid, with pseudoglandular pattern. To start, must rule out other neoplasms by means of an extended panel of antibodies.

Franco Fedeli - Favour malignant vascular neoplasm.

Andrew Folpe - R/O angiosarcoma

Jeronimo Forteza - It could be mastocytic cells in the lesion. This is an inflammatory lesion that is difficult to decide how to name. It could be a mastocytic lesion.

Janez Lamovec - Epithelioid angiosarcoma.

Markku Miettinen - Angiosarcoma with epithelioid features.

Fredrik Petersson – Looks like epithelioid angiosarcoma to me.

Murray Resnick - Fascinating case especially given the fact that it has been there for 5 years. Vascular tumor with features of both angiosarcoma and epithelioid hemangioendothelioma. Difficult to call an outright angiosarcoma if

similar features were seen 5 years earlier. Not sure if classifying it as a “malignant epithelioid hemangioendothelioma” makes any difference.

Brian Rubin - I'll go out on a limb and suggest that this is squamous cell carcinoma with a pseudoangiomatous growth pattern. Reminds me of several cases that I've seen over the years that looked more angiosarcomatous than many true angiosarcomas.

Dominic Spagnolo - Epithelioid angiosarcoma. Hard to believe she has gone 5 years with only local slowly growing disease. I interpret all the superficial component to be reactive and related to the previous surgery and suture reaction. I did wonder about atypical/malignant hemangioendothelioma, but I have to regards this as angiosarcoma.

James Strauchen - Epithelioid angiosarcoma.

Bruce Wenig - Looks like an (epithelioid) angiosarcoma pending IHC confirmation (or not).

Ady Yosepovich : Looks like a malignant vascular tumor; DD; epithelioid hamangiendothelioma; epithelioid angiosarcoma

Thomas Colby: We interpreted this as an *epithelioid angiosarcoma*, as did Andrew Folpe. FLI-1 and ERG protein were positive and high molecular weight cytokeratin was negative. INI-1 expression was retained. We thought this sort of natural history for an epithelioid angiosarcoma was very unusual (to say the least). Morphologically and immunohistochemically this case showed typical features of epithelioid angiosarcoma and it was known to have been present at that site for over five years and in retrospect similar cells were seen in one of the two prior biopsy specimens from five years earlier. We have a belief that high-grade angiosarcoma is one of the most malignant tumors that we encounter but there are always exceptions that prove the rule. I wondered if anyone had seen anything similar with epithelioid angiosarcoma.

QUIZ CASE #2 CONTRIBUTED BY: SAUL SUSTER, M.D.

Abbas Agaimy – I think this lesion is very likely metastatic melanoma in the lung. It shows the peculiar adenofibroma-like pattern adopted by several mesenchymal and spindle cell neoplasms affecting the lung including also primary intrapulmonary SFT as you have recently shown in a large series published last year in AJSP. The most important issue is to distinguish them from hamartomatous and benign lesions that they may closely mimic. yrs ago i observed highly sclerosing epithelioid fibrosarcoma metastatic to the lung that was almost indistinguishable from benign adenofibromatous lesions without the clinical history, multiplicity and MUC4 staining.

Your case shows atypical looking melanin-containing cells suggestive of metastatic melanoma with florid entrapment of alveolar spaces. was the tumor cells positive for melanoma markers?

Phil Allen - Metastatic malignant tumor with pigment laden rhabdoid cells, both lungs. I would not consider anything else until I had ruled out melanoma.

David Ben-Dor - LAM? Or is the patient too old?

Michele Bisceglia - The lesion is biphasic, with an entrapped alveolar-epithelial component and a seemingly interalveolar stromal component. I think that a malignant metastatic tumor is in the seemingly stromal component (probably carcinoma with some kind of glassy appearance). Certainly I would look for a primary in the uterine cervix (as well as in other sites), but definitely I look forward to see the correct answer from you.

Alberto Cavazza - There are malignant cells (many are pigmented) growing in the interstitium, with benign entrapped alveoli. I think at a metastatic melanoma.

Thomas Colby - Looks like metastatic melanoma with interstitial growth and secondary metaplastic change in the alveoli.

Kum Cooper - Metastatic melanoma.

Otto Dietz - Sclerosing hemangioma.

Hugo Dominguez Malagon - Fibroleiomyomatous hamartoma.

Giovanni Falconieri - Quite difficult. I would consider a proliferative stromal nodule inducing (reactive?) pseudoadenomatous changes of native bronchioalveolar units. Stretching a little bit attention I could notice some evidence of endothelial differentiation, yet not sure.

Franco Fedeli - Taking into account also the clinical data I would favor the possibility of a malignant metastatic neoplasm (?immuno).

Andrew Folpe - Metastatic epithelioid sarcoma-like hemangioendothelioma?

Jeronimo Forteza - I think this is an lymphangioleiomyomatosis.

Janez Lamovec -?Cryptogenic organizing pneumonia, ?viral

Markku Miettinen - I see melanin-like pigment so that metastatic spindle cell melanoma would be a consideration among others. Metastatic hemangioendothelioma with iron pigment is another consideration. Broad immunopanel would be employed.

Fredrik Petersson – Within the spectrum of epithelioid hemangioendothelioma ???

Murray Resnick - The patient is a bit old but could this be in the spectrum of lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia?

Brian Rubin - Many of the cells contain fine pigment. Assuming it's melanin, I wonder about metastatic melanoma or PEComa. I didn't see a lot of mitotic figures and the tumor cells appear to be lower grade than typical metastatic melanoma so I guess I'd favor metastatic PEComa. Of course if the pigment is hemosiderin or something else then just ignore what I wrote above.

Dominic Spagnolo - Have entertained numerous possibilities but don't have a definite diagnosis. Has a vascular/pseudovascular appearance with bizarre epithelioid cells and spindle cells, with pigment ?melanin or just hemosiderin. ? Could this be multicentric sclerosing pneumocytoma (sclerosing hemangioma) with bizarre atypia. ??malignant epithelioid PEComa. ?? bizarre epithelioid hemangioendothelioma. ??mets from somewhere else (e.g. renal). Have shown it to others – no definite diagnosis forthcoming but same wide range of differentials. Waiting to be put out of my misery.

James Strauchen - Sclerosing hemangioma.

Bruce Wenig - Perhaps a sclerosing hemangioma? histology not textbook and apparent bilaterality/multifocality would be uncommon although not unheard of.

Ady Yosepovich - Difficult to assess without immuno is this a biphasic lesion? glandular elements are present , there are also atypical cells with large cytoplasm and pigment - is this a primary or metastatic lesion? vascular? Melanocytic?

Saul Suster – My case: lung with *crystal-storing histiocytosis*. The lesion is composed of a proliferation of round to oval cells with large nuclei displaying open chromatin pattern and small nucleoli. The cytoplasm of the cells is abundant and has a glassy eosinophilic appearance with a faint fibrillary quality. Some of the cells contain small amounts of phagocytosed hemosiderin pigment. In areas the cells adopt a spindly appearance with a vague fascicular pattern. The cells are seen to be surrounding entrapped benign glandular structures. An extensive panel of immunohistochemical stains was done, including cytokeratin AE1/AE3, desmin, SMA, CD31, CD34, HHV8, S-100, HMB45, melanoma cocktail, TTF1, CD10 and CAM 5.2 cytokeratin. All these stains were negative (repeated in two separate labs). The only 2 stains that were strongly positive were vimentin and CD68. I recommended that the

patient be screened for lymphoproliferative or plasma cell disorder, but have not received any follow-up yet. A nice paper on localized pleuropulmonary crystal-storing histiocytosis was published from Italy by Rossi et al (Am J Surg Pathol 37:906-912, 2013) describing 5 patients with this rare condition.