

COMMENTS TO AMR SEMINAR #66

CASE NO. 1 – CONTRIBUTED BY PHIL ALLEN

Abbas Agaimy - Very well illustrated and discussed rare lesion with nice gross images. Thanks for teaching us.

Carlos Bacchi - Nice case of massive localized lymphedema associated in morbid obesity. So far, this has been a very rare disease in Brazil.

David Ben-Dor - Phil, I enjoyed very much making your acquaintance at the recent meeting in Tokyo. If the purpose of highlighting these cases is to warn pathologists *not* to overdiagnose lipoblasts and thus liposarcoma, then it failed for me, because I didn't notice any- maybe I didn't look carefully enough. Though there are situations in which it may be better not to look so carefully. To me it looks very much reactive, with abundant collagen and proliferating vessels with inflammation. Some of the interest generated by this entity may be the clinical drama associated with it.

Alberto Cavazza – Nice case, with beautiful illustrations. The vascular proliferation is benign but quite striking, and I enjoyed the comment regarding the reported cases of angiosarcoma arising in this setting (I ignored this possibility).

Thomas Colby - This looks most to me like what one sees with chronic lymphedema but clinically it sounds like it is somewhat more localized.

Kum Cooper - Localized massive lymphedema. Morphology fits with clinical and gross photograph.

Ivan Damjanov – Nice teaching case. I showed it to my dermatopathology colleague and he agreed. I asked him how did he diagnose it and he admitted that it was history and by eliminating other possible diagnoses. It prompted me to look up this subject in Pubmed. I discovered that a verrucous relative of this condition on the genitalia (illustrated with incredibly impressive clinical photos) was published recently by members of the AMR Club (Plaza JA, Requena L, Kazakov DV, Vega E, Kacerovska D, Reyes G, Michal M, Suster S, Sanguenza M. Verrucous localized lymphedema of genital areas: clinicopathologic report of 18 cases of this rare entity. J Am Acad Dermatol. 2014 Aug;71(2):320-6). Furthermore I discovered that the original paper by Farshid and Weiss (1998) was cited 53 times-- that is impressive. As stated by Phil, there is obviously quite a bit of interest in this lesion, with compliments of the most famous Colonel and related business from the food industry.

Hugo Dominguez Malagon - Massive edema associated to morbid obesity. It essentially looks like a reparative process with edema, nice case.

Goran Elmberger – Great case and discussion. Still a rarity in Sweden but I am sure we are getting there soon.

Giovanni Falconieri - Agree with all the considerations. Due to the long history and the absence of clear cut evidence of malignancy I am inclined to consider this as a reactive change related to chronic lymphedema secondary to obesity. The slit-like endothelial proliferation wrapping several vascular and adnexal units in the dermis has definitive Kaposiform qualities yet I would consider this within the end-spectrum of localized lymphedema affecting a morbidly obese individual. An excellent case and discussion, Phil.

Franco Fedeli - Nice example of this rare pseudomalignant condition. In 2000 Wu D. et al reported a series of cases among which the location to the scrotum and inguinal areas were first described (Wu D, Gibbs J, Corral D, Intengan M, Brooks JJ. Massive localized lymphedema: additional locations and association with hypothyroidism. Hum Pathol. 2000;31:1162-8). In the same series these authors also reported the association of this condition with hypothyroidism.

Cyril Fisher - Good example of massive lymphedema. Great gross image! We are indeed likely to see more of these.

Jeronimo Forteza - Interesting case. Indeed, perivascular inflammatory component shows activated macrophages, lymphocytes, fibroblasts and myofibroblasts. They show discreet atypia. It is important to interpret this inflammatory reaction within lymphedema context.

Maria Pia Foschini - Inflammatory changes on a giant keloid.

Masaharu Fukunaga - Thank you very much for the discussion of this type of lesion, massive localized lymph edema in morbid obesity and beautiful macroscopic photos. I think the lesion represents ischemic changes.

Ondrej Hes - We have 3 cases in our registry (consult cases) and cases from AMR ☺. Without anamnesis and gross description I would think first of some low-grade sarcoma.....

Jason Hornick – Nice example of massive localized lymphedema. The capillary vascular proliferations in the dermis and between the lobules of subcutaneous fat are quite prominent.

Thomas Krausz – Agree with diagnosis. The range of reactive alterations of various tissue components, not only adipose tissue but also the lymphatics and blood vessels in this condition, are well documented. In the submitted case also the reactive vascular changes are prominent. The report of five cases of angiosarcoma occurring in such a setting for me, was also surprising.

Janez Lamovec - Reactive angiomatosis with chronic edema and fibrosing panniculitis.

Thomas Mentzel - Many thanks for this example of massive localised lymphedema that is especially clinically and grossly mistaken for a sarcoma.

Markku Miettinen - Agree on reactive changes such as lymphatic dilatation, fibrosclerosis, and reactive vascular proliferation and prominent fibromyxoid septa associated with massive localized lymphedema. In this superficial sampling, fatty component is minor.

Liz Montgomery - Gotta love massive localized lymphedema in the morbidly obese. We see lots of those here in chubby Baltimore! Thanks for a very nice one.

Fredrik Petersson - No diagnosis stated. This looks like “massive localized lymphedema” (in the morbidly obese) to me. Seems to fit the clinical history.

Murray Resnick - I believe that this is a reactive vascular lesion arising in a lymphedematous background (angioendotheliomatosis and myofibroblastic proliferation) resembling in areas Kaposi's. Don't think it's ugly enough for an angiosarcoma (has been described in the context of lymphedematous abdominal pannus) but it would be in the differential.

Brian Rubin - Agree with massive localized lymphedema. This is a nice example. I liked the Kentucky Colonel comment.

Dominic Spagnolo - Phil this is as nice a case of massive localized lymphedema in morbid obesity that I have seen. Thanks for the case.

James Strauchen - Looks vaguely keloidal. The gross photo is particularly striking!

Saul Suster - Nice case! My colleague and director of dermatopathology in our department, Dr. Tony Plaza, in collaboration with Drs. Kazakov (Czech Republic) and Sanguenza (Bolivia), recently published a nice series of these cases localized to the inguinal region and genital organs (J Am Acad Dermatol 71:320-326, 2014). You should check out the images in that paper – they are the most impressive gross photographs I've ever seen of this condition!

Bruce Wenig - I would have been entirely descriptive without being able to give this a specific designation. I will make sure to stay away from the fried chicken lest I fall prey to massive localized edema. Thanks.

CASE NO. 2 – CONTRIBUTED BY VOLKAN ADSAY

Abbas Agaimy - Pretty slide of a rare variant of IPMN. Thanks Volkan.

Phil Allen - Intraductal papillary mucinous neoplasm with extensive high-grade dysplasia, pancreaticobiliary type, and microinvasion not present in the circulated slides. Thanks for the case Volkan. We have not had one of these yet at Flinders Medical Centre but I suppose it will only be a matter of time. To me and, I suppose, to the patient, the main point of interest is whether the microinvasion indicates a poor prognosis. Will it depend on whether the micro-invasion is convincing?

Carlos Bacchi - Thank you Volkan for this nice example of IPMN, pancreatobiliary type. As I learned from you, one should always look for stromal invasion in this type of neoplasm, as it is likely to find it.

David Ben-Dor - Thanks for the opportunity to become acquainted with a rare subtype of a lesion usually seen in larger medical centers with a sufficient volume of pancreatic surgery (not the case with me).

Alberto Cavazza - Clearly I am not an expert, but I knew of this entity just from the books. Thanks for sharing this rarity and for the educational comments.

Thomas Colby - Classifications are getting pretty granular but to my eye this is simply a papillary adenocarcinoma and would probably be called as such in a number of sites. Micropapilla are present and that might be a feature that I would use against calling this CIS. To assume that it is part of the spectrum of intraductal papillary mucinous neoplasia is not unreasonable, although there appears to be a paucity of mucin.

Kum Cooper - IPMN (not intestinal and not gastric). Never seen the pancreatobiliary variant before. Thanks for sharing.

Ivan Damjanov - Agree with both IPMN and high grade dysplasia. Could not find the areas of ITPN. Also could not find any obvious effects of chemotherapy.

Hugo Dominguez Malagon - IPMN with CIS pancreatobiliary type, I agree, nice case.

Goran Elmberger - Thanks for this interesting case. I hardly see any pancreatic tumors here in Örebro. They only operate 15 cases each year. Most cases in Sweden (140/year) are concentrated in one clinic - Huddinge and soon probably they will take care of all Swedish cases. Anyway question from novice: why call it mucinous when it is non-mucinous pancreatic type?? Any evidence in IHC or mucin stains.

Giovanni Falconieri - I have no experience with this kind of tumor so I cannot comment properly. I certainly agree with the proffered diagnosis. Despite the increased cellularity due to branching of papillary units, it looks low-grade, with no significant cell atypia. Quite interesting, though, Volkan. And thank you for circulating this collectible slide.

Franco Fedeli - Intraductal papillary mucinous neoplasm with extensive high-grade dysplasia, pancreatobiliary type. Agree. Very interesting discussion on the different variants of intraductal papillary neoplasms.

Cyril Fisher - Interesting discussion, many thanks.

Jerónimo Forteza - It is important to consider dysplasia in this case with microinvasion in these forms, predominantly cystic and affecting the duct. Thank you for sharing this case.

Maria Pia Foschini - Thank you for showing us this intraductal papillary mucinous neoplasm. Mucin is difficult to find, but at a closer look it is there.

Masaharu Fukunaga - Thank you very much for a case of intraductal papillary mucinous neoplasm with extensive high-grade dysplasia, pancreatobiliary type. I cannot comment on the discussion with Japanese group because I have less experience with this type of tumors.

Jason Hornick - Very interesting case of IPMN of pancreaticobiliary type. I like how in this section the IPMN appears to be floating within a large dilated duct, the lining of which is uninvolved. I recall only one convincing example of pancreaticobiliary-type IPMN from my hospital, which was associated with invasive ductal carcinoma of conventional type. I agree with Volkan that this variant is distinct from gastric-type IPMN (not simply high grade dysplastic gastric-type differentiation); both the cytomorphology and the architecture are different. Gastric-type I(P)MN uncommonly shows complex papillary architecture (they are more often flat or undulating). Thanks for sharing this great example.

Thomas Krausz - Agree with diagnosis, though using the term "mucinous" in such a case which is not mucinous in a conventional sense, a bit foreign to me (of course I understand that it is wise to stick with accepted diagnostic terminology). In contrast to the real mucinous variants, the submitted case shows nuclear grooves (a feature one can observe in papillary carcinomas occurring at other sites, such as thyroid, lung and kidney). My colleague, Dr. T. Antic told me that in her experience, this variant co-express vimentin in contrast to the real mucinous types.

Janez Lamovec - We don't see much of pancreatic pathology in our department, so this is new to me. Instructive case and educative discussion. Thank you, Volkan.

Thomas Mentzel - Great case! What is the definition for microinvasion in these neoplasms?

Markku Miettinen - Agree on intraductal papillary neoplasm (mucinous variant) with dysplasia.

Liz Montgomery - Nice example of HGD in IPMN. Thanks for sharing it.

Frederik Petersson - Non-intestinal type of intraductal papillary neoplasm with varying degrees of dysplasia. On my section the dysplasia is mostly intermediate/moderate to focally high grade. The latter with bridging and multilayered/crowded epithelial tufts where the cells have increased N/C-ratio. As you say, a tubular component is present (with relatively bland nuclei - ?only mild dysplasia). Also present is necrosis which in the WHO book is commented on: "...grossly or histologic evident necrosis....may be found in ITPNs and is not typical of IPMNs...". On my section there are some neoplastic epithelial cells with more abundant eosinophilic, a bit granular - ? oncocytoid cytoplasm. The subtyping of non-intestinal IPMNs and the relation of these to ITPN seems not very clear.

Murray Resnick - Great case. I agree with the diagnosis and your comments regarding the overlapping features with intraductal tubulopapillary neoplasms. I would also grade it as high grade, however, it is interesting that the nuclear features are quite monotonous throughout the tumor.

Brian Rubin - I'm unable to disagree with this diagnosis since I really don't know much about it. I don't see this kind of material any more. I enjoyed the discussion and certainly agree that there is an intraductal carcinoma with high grade dysplasia. The discussion was wonderful and very educational for me.

Dominic Spagnolo - Agree with intraductal papillary mucinous neoplasm of pancreatobiliary type showing high grade dysplasia/CIS. An instructive case - thanks.

James Strauchen - Intraductal papillary mucinous neoplasm. I wouldn't have guessed there were so many types!

Paul Wakely - I don't know if this patient had an EUS-guided FNA beforehand, but I'm almost certain it would have been called adenocarcinoma. We just had a gastric type IPMN with diffuse high-grade dysplasia and no invasive carcinoma that mimicked adenocarcinoma on smears.

Bruce Wenig - I did feel it was an IPMN but it appeared less mucinous and more complex papillary than what I have seen previously. Then I read about the pancreatobiliary-type and it all made sense. Not sure I would have pulled the trigger on high-grade dysplasia at least based on the findings in my slide but then again I may not have a good feel for the dysplastic changes associated with IPMN.

CASE NO. 3 – CONTRIBUTED BY CARLOS BACCHI

Abbas Agaimy - Spectacular case of "dedifferentiated" follicular lymphoma transforming into DLBCL with ALCL-like sinusoidal pattern. Thanks.

Phil Allen - Transformation of follicular lymphoma, grade 2 into CD30 positive large B-cell lymphoma with anaplastic features exclusively involving the subcapsular and medullary sinuses of a left cervical lymph node. The table mentioned in the paperwork did not transmit in the document I received. I wonder if the clinical history supports a transformation over time. Alternatively, did the transformation occur in the early stages of the neoplastic onset?

David Ben-Dor - The intra-sinusoidal anaplastic cells look very distinctive and stand out in the background of the follicular lymphoma. I remember John Chan stating at a lecture he gave in Israel years ago that B cell anaplastic lymphomas don't exist. Is that still the case and is that what disqualifies these cells from being truly anaplastic in the biological sense and not just having "anaplastic features"? I agree that this is a very impressive phenomenon. Unfortunately I couldn't find the related images or tables with immunohistochemistry results.

Alberto Cavazza - I shared this spectacular case with my hematopathologist colleague: we have seen a couple of follicular lymphomas associated with classic Hodgkin's lymphoma, but never this peculiar kind of transformation. I think it is very reasonable that the two components are clonally related: this relationship has been demonstrated (in this case or in the other published cases)?

Thomas Colby - Agree with diagnosis. Very unusual lesion. In a bygone era we might have called this malignant histiocytosis (because of the sinusoidal involvement) arising in/associated with a follicular lymphoma. In the case the atypical large cells appear to be arising within the neoplastic follicles.

Kum Cooper - Follicular lymphoma, grade 2. Sinus involvement with large anaplastic cells. My differential included metastatic melanoma, carcinoma and lymphoma. Clearly your IHC has provided the answer. Thank you Carlos for this interesting HG transformation.

Ivan Damjanov - I see it, and agree , but i have nothing to add meaningfully.

Hugo Dominguez Malagon - Follicular lymphoma transformed. Extraordinary case, thank you.

Goran Elmberger - Interesting and plausible. Today I often see progression HGT Dedifferentiation in many different tumor types. Could be fun LCM dissect out different components and check clonality and other translocations or mutations with our new NGS platform. Study progression on molecular levels.

Giovanni Falconieri - Difficult to me Carlos. Of course, after reading the full story things were clear yet the pattern of sinusoidal infiltration raised several different possibilities including a metastasis from a poorly differentiated tumor (including carcinoma or melanoma).

Franco Fedeli - Transformation of follicular lymphoma, Grade 2 into CD30-positive large B-cell lymphoma with anaplastic features with exclusive involvement of subcapsular and medullary sinuses. Nice case. It must be an innate feature of the anaplastic large cell lymphoma either of primary or secondary type to involve lymphatic sinuses in a carcinomatous like fashion.

Jeronimo Forteza - Follicular lymphoma grade 2 is evident. Especially interesting is the association with anaplastic large B-cell lymphoma CD30 positive. It is typical of these anaplastic lymphomas to show infiltration of the sinuses. Nuclear morphology is also compatible with anaplastic lymphoma. It would be interesting to check molecularly whether it is just one lymphoma transformed or whether there are two lymphomas. A differential diagnosis could be Hodgkin's, but it is reasonable to discard it in this case.

Maria Pia Foschini - Thanks for this not previously seen case of follicular lymphoma with divergent differentiation. Large cells are present within the follicles which makes the occurrence of two different types of neoplasm in the same lymph-node unlikely.

Masaharu Fukunaga - A very interesting and beautiful case of follicular lymphoma, grade 2 transforming into CD30-positive large B-cell lymphoma. Thank you, Carlos.

Jason Hornick - Amazing case! Is this a recognized pattern of transformation of follicular lymphoma? I've only seen typical sheet-like/infiltrative large cell lymphoma ex-follicular lymphoma. The remarkably distinct patterns in this lymph node might raise the possibility of two separate lymphomas...

Thomas Krausz - The confinement of the anaplastic lymphomatous component to the sinuses is puzzling. Yes it makes sense that the follicular lymphoma is transforming to an "anaplastic" one, but because of the sinus-confined infiltrate of the latter, I am wondering about the possibility of an independent neoplastic process.

Janez Lamovec - A very convincing case of two different lymphomas in the same lymph node. I wonder, if there is any relation between the two or do you consider this as some sort of "collision" lymphoma.

Thomas Mentzel - A nice case showing very convincingly the progression to a high-grade anaplastic lymphoma.

Markku Miettinen - Follicular lymphoma with sinusoidal large cell malignancy (lymphoma), agree with you.

Liz Montgomery - Gracious, that extensive intravascular presentation of the high-grade component is fascinating. In this case, it is easy to spot but I imagine that some cases are sneaky..

Fredrik Petersson - Agree. Clearly biphasic appearance with follicular and sinusoidal patterns. I was holding my guard up for the possibility of a carcinoma metastasis to a lymphomatous (follicular) node. (Abbas INI-negative colonic carcinoma looks like high-grade lymphoma). Were the sinusoidal large anaplastic cells also positive for bcl2?

Murray Resnick - Excellent case. Very nice discussion.

Brian Rubin - This is a fantastic case with very convincing morphological transformation. I agree with the diagnosis. Does anyone ever use the term dedifferentiated when referring to lymphomas? I personally hate the term as dedifferentiation is really just high-grade progression or transformation to me.

Dominic Spagnolo - This is so pretty Carlos! Have seen a few of these, some with the ALCL developing down the track and where we could establish clonal identity with the original follicular lymphoma. In occasional cases I have found scattered anaplastic CD30+ cells within the original neoplastic follicles. Thanks for the case.

James Strauchen - Follicular lymphoma/CD30+ anaplastic diffuse large B-cell lymphoma. Very striking case!

Saul Suster – This is a truly spectacular case – have never seen one like it! I think the interpretation of transformation of follicular lymphoma to diffuse sinusoidal (ALCL-like) lymphoma is quite plausible. It would be great if this could be supported with molecular data (now that we have the means for it!). I believe if this can be worked up it would be an eminently reportable case. My only comment would be to skip the "dedifferentiated" terminology. This term has been, unfortunately, widely abused in recent years and applied indiscriminately for a process that actually represents progression of malignancy or rather "progressive loss of differentiation" rather than "dedifferentiation".

Paul Wakely - I was thinking this was going to be a large cell carcinoma metastatic in a sinusoidal pattern to a node in a patient with known follicular lymphoma.

Bruce Wenig - Looked like a follicular lymphoma with high-grade features beyond that I am out of my depth. Thanks, Carlos.

CASE NO. 4 – CONTRIBUTED BY DAVID BEN DOR

Abbas Agaimy - Pretty and difficult case. Having only the circulated slide, one would consider cribriform basal cell adenoma. Thanks for the nice discussion of a complicated topic. A lesson for sampling.

Phil Allen - Basal cell parotid tumor with cribriform foci and invasion of the extra-parotid fat, presumably justifying a title of basal cell adenocarcinoma. I do not like calling tumors malignant unless metastases occur in at least a small percentage of cases. Some at least should also recur locally. On the basis of David's extensive discussion, I would be tempted to call this a basal cell tumor of unknown malignant potential.

Carlos Bacchi - In the slide I received basal cell adenoma would fit well. Nothing to add after your discussion and the comments by Bruce!

Alberto Cavazza - On the slide, I thought the lesion was basal cell adenoma, but your images are convincing and at the end I agree with the diagnosis of low-grade basal cell adenocarcinoma. Very nice discussion on cribriform features in this context. These cases can be a problem particularly on small biopsies (I enjoyed the practical approach recently proposed by Dr. Wenig in *Adv Anat Pathol* 2014;21:1-11).

Thomas Colby - Agree with the diagnosis (based on the discussion and slides not sent for review). I might have overlooked the cribriforming in this case but I must say I don't face this problem very often.

Kum Cooper - On my slide, basal cell adenoma. On photographs basal cell adenocarcinoma. This case also reiterates the importance of circumscription vs breach of capsule/invasion in salivary gland tumors.

Ivan Damjanov - My impression is that this is still a benign tumor, but maybe some other parts make it more worrisome.

Hugo Dominguez Malagon - My opinion is basal cell adenoma. The membranous variety can resemble ACC because shows punched out spaces that contain redundant basal lamina nicely visible by EM, the presence of mucoid material is also immature basal lamina.

Goran Elmberger - . Thanks for bringing up many interesting, difficult and important topics in salivary gland pathology. My first diagnosis on slides the from you was basal cell adenoma but I did note the peculiar cribriform pattern and unusual cytology with angulated peripheral nuclei in cells with clear cytoplasm – a feature of adenoid cystic carcinoma. I have also seen cases of benign tumors with cribriform pattern so to me its occurrence does not equal adenoid cystic carcinoma. In cytology, core biopsies or in fragmented biopsy material from presumed odontogenic cyst one has to be very cautious when dealing with biphasic salivary gland tumors. Invasion is the absolute criterion as you stated. However, having said that, invasion in SGT's with a myoepithelial component is something different than infiltration in thyroid pathology. Many times a pleomorphic adenoma or myoepithelioma can show subtle insinuating infiltration with its stromal and possibly myoepithelial component of surrounding tissues. Also the capsule itself can at times be hard to define and fat tissue can be part of stromal differentiation in some myoepithelial containing tumors i.e.: PA. This makes judgment of infiltration at times very difficult. To be honest I am not sure the pictures you provide are convincing for infiltrative growth in the present tumor. If you could show me destructive blending with benign salivary gland epithelium or a bona fide perineural growth I would be fully convinced but as for now I would probably stick to a benign or at most a guarded diagnosis suspicious for malignancy. I have some desperate tips such as performing IHC for NFP or synaptophysin in order to track intratumoral neuritis as sign of subtle invasion or performing CD34 stain for detecting incorporation of naive stroma in tumor that sometimes can be helpful. Then again detection of translocation marker MYB-NFIB would certainly strengthen the case. Maybe time will tell.

Giovanni Falconieri - Quite a case, David. I must confess that I would also regard this as benign (hence adenoma) exactly for the same reasons that you have outlined in the case history you have provided. In addition, due to overall circumscription of the tumor I am not totally sure that I would sign this out as clear-cut malignant based on a small focus of invasion, especially in the absence of perineurial or intravascular infiltration. I fully agree with you that this

topic necessitates an in-depth reappraisal, and till the I may likely resort to the safer “uncertain malignant potential” label.

Franco Fedeli - Basal cell adenocarcinoma of parotid, possibly developing over time in a pre-existing basal cell adenoma. Agree. A rare case and an exhaustive discussion. Thank you, David.

Cyril Fisher - I would likely have called this basal cell adenoma. Thanks for detailed analysis and images.

Jerónimo Forteza - This is a very interesting case of cribriform pattern. Thank you for sharing this case.

Maria Pia Foschini - Thanks for the detailed hand-out. The tumour is very circumscribed, no necrosis nor atypical mitoses are present, therefore I am quite reluctant to consider it as malignant.

Masaharu Fukunaga - A very difficult case! My first impression was adenomyoepithelioma. Thank you very much for the detailed discussion.

Ondrej Hes - Great case. To be honest, facing such case I would send it to Alena Skalova immediately. I have very limited experience with salivary gland tumors. But if I was forced to make a diagnosis, I would label this case as adenoma (basal cell). But I remember David’s description and photo 1 of invasive focus in another slide.

Jason Hornick - Very pretty case - I would have thought basal cell adenoma (without the invasion!). This case is mildly polymorphous; areas of the tumor look slightly stellate reticulum-like, and the ducts are quite extensive.

Thomas Krausz - This tumor shows gradual (both cytologic and architectural) differentiation throughout the lesion, resulting in an “organoid” pattern. In several cribriform regions the cells are attenuated and streaming with their nuclei arranged along the longitudinal axis in contrast to carcinomas. As the tumor islands outside the capsule in the adjacent adipose tissue look morphologically very similar to the main tumor mass which essentially looks adenomatous (benign), I am wondering whether a carcinoma diagnosis is justified purely on the basis of “invasion”. In a different setting like pleomorphic adenoma, one may see tumor islands outside the capsule but this feature does not indicate to change the diagnosis to carcinoma.

Janez Lamovec - To me this tumor would appear as basal cell adenoma if it were not for invasion documented in the microphotographs. I wouldn’t think of ACC since the cytomorphology in the latter is distinctly different from the one in presented tumor that shows two types of basaloid cells (pale and dark), etc . In spite of the presence of cribriform spaces, the rest of the histologic appearance just doesn’t fit to one in ACC. I am not sure whether the presence of cribriform spaces bears any significance as to biologic behavior.

Thomas Mentzel - Many thanks for this example of a rare neoplasm and the useful comments.

Michal Michal - Trichoepithelioma-type basal cell adenoma. It has even trichogenic type stroma with lipomatous metaplasia. Maybe it might belong, beside spiradenoma and cylindroma, to other cutaneous type salivary gland lesions.

Markku Miettinen - Basal cell adenoma, parotid based on sampling. The slide contains a circumscribed, well-differentiated lesion with no evidence of invasion in the sampling. Certainly other type of morphology elsewhere could modify this classification.

Liz Montgomery - Very interesting. I know nothing about salivary tumors so this looks like an adenoma to me rather than a low-grade carcinoma. I am relieved that the anticipated outcome is favorable in case I have made a bad diagnosis in the past.

Frederik Petersson - Scholarly discussion. Adenoid cystic-carcinoma-like areas may be encountered in many instances – and the cribriform morphology has to be interpreted in the architectural context. As you say, based on the section, nothing but a benign tumor can be diagnosed. However, the case also highlights the importance of complete sampling of salivary gland tumors, although the risk of recurrence likely correlates with extent of invasion

and absence of high-grade (cytological) features, and thus is minimal in this case, if completely excised. To come back to the “adenoid cystic carcinoma-like/cribriform” problem, it is not, in my view, always easy to make the distinction between a frankly invasive basal cell adenocarcinoma with cribriform areas and adenoid cystic carcinoma. In these instances, and as you state, one may get some assistance from Ki-67 IHC. There is a paper from 1997 on a similar topic (adenoid cystic carcinoma vs PLGA) by Alena *Skalova et al. Pathol Res Pract. 1997;193(10):695-703*. Assessment of proliferative activity using the MIB1 antibody help to distinguish polymorphous low grade adenocarcinoma from adenoid cystic carcinoma of salivary glands. Molecular genetics identifying the t(6;9) MYB-NFIB gene fusion applicable. Another interesting possibility is IHC for MYB ? Anybody has any experience ?? On a final note, adenoid cystic carcinoma-like areas in the cutaneous counterpart to basal cell adenoma (spiradenoma and spiradenocylindroma) has been well characterized: Adenoid cystic carcinoma-like pattern in spiradenoma and spiradenocylindroma: a rare feature in sporadic neoplasms and those associated with Brooke-Spiegler syndrome. *Am J Dermatopathol. 2009 Oct;31(7):642-48*.

Brian Rubin - Really great discussion and believable diagnosis. I've seen a few “benign” things over the years that progressed to malignant lesions when they were followed without resection for many years. It's interesting how this happens often in some tumors and rarely in others.

Dominic Spagnolo - I would have called this a basal cell adenoma on the appearances here. Given the capsular invasion, and from your insightful discussion, the issue is whether to still call this basal cell adenoma with limited extracapsular invasion, or basal cell adenocarcinoma but with limited malignant potential. Great case and discussion David.

James Strauchen - Absent invasion I would have considered this basal cell adenoma.

Saul Suster: Very nice example of basal cell adenoma with “membranous” areas (i.e., cribriform architecture) that can resemble adenoid cystic carcinoma. I've seen cases in which the “membranous” areas are rather quite convincing for ACC. In such instances, in the absence of convincing perineurial invasion, I prefer to back off and go with “membranous” basaloid adenoma. In this particular case, I would need to see pretty impressive and convincing invasion before I call it malignant. I'm not sure if what's depicted as a capsule in the illustrations is convincing and does not represent a fibrous septa within the tumor. The fat at the periphery could well be part of the tumor.

Ady Yosepovich: Thank you David for this very unusual and complicated case, a first glance I thought it is benign but your arguments convinced me it's malignant.

Bruce Wenig - I had the opportunity to review the entire case but based on the one slide sent there is no invasion so a diagnosis of basal cell adenoma with cribriform features. The presence of invasion confers a diagnosis of basal cell adenocarcinoma. As David details the overall cytomorphology are not those of an adenoid cystic carcinoma.

CASE NO. 5 – CONTRIBUTED BY GORAN ELMBERGER

Abbas Agaimy - Nice case and one of my major weaknesses. I feel that I understand something about interstitial lung disease only when listening to Tom Colby but soon thereafter when facing a case like this, I give up. Thank you for sharing this impressive case Göran.

Phil Allen - Hard metal/cobalt pneumoconiosis, biopsies from right middle and right lower lung lobes. I have to admit I had forgotten about Tom's case. Thanks for the reminder.

Carlos Bacchi - Thank you for teaching me about this group of disease, which I am totally unfamiliar with.

David Ben-Dor - There seems to be a lot of architectural distortion with fibrosis, hence the designation of this entity as an interstitial pneumonia, though the index histological findings are intra-alveolar, with accumulations of histiocytes and giant cells not seen everywhere. Is it sufficient to make the diagnosis on the basis of the histology along with corroborating clinical history or should one have the proper chemical analyses performed (if available)? Very nice slide and interesting case. Good to have seen you again in Japan along with your most charming consort.

Alberto Cavazza - I agree. There are features of DIP with increased eosinophils, but I think the main feature is a bronchiolocentric inflammatory disease with giant cells, consistent with GIP. Recently I have seen a classic example of GIP in a patient with just a brief exposure to drilling; from this case I learned that hard metal pneumoconiosis is not dose dependent, and in predisposed individuals it may occur even after a brief exposure to hard metals.

Thomas Colby - Agree with diagnosis of cobalt GIP. In addition to multinucleated histiocytes, this case nicely illustrates multinucleated type 2 cells in some regions. Sometimes in cases like this the findings on BAL are sufficient for diagnosis. Fortunately for us, this patient went on to have a surgical lung biopsy.

Kum Cooper - Giant cell interstitial pneumonitis C/W the history of heavy metal exposure. Nice case Goran, thanks for the succinct notes and follow-up.

Ivan Damjanov - Interstitial pneumonia with giant cells, I was thinking that it was hypersensitivity pneumonitis. However you convinced me that it could be due to cobalt.

Giovanni Falconieri - Difficult and excellent teaching case Goran. In 2001 Tom Colby circulated the first (and the last, till now) case of interstitial giant cell pneumonia; that was case # AMR35-15. In your slide the desquamative changes and intraalveolar macrophages are likely more pronounced and "eye catching". By the way, in his case comment sheet Tom said that giant cell pneumonia can be rarely seen in patients with *no* history of hard metal exposure (AJSP 13;581-587, 1987)

Franco Fedeli - Hard metal/Cobalt pneumoconiosis (giant cell interstitial pneumonia; GIP). Beautiful case of hard metal pneumoconiosis. Cobalt is believed to be the injurious agent but tungsten can also be identified by ultrastructural studies.

Jerónimo Forteza - Giant cells histiologic lesion as well as interstitial pneumonia pattern are both evident. It is interesting to highlight that hard metals, especially cobalt, can result in this pathology.

Maria Pia Foschini - Thanks a lot for sharing this case of cobalt pneumoconiosis with us. I have never seen before giant cell emperipolesis of such degree.

Masaharu Fukunaga - Hard metal/Cobalt pneumoconiosis (giant cell interstitial pneumonia). I have never seen such a remarkable case. Thank you for the beautiful case and discussion.

Jason Hornick - Very interesting histiocytic/giant cell reaction, way beyond me! I'm glad some of you can work out these inflammatory lung diseases! Thanks for sharing this case - I like your cannibalism comment.

Thomas Krausz - Highly educational case. When I looked at the slide without the discussion, I felt this predominantly interstitial lung disease was within the morphologic spectrum of hypersensitivity pneumonitis. Thank you very much for the helpful discussion.

Thomas Mentzel - An impressive case with severe histiocytic, tumour-like inflammation of the lung.

Markku Miettinen - Lung, histiocytic reaction, could not connect with cobalt but certainly agree with your assessment.

Liz Montgomery - Cobalt pneumoconiosis looks like a neoplasm at low magnification!!! Plus you see no material in the histiocytes (or I missed it).

Frederik Petersson - Lung with massive macrophage/histiocyte infiltration. Occupational history - bugs ?? Without actual demonstration of the substance; "consistent with.." ? Overlapping morphologies in conditions with different etiologies ??

Murray Resnick - Striking case, great example.

Brian Rubin - Really interesting case. You can see metal particles in the histiocytes just like cases containing metal wear debris adjacent to a decrepit joint prosthesis.

Dominic Spagnolo - Spectacular case of hard metal pneumoconiosis (giant cell interstitial pneumonia). I remember Doug Henderson describing such cases years ago. Thanks for the case.

James Strauchen - Nice giant cells in hard metal pneumoconiosis! Thank you!

Bruce Wenig - Nice case. Unfortunately, I was not in Tokyo for Tom's discussion so thanks Goran.

CASE NO. 6 – CONTRIBUTED BY FRANCO FEDELI

Abbas Agaimy - A very rare and teaching case with nice description. Some are likely mistaken for some types of HCC. Thanks Franco.

Phil Allen - Fetal type hepatoblastoma in a 34-year-old male, left lobe of liver. The late Kamal Ishaak observed on page 159 of his 1999 AFIP liver fascicle: "At the Armed Forces Institute of Pathology, where we have the world's largest experience with liver tumours, we have never seen a case of hepatoblastoma in an adult." It is a pity he did not live to see this case, although I have to admit that the histological criteria listed in the table distinguishing hepatoblastoma from hepatocellular carcinoma do not seem to me to be capable of consistent, interobserver interpretation.

Carlos Bacchi - Nice example of hepatoblastoma.

David Ben-Dor - After learning what the diagnosis was the tumor cells do look like immature liver cells even if architecturally abnormal.

Alberto Cavazza - Beautiful example of an entity so rare, particularly in this age.

Thomas Colby - Agree with diagnosis. One might wonder if the hepatoid neoplasms that arise in the stomach might occasionally mimic a fetal-type hepatoblastoma.

Kum Cooper - Find it difficult to distinguish this hepatoblastoma from HCC. Trabecular pattern present but two population of cells (with the more primitive cells showing rosettes (? canaliculi). Also no mesenchymal components. Thank you Franco.

Ivan Damjanov - I agree with the diagnosis of hepatoblastoma. It must be very rare in adults. Very useful table ,thanks.

Hugo Dominguez Malagon - Agree with the diagnosis of hepatoblastoma, fetal type. Nice example

Goran Elmberger - . Challenging case. Admittedly the size of the hepatocytic cells is smaller than in usual HCC and there seems to be a clear and dark cell pattern and those observations could be in favor of a hepatoblastoma dx. However a dx of hepatoblastoma in this age group is highly unusual and criteria must then be rigid. An alternative dx would be HCC clear cell phenotype. The number of mitotic figures is much higher than expected for an

hepatoblastoma and necrotic areas are commonly seen. Also the dark cell/light cell pattern seems to be a reflexion of the distance from a feeding sinusoid – possibly reflecting hydropic degeneration in oxygen deprived tumor cells. Finally, the absence of extramedullary hematopoiesis and mesenchymally derived tissue is not supporting hepatoblastoma dx. Don't know for sure.

Giovanni Falconieri - I guess that this is the first case of hepatoblastoma circulating in this seminar, for sure the first I have come across. Very difficult to me and educational as well. Thank you Franco for this contribution.

Cyril Fisher - Hepatoblastoma in adult, a very rare and instructive case.

Jeronimo Forteza - Thank you for this case as well as for the interesting table dealing with differential diagnosis between hepatoblastoma and hepatocellular carcinoma.

Maria Pia Foschini - Thanks for your interesting discussion on this rare case. The case was seen in a 34 yr old man. Therefore as a matter of nomenclature, probably, it would be better to call this tumour as fetal hepatoblastoma in an adult.

Masaharu Fukunaga - Thank you for sharing the interesting and rare case of adult type of hepatoblastoma, Franco. The table is very informative.

Ondrej Hes - I haven't seen pediatric or adult hepatoblastoma. Thank you. In our country, all pediatric oncological patients are concentrated just to 2 big centers out of Plzen.

Jason Hornick – Very nice example of hepatoblastoma - I don't think we've had an adult case in my hospital.

Thomas Krausz - Diagnostically difficult case. Before reading the discussion I was considering hepatocellular carcinoma (despite the relatively small nuclei) but my differential also included metastatic adrenocortical carcinoma. It would be interesting to see whether arginase, another hepatocytic marker, is positive in this case. In several areas the plates are composed of many cell layers. I am also wondering whether the serum AFP was very high in this patient (as expected in a hepatoblastoma).

Janez Lamovec - Hepatoblastoma, fetal type, in an adult. Typical and extremely rare case. Thank you.

Thomas Mentzel – I've never seen a case like this, many thanks!

Markku Miettinen - Hepatocellular neoplasm with clear cell features. When this is monotypic, hepatocellular carcinoma becomes an alternative interpretation.

Liz Montgomery - Franco, this is a stunning case. Thanks for sharing it.

Frederik Petersson - Very nice and convincing case. Thank you.

Murray Resnick - Nice case and excellent table comparing HCCs to hepatoblastoma

Brian Rubin - Very interesting and informative discussion. I showed it to one of my neighbors who is a liver maven and she agreed with the diagnosis.

Dominic Spagnolo - I find this one troublesome. It certainly does have the low power appearance of fetal type hepatoblastoma, but there is undue mitotic activity (far in excess of 2/10hpf) including atypical forms, the cells have higher N/C ratios than pure fetal hepatoblastoma and there are solid sheets of cells. At the interface with the areas of coagulative necrosis it shows a focally macrotrabecular pattern in my slide. If it is hepatoblastoma then I would regard it as either the mitotically active "crowded" fetal hepatoblastoma, or a more aggressive unclassified hepatoblastoma. I can't even be sure this isn't a hepatoblastoma-like HCC.

James Strauchen - Hepatoblastoma in an adult!

Bruce Wenig - Rather unusual case for an adult. Excellent discussion. Thank you, Franco.

CASE NO. 7 – CONTRIBUTED BY JERONIMO FORTEZA

Abbas Agaimy - I am not sure if this is the right slide. I couldn't see Ewing-typical areas but rather a lesion with myofibromatosis-like pattern. If yes it looks very atypical Ewing!

Phil Allen - Large (16 cm), possible sclerosing inflammatory myofibroblastic tumour, retroperitoneum, female age is 25. I doubt that this is a Ewing's group sarcoma.

Carlos Bacchi - I wonder if there were other areas in this large tumor more cellular (small blue round cells-type of morphology) in order to think about the diagnosis of PNET/Ewing.

David Ben-Dor - The tumor seemed to be negative for almost all the immunostains attempted, except for CD99 (not included in the list but illustrated in the images). The cells look very non-descript and aren't forming any structures. In my section there are numerous fibrous bundles with tumor cells percolating in between them - is this related to the tumor or is this unrelated retroperitoneal tissue invaded by it?

Alberto Cavazza - On hematoxylin-eosin I considered the possibility of inflammatory myofibroblastic tumor/inflammatory fibrosarcoma, and your immunohistochemical results may be consistent with this hypothesis (probably I would add an ALK staining). To my untrained eyes CD99 is more cytoplasmic than the typical diffuse membranous positivity of Ewing/PNET, but I am waiting for the opinion of the experts.

Thomas Colby - High-grade sarcoma with variegated appearance, including spindled paucicellular fibrotic regions and cellular regions with high mitotic activity. I am not sure I would have thought to look for Ewing-PNET translocations.

Kum Cooper - Sorry my slide does not have tumor. My slide looks like retroperitoneal fibrosis aka IgG4 lymphoplasmacytic sclerosing disease.

Ivan Damjanov - Without FISH, I am not sure I would have made the diagnosis of Ewing/PNET.

Hugo Dominguez Malagon - Sorry I missed that, there is nothing in my slide that made me think about PNET. The cells shown by EM (consistent with PNET) do not look like the ones on HE.

Goran ElMBERGER - Very difficult case. Problem CD99 IHC not very specific, EWSR1 promiscuous marker and desmosomes rather non-specific finding in EM. Morphology gold standard and this case would be very atypical presentation of Ewing/PNET. I am in deep water but fibrosis reminds me a bit of Castleman and also in secondary tumors to this condition such as like reticulum cell sarcomas in which EWSR1 rearrangements have been described. Some help from our soft tissue aficionados?

Giovanni Falconieri - Almost impossible for me, Jeronimo! The heavily collagenized stroma often with sclerotic qualities swayed completely me toward some other exotic options. Thanks for trying to educate me!

Franco Fedeli - EWING-PNET retroperitoneal sarcoma. Although this tumor has the same phenotypic and immunophenotypic characteristics as lesions elsewhere, it is usually considered only after extensively labeling for other malignancies such as lymphomas and small cell carcinomas.

Maria Pia Foschini - I find the present case quite difficult.

Masaharu Fukunaga – My impression of this case was follicular dendritic cell tumor or IgG4 related diseases. Very interesting and difficult case. I have never seen this type of Ewing sarcoma or PNET.

Jason Hornick - Unusual histology with extensive stromal reaction - I would have considered desmoplastic small round cell tumor. The cells have quite a bit of eosinophilic cytoplasm with a syncytial appearance. Very challenging based on morphology.

Thomas Krausz - Before reading the discussion, I was considering a peculiar variant of solitary fibrous tumor. I was not familiar with this type of Ewing/PNET sarcoma exhibiting extensive, focally "storiform/whorling" sclerosis.

Janez Lamovec - On morphologic ground, I would never suspect that this tumor could be one of the Ewing/PNET group of tumors. It is very unusual but I would rather think of it as belonging to some kind of fibroblastic or myofibroblastic family of tumors (?unusual type of sclerosing epithelioid fibrosarcoma, ?low grade fibromyxoid sarcoma) that may also show EWSR1 translocation. I wonder what will be the opinion of other members of the club.

Thomas Mentzel - Given the stromal fibrosis and desmoplasia I was not even thinking on a neoplasm of the Ewing's sarcoma/MPNET spectrum. Has it been reported as a stromal-rich variant?

Markku Miettinen - Very difficult case, unclassified sarcoma with EWSR1 gene rearrangement. Cannot definitely connect with Ewing family tumors (except in a broad sense, tumors containing EWSR1 gene rearrangements). Wondering if this is post-chemotherapy specimen given the prominent fibrosclerosis. Potential entities with EWSR1-rearrangement such as angiomatoid FH and myoepithelioma might warrant consideration for further studies although morphology does not seem typical of either. Determining the partner for the EWSR1 fusion could also be useful.

Liz Montgomery - Hmmm. I am confused. My slide looks strange for Ewing sarcoma and I was thinking of a sclerotic inflammatory myofibroblastic tumor. Maybe I missed a key area.

Frederik Petersson - Unusual histological pattern. Relatively large lesional cells with prominent nucleoli intermingled with lymphoplasmacytic cells. Extensive fibrosis. EWSR1 rearrangement identified. Could this be an unusual (site and morphology) variant of angiomatoid (M)FH ? Desmin is only positive in approximately 50% of a(M)FH. Actin (both smooth muscle- and muscle specific-) may be positive in up to 15% of cases and the corresponding figure for CD99 is 50% (sic!). There is a good paper by John Chan dealing with unusual patterns in sites (including one retroperitoneal case !) of angiomatoid (M)FH: Angiomatoid fibrous histiocytoma: unusual sites and unusual morphology. Mod Pathol. 2011 Dec;24(12):1560-70. Additional molecular genetics to investigate if the tumor carries a fusion of EWSR-ATF1?

Brian Rubin - I'm wondering if I received the correct slide – doesn't seem to correspond with the description.

Dominic Spagnolo - Interesting case! I think this is a sclerosing angiomatoid fibrous histiocytoma. It is a recognised morphologic "variant" and the site, whilst very unusual, is also now described. There have been several recent papers iterating these unusual features in AFH. The EWSR1 breakapart would go along with AFH. Would be interesting to pursue possible translocation partners if possible. Thanks for the case.

James Strauchen - From the histology I wouldn't have thought of Ewing/PNET!

Saul Suster – I thought I might have received the incorrect slide but I checked with my secretary and this is, indeed, the correct slide! I think Ewing's is certainly an interesting and imaginative interpretation for this tumor, but it doesn't really fit in my mind for that entity. The lesion essentially shows a sclerotic/inflammatory low-grade spindle cell lesion, which is actually quite different from the high-grade small round blue cell tumor construct that Ewing's sarcoma represents. I would have to assume that the diagnosis was based on the results of CD99 positivity and EWSR1 translocation alone. Unfortunately, neither CD99+ nor EWSR1 positivity by FISH are restricted or specific for Ewing's, and in the context of the morphology I would have explored other alternatives. There are a number of spindle cell lesions that can stain with CD99 and show the EWSR1 translocation, including angiomatoid fibrous histiocytoma, lipomatous hemosiderotic tumor and others. In fact, given the good circumscription of the lesion, absence of nuclear pleomorphism, mitotic activity and necrosis, I doubt that this is going to behave as a high-grade malignancy such as Ewing's. I think it would definitely be worth exploring what the fusion partners are for this case

to fine-tune the diagnosis. EWRS1 by FISH is now rapidly becoming the equivalent of vimentin by immunohistochemistry. Caveat emptor!

Bruce Wenig - Not the prototypical Ewing sarcoma. I wonder if this tumor would fit for *CIC-DUX-4* positive Ewing sarcoma like tumor.

Ady Yosepovich - a very peculiar morphology for PNET/Ewing – I guess FISH wins this case.

CASE NO. 8 – CONTRIBUTED BY MASAHARU FUKUNAGA

Abbas Agaimy - Very nice lesion that I have never heard of, thanks Masa.

Phil Allen – Mixed epithelial papillary Mullerian cystadenoma of borderline malignancy with squamous overgrowth, left ovary. I have never seen one of these before. Thanks for the contribution Masa.

Carlos Bacchi - Very unusual case!

David Ben-Dor -Fascinating case- I've never seen squamous epithelium in the context of a borderline tumors. Here everything is squamous with condylomatous features. I didn't see any non-squamous epithelium. The atypia is low grade and could fit for LSIL of the cervix. Origin in an endometriotic lesion makes sense. Thanks for showing it.

Alberto Cavazza - Thanks for this spectacular case. I ignored the possibility of such a degree of squamous overgrowth in this kind of tumor.

Thomas Colby - Remarkable case. I am not sure I have seen anything quite like this.

Kum Cooper - Instinctively metastatic SCC from the cervix. Review shows focal areas of cuboidal/columnar lining cells and even serous lining. Never seen this much squamous overgrowth in an endometriotic cyst nor cystadenoma before. Some parts look borderline sero-mucinous too. I suppose this would fit with the ARID-1 related ovarian tumors (AROT). Thank you Masa.

Ivan Damjanov - Good name and explanation. I assume that patient was cured and there was no recurrence.

Hugo Dominguez Malagon - I agree with the diagnosis of ovarian MEBMM with SO - spectacular case!

Goran Elmberger - Unusual case. I guess I was considering some kind of teratoma with somatic malignancy of Müllerian serous type due to the mixed component of squamous epithelium, ciliated epithelium, smooth muscle and fat in addition to high grade atypical serous looking epithelium covering one cyst wall. Is MEBMM related to present WHO classification or not yet in?

Giovanni Falconieri - Beautifully instructive case, Masara, illustrating how challenging the variegated spectrum of Mullerian tumors can be. I have no experience with this subject, hence I cannot proffer an intellectually decent comment. By the way, thank you once again for the warm hospitality during the last AMR meeting hosted in Tokyo, and the excellent organization thereof. We have come back home with great memories!

Franco Fedeli - Mixed-epithelial papillary cystadenoma of borderline malignancy, Mullerian type MEBMM with squamous overgrowth. Interesting case. Agree on the fact that cases like this may well arise in endometriotic cyst.

Cyril Fisher - Striking squamous component, rarely seen.

Jeronimo Forteza - I had not seen before such a representative case of squamous metaplasia in a borderline cystadenoma. Thank you for sharing such a representative case.

Maria Pia Foschini - Very difficult case. I agree with the proposed diagnosis.

Ondrej Hes - This is great case. It reminds me of a second opinion case I got recently. It was a "kidney" tumor, which I believe is Mullerian carcinosarcoma arising in endometriosis. Its adenomatous component was focally very similar to cystadenomatous component of this case. Has anybody seen "primary" Mullerian carcinosarcoma within kidney?

Jason Hornick – I've never seen such a case (though I don't review gynecologic pathology very often) - the predominantly squamous differentiation is interesting and could be quite confusing in a more limited sample. It seems remarkable that a lesion such as this could progress.

Thomas Krausz - Striking mixed-differentiation. I agree it looks that it is arising in an endometriotic cyst.

Janez Lamovec - The squamous epithelial overgrowth in this tumor is striking, indeed. This may be very tricky lesion easily to be confounded with some others you mentioned in your discussion. Thank you, Masa.

Thomas Mentzel - A nice case of a squamous cell predominant mixed epithelial neoplasm of the ovary.

Michal Michal - Very interesting case. The squamous cell epithelium has koilocytic appearance. Could metastasis of ectocervical carcinoma into the serous borderline tumor excluded?

Markku Miettinen - Tubo-ovarian squamous papillomatosis, agree.

Liz Montgomery - Stunning case with all the squamous overgrowth

Fredrik Petersson - Wow – good case! I was not aware of this entity. In some parts of the cystic component, the epithelium looks a bit like what may be encountered in endometriosis.

Murray Resnick - The predominance of the squamous component is quite striking. Insufficient sampling of such a tumor could lead one down a different path.

Brian Rubin - I'm embarrassed to say that I've never heard of this. I probably would have just called this a teratoma based on the squamous differentiation but there really are two components. Many thanks for educating me.

Dominic Spagnolo - Beautiful example of this uncommon ovarian mixed borderline neoplasm Masa – thanks.

James Strauchen - I was unaware of this entity. Thank you!

Bruce Wenig - While this may be a typical example of MEBMM with SO I never get to see such lesions which is a learning experience for me. Thank you, Masaharu.

Ady Yosepovich - Thank you for this nice and unusual case.

CASE NO. 9 – CONTRIBUTED BY ALLEN GOWN

Abbas Agaimy – Agree, favor endometrioid. Given the very prominent lobular pattern and focal spindle stroma, I suppose the tumor developed in endometrioid adenofibroma-like lesion. Would ignore the immunos in such a case.

Phil Allen - Moderately differentiated adenocarcinoma with neuroendocrine differentiation, probably endometrioid and probably primary in the left ovary with metastases to the right ovary. When immunohistochemistry results and other such newfangled inventions become too contrary to interpret, I usually downplay the new and upregulate the old, a tendency that once led a club member to describe me as a "dinosaur." I naturally appreciated the complement because dinosaurs were very effective animals when they were alive. In this case, the largest tumor mass is in the left parametrium and no other primary is apparent. The most likely primary is the biggest one. I find that this old fashioned approach usually trumps the ambivalent cards played by immunohistochemists in difficult cases.

Carlos Bacchi - It looks endometrioid adenocarcinoma, metastatic? or primary?

David Ben-Dor - As it happens I have on my desk at this very moment a case of adnexal adenocarcinoma presenting a similar problem. Regarding the case under discussion in the seminar, curiously I extracted the slide out of the box and looking at it without reading any of the written materials I thought it looked like breast. An interesting feature is that though the cytologic atypia is high grade the cells all form acini which are neatly clustered; no invasion in sheets or as single cells. I wouldn't expect a metastatic breast tumor to behave like that. According to the algorithms a large mass in one ovary favors a primary tumor over a secondary one. I personally don't see anything in this tumor reminiscent of endometrial differentiation but I won't argue with Prof. Young. How about a new entity not previously described such as a breast-like primary ovarian carcinoma? I assume she was mammographed already. I notice that GATA-3 wasn't performed: is the bloom already off that rose for this marker after Markku Miettinen showed that it can be positive in many sundry tumors?

Alberto Cavazza - I favour an immunohistochemically unusual endometrioid adenocarcinoma of the ovary, particularly if clinically there is nothing elsewhere.

Thomas Colby - Interesting discussion of what appears to be an insoluble problem unless a primary site outside the pelvis could be identified. In the presence of this sort of discordant data, I probably also would have reverted to my H & E gut; i.e. endometrioid adenocarcinoma.

Kum Cooper - Interesting and confusing Allen. What about GATA3 for breast? I prefer metastatic!

Ivan Damjanov - Endometrioid adenocarcinoma, forget about the immunos (I guess by now metastases from some "funny" place was ruled out).

Hugo Dominguez Malagon - I favor metastatic tumor; however the possibility of an endometrioid is strong.

Goran Elmberger - In a case like this we may be better off leaving final decision to clinicians. If histology and IHC phenotype are confusing they have to look out for another primary before accepting the case as of ovarian origin. Probably molecular tissue of origin analyses may be just as confusing but on a higher (?) level.

Giovanni Falconieri - A challenging case, unquestionably. Due to the inconclusive IHC profile my "exit strategy" is to resort to the clinical presentation and, in this particular case, to go along with a primary tumor, unless disproven by other evidences.

Franco Fedeli - Adenocarcinoma, primary or metastatic to ovary. Favour primary (endometrioid) adenocarcinoma. Also of interest is the neuroendocrine differentiation.

Cyril Fisher - The balance of evidence favors adenocarcinoma with endometrioid features, presumably of ovarian origin.

Jeronimo Forteza - If there is not any neoplasm in the gastrointestinal tract nor in breast and there is a morphology for endometrioid adenocarcinoma, I would keep the diagnosis of ovarian endometrioid adenocarcinoma, which is also related to the possibility of estrogen receptors. Other markers are of focal or variable positivity. Thank you for the information, especially for the images and the table.

Maria Pia Foschini - I favor the diagnosis of endometrioid adenocarcinoma, mainly based on H&E features, than on immuno.

Masaharu Fukunaga - A very problematic case. I prefer endometrioid adenocarcinoma or mesonephric adenocarcinoma.

Ondrej Hes - Challenging. I would sign it out as possible primary ovarian adenocarcinoma (despite PAX 8 negativity) and ask for mammographic screening and for considering an examination of GIT (colonoscopy, gastroscopy eventually). I think clinicians should help us in such situation and final diagnosis should be done after clinicopathologic correlation of all findings.

Jason Hornick - Very strange immunophenotype Allen! I don't think this is a GI tumor - the cytoarchitectural features and strong ER argue against that. I agree with the MGH folks that the histology fits better with endometrioid than breast. I think it's endometrioid with a strange immunophenotype. I've seen several prototypical endometrioid adenocarcinomas (of both endometrium and ovary) that were completely negative for PAX8 (though indeed that is uncommon). I would ignore the CDX2 and neuroendocrine markers!

Thomas Krausz - I cannot exclude metastasis either. I would consider pancreas as primary site.

Janez Lamovec - Without reading your text I thought that this could be endometrioid adenocarcinoma. Morphologically, I would have great problem to accommodate this tumor into any type of breast carcinoma, however, G-I tract carcinoma may be more similar to it. Clinical data may be more relevant in this case. What I firmly believe, though, is that none of the immunohistochemical markers is absolute to determine the true nature of an individual tumor.

Thomas Mentzel - The reported immunophenotype with CDX-2 expression is strange indeed, however, if there is no carcinoma of the gastrointestinal tract we have to accept the diagnosis of endometrioid adenocarcinoma.

Markku Miettinen - Ovary, consistent with endometrioid carcinoma. Clinical correlation is needed to prove metastatic origin from somewhere else.

Liz Montgomery - Please ignore the immunolabeling. This looks like a gynecologic lesion.

Fredrik Petersson - I guess the morphological features of this tumor do not really fit for a malignant Sertoli cell tumor or a YST with glandular differentiation. Bilaterality difficult to reconcile with these suggestions. Additional IHC; calretinin, sox4, melan A ???

Murray Resnick - Agree, very confusing IHC. Does not really have any features to suggest a specific GI primary except for some focal dirty necrosis. The CDX2 looks pretty convincing in the pictures albeit it's not strongly diffusely positive which would be more convincing for a GI primary. Cadherin 17 staining as another GI marker might be of interest. Given the young age of the patient, MSI and BRCA testing should also be considered.

Brian Rubin - I always liked this comment from the introduction to the Diagnostic Histopathology of Tumors, Edited by Chris Fletcher "Immunohistochemistry.....must always be interpreted in context. A seemingly aberrant result, especially if this is a negative result, should never be allowed to overrule an obvious morphologic diagnosis". Not that this case has an obvious morphologic diagnosis but I do think the histology looks more endometrioid than colorectal for what it's worth.

Dominic Spagnolo - Everything seems to point to a high grade endometrioid carcinoma with an ambiguous immunophenotype. Very interesting case, thank you.

James Strauchen - Adenocarcinoma, NOS.

Paul Wakely - If the patient has had an extensive imaging work-up, and no other primary disease was found, you are forced to conclude this is primary to the ovary, and ignore the immunoprofile.

Bruce Wenig - Without looking at the immunohistochemical findings, I thought this was an endometrioid adenocarcinoma. Given the confusing IHC results coupled to your review as well as Robin's and Esther's comments, I would fall back on the histology and diagnose it as an endometrioid adenocarcinoma. Unless there is some evidence to support a metastasis I would consider it to be of ovarian origin.

Ady Yosepovich - Unless there is another primary I prefer endometrioid adenocarcinoma.

CASE NO.10 – CONTRIBUTED BY THOMAS KRAUSZ

Abbas Agaimy - Nice example of steroid cell tumor. I recently had 2 pretty identical cases; thanks Thomas for fine discussion on this rare tumor.

Phil Allen - Malignant ovarian steroid cell tumor, not otherwise specified, right ovary. Yet another tumor that I have not seen before. Thanks for the contribution and the excellent discussion.

Carlos Bacchi - Nice case and discussion.

David Ben-Dor - An interesting and unusual case accompanied by an erudite and complete discussion. A good easy to remember take away point is that if the tumor is large enough to almost replace the entire ovary as in this case then it probably isn't a Leydig cell tumor.

Alberto Cavazza - Nice case and discussion

Thomas Colby - Agree with diagnosis

Kum Cooper - Thank you Thomas for this rare case and excellent write-up.

Ivan Damjanov - Ovarian steroid cell tumor, one of the rare examples where I would have stuck out my neck and called it malignant on the basis of histology. We had a huge one in which we favored malignancy, but it recurred only some 7 years after initial surgical removal.

Hugo Dominguez-Malagon - Steroid cell tumor NOS, nice discussion.

Goran Elmberger - Nice case! Agree. Differential diagnosis is adrenal cortical carcinoma originating from hilar rests. Possible to differentiate? Same same?

Giovanni Falconieri - A phenomenal case, Thomas. Never seen it before. Thank you for circulating another collectible item.

Franco Fedeli - Ovarian steroid cell tumor, not otherwise specified (malignant). Nice case and beautiful discussion. Looking at this case "blind", it looks like an oncocytic carcinoma of whatever origin.

Cyril Fisher - Steroid cell tumor of ovary, very useful discussion, thanks Thomas.

Jeronimo Forteza - Interesting case. Mainly approaching the possibility with immunohistochemistry markers in differential diagnosis between steroid cell tumors and sex cord-stromal tumors. Maybe electronic microscopy, reviewing retrospectively casuistic, could also help to differentiate between the two kinds of tumors.

Maria Pia Foschini - Steroid stromal tumor not otherwise specified. Thank you for the lucid and detailed handout.

Masaharu Fukunaga - A very rare and beautiful case. Thank you, Thomas. The discussion is very informative.

Ondrej Hes - I have just a short comment. It is not always easy to find Reinke crystalloids in Leydig cell tumors. They are present in up to 40-50% of the cases and even in typical Leydig cell tumors sometimes it is not easy to interpret small PAS positive things ☺ as real Reinke crystals.

Jason Hornick – Nice case Thomas. Without the clinical information, I would have favored an oncocytic adrenal cortical carcinoma (!); malignant steroid cell tumor NOS sounds appropriate to me!

Janez Lamovec - Steroid cell tumor, NOS. A teaching case.

Thomas Mentzel - Many thanks for the nice discussion

Markku Miettinen - Ovary, steroid cell/Leydig cell tumor

Liz Montgomery - Glorious case.

Frederik Petersson - Nice case. Steroid cell-/Leydig cell tumor. Artificial distinction? Malignant.

Murray Resnick - Excellent example. Never used the SF-1 antibody. Was quite appropriate in this case.

Brian Rubin - Fascinating case and great discussion. I thought I saw Reinke crystalloids which are probably the hyaline globules that were mentioned so I probably would have classified this as a malignant Leydig cell tumor, not knowing any better.

Dominic Spagnolo - Great example of an ovarian malignant steroid cell tumour NOS, and excellent discussion, thank you.

James Strauchen - Steroid cell tumor!

Paul Wakely - This case reminds me of an example we published in an 8-year old child some time ago [Arch Pathol Lab Med 1991; 115:150] whose presentation was progressive virilization with markedly elevated serum testosterone levels. Only a small number of these have arisen in the pediatric population.

Bruce Wenig - Without looking at the history I thought this lesion may be an adrenal cortical carcinoma so not surprised by designation as malignant steroid cell tumor of the ovary (no ovarian parenchyma in my slide). Highly informative discussion; thanks, Thomas.

CASE NO.11 – CONTRIBUTED BY THOMAS MENTZEL

Abbas Agaimy - Thank you for sharing this interesting case of dedifferentiated SFT.

Phil Allen - Dedifferentiated solitary fibrous tumour, right parietal pleura. I have never had any difficulty with the concept of dedifferentiation. One wonders how long the benign component of the solitary fibrous tumour had been present in this patient before it underwent dedifferentiation.

Carlos Bacchi - Very good example of side by side of areas of classic SFT and dedifferentiated features.

David Ben-Dor - I think that the slides I have show both aspects. The dedifferentiated area is composed of poorly differentiated cells but there are a few gaping vessels and some streaming. I hope that with an appropriate imaging history I would at least consider the possibility in the differential diagnosis.

Alberto Cavazza - Unusual case. Malignant solitary fibrous tumor may lose CD34 and occasionally assumes cytokeratins, and this may be a pitfall particularly in small biopsies.

Thomas Colby - Essentially agree with diagnosis. I probably would have simply called this a malignant solitary fibrous tumor with various patterns present. I can understand using the term "dedifferentiated" because of the relatively localized region of high-grade malignancy.

Kum Cooper - Lovely case, Thomas. Question: the expression of STAT6 in the cytologically malignant indicates "differentiation". So would "malignant SFT" be more appropriate than "dedifferentiated" SFT?

Ivan Damjanov - Very convincing. I wonder if we should review our cases of malignant SFT and look for this type of transition.

Hugo Dominguez Malagon - Dedifferentiated SFT is a rare phenomenon, fortunately STAT6 is preserved in the dedifferentiated areas.

Goran Elmberger - Great case. Agree. Always look for the smoking gun (well differentiated component)!

Giovanni Falconieri - Agree with your assessment and conclusion, of course. I have seen this in a few cases much before the introduction of STAT6 and mutational analysis, and in these particular cases the diagnostic assessment was made on genuine morphologic criteria, including abrupt transition from customary SFT to high-grade looking tumor areas.

Franco Fedeli - Dedifferentiated solitary fibrous tumour. Nice case. Maybe the first case of dedifferentiated solitary fibrous tumor is the renal one which was reported by Dr. Magro from Italy a few years ago (Solitary fibrous tumour of the kidney with sarcomatous overgrowth. Case report and review of the literature. [Magro G](#), [Emmanuele C](#), [Lopes M](#), [Vallone G](#), [Greco P](#). *APMIS*. 2008;116:1020-5).

Cyril Fisher - Dedifferentiated solitary fibrous tumor, very nice example. The diagnostic value of STAT6 in CD34 negative areas is demonstrated.

Jerónimo Forteza - This is very interesting case in which dedifferentiation is really evident, although it is unusual in these tumors, especially when there is no chondrosarcoma or liposarcoma or leiomyosarcoma. I am not sure whether MIB 1 could be of some help in these cases.

Maria Pia Foschini - Very nice example of dedifferentiated solitary fibrous tumour.

Masaharu Fukunaga - A very beautiful case of dedifferentiated SFT. It is very similar to my case of malignant SFT of the peritoneum. *Histopathology* 1996; 28: 463- 6.

Jason Hornick – Beautiful example of a rare phenomenon, Thomas. I recently saw a case of dedifferentiated SFT in which the patient experienced 5 local recurrences in the thoracic cavity over 20 years or so before developing a metastasis below the diaphragm. Remarkably most of the abdominal metastasis still resembled conventional SFT, but a few slides transitioned to an undifferentiated round cell appearance. Similar to your case, CD34 was absent in the dedifferentiated component, but there was still strong nuclear STAT6.

Thomas Krausz - Superb example of dedifferentiated SFT.

Janez Lamovec - Dedifferentiated SFT. Fantastic case, I wonder if some gross features suggest dedifferentiated areas which is important to know when sampling the tumor of such size.

Markku Miettinen - Agree on solitary fibrous tumor with malignant transformation (dedifferentiation).

Liz Montgomery - This is a really great slide with both the regular SFT and then the dreadful nasty tumor. Thanks so much for sending it.

Frederik Petersson - Could not agree more. Nice to see our paper in the reference list!

Brian Rubin - Nice case of dedifferentiated SFT – I'm patting myself on the back for finally recognizing something. I think this pattern of tumor progression is one of the more common patterns in dedifferentiated SFT.

Dominic Spagnolo - Very nice example of a dedifferentiated solitary fibrous tumour – thanks.

James Strauchen - Dedifferentiated solitary fibrous tumor. Thank you for this informative case!

Saul Suster – Malignant solitary fibrous tumor with low-grade and high-grade areas. If I understand correctly, the term “de-differentiated” implies that something that had a well-defined line of differentiation has somehow switched into a different form of cell type, such as a fibrosarcoma or rhabdomyosarcoma arising in a “de-differentiated” chondrosarcoma. In this particular example, since the “dedifferentiated” area is also staining for STAT6 (which we all currently agree is a marker for SFT), shouldn't we just regard these areas as a high-grade component of the lesion (i.e., a focus of progression of the disease) rather than a focus of “de-differentiation”? It was part of Dr. Rywlin's legacy that pathologists should be the guardians of sensible and proper terminology (since we were the ones

responsible for inventing, discovering and describing or naming most tumors), and he would insist with his students that we needed to always be vigilant and critical of terminology so that we may be consistent, make sense, and be scientifically accurate. He wrote a pertinent letter on this topic in Hum Pathol (Vol. 13:963-964, 1982). He was also known for making the observation that most pathologists tend to practice "elephantine" pathology, by which he meant that we often show a tendency to uncritically follow the lead of others (like elephants in a line with the trunk attached to the tail of the next elephant), and he would caution that simply because a person of authority comes up with a concept or proposes any given terminology, we don't necessarily have to accept it and should always critically examine everything.

Bruce Wenig - I completely agree with the diagnosis.

Ady Yosepovich - Thank you, a very illustrative case

CASE NO.12 – CONTRIBUTED BY SANTIAGO RAMON Y CAJAL

Abbas Agaimy - Thanks for refreshing my neuropathological memory. Nice case.

Phil Allen - Pleomorphic xanthoastrocytoma, superficial aspect of right frontal lobe. We do not see any childhood neuropathology so I appreciate seeing this case.

Carlos Bacchi - The finding of very low mitotic figures in a pleomorphic type of tumor in the CNS should raise the possibility of pleomorphic xanthoastrocytoma with other features, of course.

David Ben-Dor - I shouldn't be so eager to display my ignorance but in my initial review I thought it was a meningioma as the tumor seemed to have a rather clear cut interface with the cerebral cortical tissue included in the slide. My excuse is that I don't see surgical neuropathological material- I plead for the mercy of the court on this.

Alberto Cavazza - My experience in neuropathology is very limited, and I enjoyed this case and the nice discussion.

Thomas Colby - Agree with diagnosis. Lovely case.

Kum Cooper - Thank you Santiago. Nice example of PXA grade 2.

Ivan Damjanov - PXA. A "local-patriotic note", the first case was recognized in Kansas by the legendary Dr John J.Kepes, who always called it "my baby". Here is a photo of Dr Kepes (1928-2010) from that time.



Hugo Domionquez Malagon - Pleomorphic xanthoastrocytoma. I missed that, I thought of meningioma because of the nuclear pseudoinclusions and the psammoma bodies.

Goran Elmberger - Important mimicker to HG lesions. Thanks for this nice case

Giovanni Falconieri - I have seen this only once, and the clinical setting was comparable (young patient, cystic tumor). A great teaching case, Ramon. Thank you for circulating this.

Franco Fedeli - Pleomorphic xanthoastrocytoma, Grade II, WHO 2011. Beautiful case. A tumor which typically occurs in children and teenagers; however, very rarely it may also be seen in adults.

Cyril Fisher - Pleomorphic xanthoastrocytoma. The importance of the mitotic index in avoiding over-diagnosis of malignancy is well emphasized.

Jeronimo Forteza - It is a very interesting case. Synaptophysin and GFAP expressions as well as presence of neurofilaments refer to the glial origin of these tumors. I do not know whether it could have some kind of relation with microglia too. Another issue that calls my attention in this case is the abundant presence of psammoma bodies.

Maria Pia Foschini - Thank you for this interesting and difficult case. As underlined in the handout, the diagnosis of pleomorphic xanthoastrocytoma is often difficult. As underlined in the handout, age of the patient, involvement of the frontal lobes, together with the histological pictures are helpful in the differential diagnosis with high grade astrocytoma. Atypical features are so pronounced in the present case that could be misleading for malignancy.

Masaharu Fukunaga - Pleomorphic xanthoastrocytoma, grade II. I have not ever seen this type of brain tumor. Thank you Santiago.

Ondrej Hes - I have a possible similar case. It is 60+ year-old male with anamnesis of "glioblastoma" resected 50(!!) years ago without any further progression (after radiotherapy). I found the block, where it is, according my opinion, pleomorphic xanthoastrocytoma with necrosis (anaplastic variant). I sent the case to my colleague for his opinion a few days ago.

Jason Hornick – Very nice case. It's amazing to me that most of these tumors are essentially benign, despite the histology. Similar to recent publications, our group has begun using the anti-BRAF V600E antibody VE1 to support the diagnosis.

Thomas Krausz - Highly educational case. Despite the marked nuclear pleomorphism there is neither significant mitotic activity nor necrosis which helps not to diagnose some high grade malignant neoplasm.

Thomas Mentzel - Many thanks!

Liz Montgomery - This is so lovely. Looks like GBM until you analyze it carefully. The psammoma bodies are really nice.

Fredrik Petersson - Got that one! Everybody that performs brain frozen section must be aware of this tumor. The clue is the discrepancy between the ugly cytomorphology, the low proliferation and the (variable) presence of vacuolated cytoplasm. Main DDX giant cell glioblastoma, gliosarcoma, anaplastic ganglioglioma.

Murray Resnick - Very nice example.

Brian Rubin - Nice example of one of the only brain tumors I can remember because it's so odd.

Dominic Spagnolo - Agree with pleomorphic xanthoastrocytoma – a very nice example, thank you.

James Strauchen - Pleomorphic xanthoastrocytoma. Thank you for this informative case!

Saul Suster – Great teaching case, Santiago. Thank you for sharing it!

Paul Wakely - Santiago, I was not aware these could have so many psammoma bodies as I have in my slide.

Bruce Wenig - Given the cellularity and nuclear pleomorphism I thought this would be higher grade but given the absence of significant increase in mitotic activity, necrosis and vascular proliferation I guess not.

CASE NO.13 – CONTRIBUTED BY BRIAN RUBIN

Abbas Agaimy - Very interesting case. thanks Brian. Not aware of this variant at this site. Initially I thought of some odd glomus.

Phil Allen - STAT 6 positive angiomatoid tumour with occasional giant cells and extra-medullary haematopoiesis, wall of stomach, possibly a variant of solitary fibrous tumour. In keeping with my dinosaural propensity, I am cautious about accepting the claimed specificity of parvenu histochemical stains until they have been around for 20 or 30 years and all plausible but false claims have been weeded out by further studies.

Carlos Bacchi - Nice example of SFT, giant cell angiofibroma variant.

David Ben-Dor - Fascinating thought provoking case and great discussion. My thoughts would gravitate to a lymphangiomatous tumor though architecturally it should be malignant even if the cells look too bland for that. Nothing in the slide that would make me think of SFT but they are by definition "patternless"- does this mean that they could look like anything? The overlying mucosa looks hyperplastic as in Menetriere's disease with smooth muscle fibers between the glands- secondary to the underlying tumor?

Alberto Cavazza - I missed the diagnosis, but in retrospect you are perfectly right. Very nice case!

Thomas Colby - I got as far as solitary fibrous tumor with rich vascular network. The giant cell angiofibroma variant features are above my pay grade. "STAT" is taking on a new meaning in medicine.

Kum Cooper - This is the "man in Istanbul" phenomenon again. Thank you for the valuable lesson Brian and the great write-up.

Ivan Damjanov - Agree. Thanks for the note about the STAT6 Santa Cruz antibody.

Hugo Dominguez Malagon - Agree with the diagnosis of SFT nice case.

Goran Elmberger - Great case and education about STAT6. I added to my growing list of antibodies to introduce. Why still keep extrapleural in the name if it's an tumor occurring in many locations.

Giovanni Falconieri - What a case, likely we have to consider to add the new STAT-6 marker to the IHC panel in mesenchymal tumors defying classification on traditional morphologic criteria. Thank you for the additional insight regarding the NAB2-STAT6 fusion.

Franco Fedeli - Extrapleural solitary fibrous tumor, giant cell angiofibroma variant. Agree. In other terms regarding this specific cases and as far as the site of occurrence is concerned, it is both a variant of solitary fibrous tumor in that it is extrapleural and a variant of giant cell angiofibroma in that it is extra-orbital.

Cyril Fisher - Very good diagnosis of a difficult case in an unexpected location. We also find STAT6 useful though this needs to be strong, clean and nuclear, since other tumors can show weak/cytoplasmic reactivity. We too find it in some examples of dedifferentiated liposarcoma (which can also be CD34 positive) but as you say detection of MDM2 or CDK4 amplification resolves this.

Jerónimo Forteza - This is an interesting case of solitary fibrous tumor representative of giant cell angiofibroma variant.

Maria Pia Foschini - I agree with the diagnosis of solitary fibrous tumour in an unusual location.

Masaharu Fukunaga - Giant cell angiofibroma or SFT, giant cell angiofibroma type. The discussion is excellent.

Jason Hornick – Thanks Brian for sharing this nice case of SFT with the "giant cell angiofibroma" pattern. I don't think I've seen a gastric mural SFT. As we've discussed, it's interesting your experience with the STAT6 antibodies is so different from ours - I'm very happy with the Santa Cruz polyclonal antibody; I haven't seen any background staining in hundreds of cases. I suspect the difference may be related to the automated platform.

Thomas Krausz - What an amazing morphologic variant of SFT. Brian, thank you very much.

Janez Lamovec - Another rare variant of SFT – unusual morphology, unusual location. Foci of EMH are quite numerous. Is the latter more common in giant cell angiofibroma variant since I don't remember seeing it in more usual types of SFT?

Thomas Mentzel - A very nice case, and I like your description of the lesion as "reminiscent of fibrotic lung tissue" – great!

Markku Miettinen - Agree on solitary fibrous tumor involving the stomach.

Liz Montgomery - Have no better diagnosis but the lesion looks odd for giant cell angiofibroma/SFT.

Fredrik Petersson - Got a "distinct SFT-feeling" when I saw the case. I also thought that there was some extramedullary hematopoiesis going on ?? Educational on STAT6.

Murray Resnick - Would never have considered a SFT. It will be interesting to see how STAT6 staining pans out in the future as far as its specificity is concerned.

Dominic Spagnolo - Common tumor in an uncommon site. It certainly looked like SFT and the STAT-6 is stunning. We have been struggling with the polyclonal and are changing to the rabbit monoclonal. Thank you.

James Strauchen - Peculiar microcystic pattern in my slide. Didn't think of SFT or angiofibroma.

Saul Suster – This is certainly a rare and very unusual case. I can certainly understand how solitary fibrous tumor would be considered in this case. The STAT6 positivity is certainly quite convincing. There are however some significant features that distance this case from SFT: 1) immunohistochemically, only STAT6 is positive, but CD34 was only focal; was bcl-2 and CD99 done? Bcl-2 is positive in nearly 100% of SFT; 2) Location: this is the first case of SFT I would have seen in the wall of the stomach; 3) Histology: the tumor does not really resemble any variant of SFT that I've ever seen before and also does not fit well for a giant cell angiofibroma; the overall pattern (retiform/microcystic appearance) is not what I'm accustomed to see in such tumors. Unfortunately, I don't have any better suggestions. But I always feel uneasy about rendering a definitive diagnosis on a tumor with an unfamiliar histology and in an unexpected location based on the results of a single stain. Was the case studied for the 1;10 translocation? Was an MDM2 stain used to exclude dedifferentiated liposarcoma?

Bruce Wenig - Great case. Prior to this case I had only seen angiofibromatous foci very focally in SFT not predominantly/exclusively. Thanks, Brian. We have been using STAT6 for some time and it is an excellent marker.

CASE NO.14 – CONTRIBUTED BY MANUEL SOBRINHO SIMOES

Abbas Agaimy – Very interesting case, I fully agree with SFT. Although SFT may rarely be primary hepatic, metastases should be ruled out clinically. For me, SFT in the liver should always remind me of a possible remote history of leptomeningeal SFT/hemangiopericytoma which very characteristically metastasizes to the liver, even after a very long time.

Phil Allen - Malignant solitary fibrous tumor, liver. I did not need the immunohistochemistry results to come to this diagnosis. When the brown stains appear to coincide with my opinions, I am happy to support their interpretation.

Carlos Bacchi - Very difficult case to diagnose.

David Ben-Dor: How many iterations of SFT can one take in one sitting? I suppose that for the average general pathologist this is a lifetime's experience compressed into one slide container (with spare change!). It's interesting to see how genetics and the corresponding immuno reactivity is validating histomorphological conceptions- Dr Fatima Carneiro who contributed the case illustrated this beautifully with regard to gastric tumors in the wonderful lecture she gave in Jerusalem a short time ago.

Alberto Cavazza - Probably in the pleura this would be a quite classic solitary fibrous tumor, but clearly in the liver things are different! I missed the paper on GRIA2, thanks for the information.

Thomas Colby - Malignant solitary fibrous tumor. STAT-6 to the rescue. I must admit that I thought the routine morphology was probably SFT.

Kum Cooper - Agreed malignant SFT (CD 34/STAT6). The meningeal SFT (previously known as meningeal hemangiopericytoma) favors the liver as a metastatic site. I would want to rule out a primary meningeal tumor.

Ivan Damjanov - SFT. I am writing this diagnosis not to show off and present myself as a good diagnostician, but just a knee jerk reflex--I call all "patternless" spindle cell tumors that are CD34+ SFT. I was not sure that I could make the diagnosis of malignant SFT from this slide, but if Chris says so, then it is. Antibodies to STAT6 seem to work (see also case 13). By the way, allow me to say that in my youth, I published a similar case and called it a giant fibrous mesothelioma of the liver (in Cancer, when you could publish case reports in Cancer!!). That case was later properly identified by others as SFT!

Hugo Dominguez Malagon - One more case to highlight the variability of SFT and the usefulness of STAT6.

Goran Elmberger - Diagnosis a la mode – third case in a row! Striking variation in pattern – better get STAT6 going and widely include in IHC work-up of spindle cell tumors

Giovanni Falconieri - Great case, Manuel. My way of thinking would be exactly the same as yours, since this is a spindle cell proliferation with a variegated pattern, mostly cellular but featuring areas with sclerosis, as most SFTs do. The mitotic count, must say, is distressing enough and warrant the designation of this tumor as malignant/sarcoma, although encapsulation and complete resection may perhaps portend a better outcome in this particular patient. I missed you during my last trip to Porto.

Franco Fedeli - Spindle cell sarcoma, NOS, "consistent with malignant solitary fibrous tumor, likely primary of the liver". I also learned a lot with this case.

Cyril Fisher - Solitary fibrous tumor with histologically malignant areas. The immunophenotype of CD34/STAT6 is seemingly specific (except, as discussed in the case above, for dedifferentiated liposarcoma).

Jeronimo Forteza - Thank you for this interesting malignant solitary fibrous tumor case as well as for the information on a novel diagnostic marker for solitary fibrous tumor (GRIA2).

Maria Pia Foschini - Thanks for showing this truly malignant type of solitary fibrous tumour.

Masaharu Fukunaga - Malignant SFT, I agree. Thank you very for sharing this case. Could it be dedifferentiated SFT?

Jason Hornick - Nice case. Despite the lack of "hemangiopericytoma" histology, I would wonder whether the patient might have had a meningeal primary in the (distant) past...

Thomas Krausz - Yes, STAT6 is very helpful, especially in diagnostically difficult cases.

Janez Lamovec - As discussed in the previous case, STAT6 is quite specific for SFT, so far.

Thomas Mentzel - A nice example of SFT arising in an unusual (but described) anatomic location.

Michal Michal - Third solitary fibrous tumor in a row ☺ -it looks like a conspiracy☺.

Markku Miettinen - Agree on solitary fibrous tumor with a malignant transformation (round cell component with mitoses >20/10 HPFs).

Liz Montgomery - Seems fine for a strange SFT – whatever that is!

Fredrik Petersson - "Spindle cell sarcoma with some more cellular epithelioid areas", was my initial designation of this case. Difficult to argue against CD34 and STAT 6. However, more than one new specific marker has had to bite the dust with time. Genetics?

Murray Resnick - Another SFT case where STAT6 staining is very helpful. Two in a row!

Brian Rubin - Funny that so many SFT's surfaced in this slide seminar. Liver is an unusual site for a primary malignant SFT. Nice example though and it has a similar pattern of malignant progression/dedifferentiation as Thomas Mentzel's case.

Dominic Spagnolo - An SFT-dominated seminar! Agree with malignant SFT. In the absence of an alternate primary site, this would seem to be a hepatic primary. Thanks for the case

James Strauchen - Sarcoma, NOS.

Saul Suster – Agree. I think a good medical check-up an anamnesis is required before declaring this a primary tumor.

Bruce Wenig - STAT6 to the rescue! Agree with malignant SFT.

CASE NO.15 – CONTRIBUTED BY DOMINIC SPAGNOLO

Abbas Agaimy - Nice and rare example of EBV associated smooth muscle neoplasm in congenital immunodeficiency, thanks.

Phil Allen - EBV associated smooth muscle neoplasm in congenital common variable immunodeficiency, mesentery with spread within the mesentery, to the retroperitoneum and presumably to the lung. I regard EBV associated smooth muscle tumors as a different clinicopathological entity from leiomyosarcoma.

Carlos Bacchi - Thank you for the case.

David Ben-Dor - In my admittedly very cursory microscopic examination I wasn't impressed with anything untoward. In the uterus this would obviously pass muster for a benign leiomyoma though the rules for soft tissue

smooth muscle tumors are much more stringent. Are there particular rules for immune deficiency related EBV + smooth muscle tumors? Assuming there aren't any then I agree with Dominic's approach and say it has uncertain potential.

Alberto Cavazza - I have seen a few of these tumors in HIV, but never in patients with CVID. Thanks for sharing this very unusual case.

Thomas Colby - Agree with diagnosis. Very interesting case. I suspect we should keep an eye out for these EBV-associated smooth muscle tumors in any sort of immunosuppression. Has anyone seen one associated with the TNF inhibitors?

Kum Cooper - EBV-associated well differentiated SMT. Thank you Dom. There has also been a number of papers from South Africa with this phenomenon in HIV/AIDS patients.

Ivan Damjanov - Agree. We used to see similar cases in AIDS patients in the 1980s, but somehow either they have become less common, or they do not come to pathology. We have no pediatric patients (to speak of) in our hospital either.

Hugo Dominguez Malagon - EBV-associated LMS in a immunodeficient patient, beautiful case.

Goran Elmberger - Good case. Agree completely.

Giovanni Falconieri - Thank you Dom, quite a teaching case! I did not know the entity. With the benefit of the hind-sight I would probably call this "smooth muscle tumor of uncertain malignant potential" since this is my prudent policy of appellation for any solid tumor sitting deep in the abdominal (and intrathoracic) soft tissue.

Franco Fedeli - EBV-associated smooth muscle neoplasm (EBVSMN) in the setting of congenital immunodeficiency. What an interesting case! I recall Dr. Bisceglia also presented in Israel in 2013 a similar (and dramatic) case in a very young child who was affected by congenital immunodeficiency.

Cyril Fisher - EBV-associated smooth muscle tumor, in a rare context, very nice example. We are mostly seeing these in post-transplantation settings. Thanks Dom for the nice images.

Jeronimo Forteza - Interesting case of soft tissue tumor related to EBV.

Maria Pia Foschini - EBV-associated smooth muscle cell neoplasm in an immunocompromised patient. I have seen two similar cases in HIV positive patients.

Masaharu Fukunaga - A great case and very informative comments, thank you Dominic. At first it seemed to indicate leiomyoma or smooth muscle tumor of uncertain malignant potential. With the clinical information and the images it helps us to make a diagnosis of EV-associated leiomyosarcoma. I have never encountered this type of tumor, I might have missed it.

Jason Hornick – Thanks for sharing this case - without the myopericytoma-like area with a smattering of lymphocytes, I would not have imagined this smooth muscle tumor was EBV-associated.

Thomas Krausz - I haven't seen EBV-associated smooth muscle neoplasm in this clinical context. I would classify it as smooth muscle neoplasm of uncertain malignant potential. I am also not sure what the adjacent vascularized loose tissue represents. I assume this tissue did not express EBER/EBNA2.

Janez Lamovec - Unknown association to me. Thank you very much for this educative case and discussion.

Thomas Mentzel - Many thanks for this rare example of EBV-associated smooth muscle tumour, that has to be regarded as a low-grade leiomyosarcoma of deep soft tissues. Given the mild degree of atypia every mitotic activity is suspicious for low-grade leiomyosarcoma.

Markku Miettinen - Agree on EBV-associated smooth muscle tumor. This example shows that that it can be almost perfectly differentiated, with the looks of conventional smooth muscle tumor, although in the periphery of the slide there may be a hint for a myopericytic-like component often present in these smooth muscle tumors.

Liz Montgomery - This is a really fabulous case. Love that the reason for immunosuppression revolved around common variable immunodeficiency. I have only seen HIV-associated ones in our population (or missed one).

Frederik Petersson - Nice and unusual case. Bland smooth muscle tumor with EBER+ in the setting of CVID. I think it is important to be aware of the fact that EBV-associated SMTs have different clinical behaviour than non-EBV associated SMTs in relation to the morphological features. The same argument can be said in relation to uterine and somatic SMTs and within the group of uterine SMTs, eg. myxoid and epithelioid types vs "conventional". As stated round cell areas are seen in about half the cases. We have published one laryngeal case that simulated a LMS: Epstein Barr virus associated smooth muscle tumor of the larynx: report of a rare case mimicking leiomyosarcoma. Huang J, Loh KS, Petersson F. Head Neck Pathology 2010 Dec;4(4):300-4, and one case that perfectly well mimicked a cutaneous vascular leiomyoma/angioleiomyoma: Epstein-Barr virus-associated smooth muscle tumor mimicking cutaneous angioleiomyoma. Petersson F, Huang JX. Am J Dermatopathol 2011 Jun;33(4):407-9. In most cases the accompanying lymphoid component is composed of T-cells, however, rarely there may be an associated prominent B-cell component: Epstein-Barr Virus Associated Smooth Muscle Tumor - Report of three tumors including one intracerebral case with a prominent intratumoral B-lymphocytic component and plasma cells. Petersson F. Annals Diagn Pathol 2013 Feb;17(1):91-8.

Brian Rubin - Cool example of a really rare entity. I wonder if we should consider this a neoplasm or an infectious disease, like Kaposi sarcoma. I guess I'd come down on the side of infectious disease since some patients respond to antiviral therapy.

Dominic Spagnolo - My case. Apologies to all – I omitted reference to specific image numbers in my description of the case. Images are as follows: #1, CD34; #2, EBNA-2; #3, EBER; #4-9, subsequent resection specimen.

James Strauchen - EBV associated smooth muscle neoplasm.

Bruce Wenig - EBV-associated leiomyosarcoma. I was aware of the association with post-transplant and HIV patients but not in the setting of congenital immunodeficiency. Thank you.

CASE NO.16 – CONTRIBUTED BY JAMES STRAUCHEN

Abbas Agaimy – Very unusual case, large multilobated atypical looking cells in background of prominent IPT-like reaction. Focal increase in spindle cells. All markers negative. Having encountered a pretty identical case of dedifferentiated inflammatory liposarcoma of thigh metastatic to lung, I started to stain any such a case for MDM2 and CDK4. Was the clinical history definitely unremarkable?

Phil Allen - ALK-1 and myofibroblastic markers negative, probable lymphocyte rich inflammatory myofibroblastic tumor, upper lobe of right lung. I cannot think of a better diagnosis but I have never previously seen so many lymphocytes in an inflammatory myofibroblastic tumor.

Carlos Bacchi - Very unusual morphology with not definitive immunohistochemistry results.

David Ben-Dor - I guess even deep into the immunohistochemistry era there are still cases where the pathologist still needs to rely on his accumulated experience and intuition for making a diagnosis, and can't point to any

particular "magic bullet" stain to deliver him from his dilemma. It would have made life much easier if ALK were positive, though in that case maybe the case would have been too straightforward for contribution to the seminar. But if we're talking immuno, maybe it would have been interesting to try the new marker for SFT (stat 6) because I can't think of anything else that would be remotely relevant. I found one fragment with abundant mononuclear cells showing partitioning by a vascular network (reminiscent of "chicken-wire") to be curious. If I had received the case my major worry would have been to rule out lymphoma which was done.

Alberto Cavazza - I found this case very difficult. I would be a little bit reluctant to make a diagnosis of inflammatory pseudotumor/inflammatory myofibroblastic tumor, although the terms are descriptively correct. A lymphoma remains at the top of my diagnostic considerations. The large cells have peculiar viral-like inclusions: in hematoxylin-eosin I thought they were part of the lymphoid spectrum, but your immunostains do not support this interpretation. At the end I do not know what this is, and I am curious of the opinion of the experts.

Thomas Colby - Don't know what this is. Can understand default in the direction of IMT but there are more lymphocytes than typically seen in IMT and the background spindle cells are somewhat different. The scattered atypical cells can be seen in IMT but they are typically described as "ganglion-like" cells. I too wondered about a dendritic cell tumor. The big cells have intranuclear inclusions and I have seen a melanoma look a little bit like this but in that case the melanoma markers were positive and there was focal melanin. It looks like it is close to/in the ink and careful follow-up is indicated. If this were my case I would make a descriptive diagnosis and say I was not sure what it was and was not sure it was benign or malignant although I would favor the latter.

Kum Cooper - I recently saw a similar case at autopsy a few weeks ago. Had similar features which we call inflammatory pseudotumor/IMT.

Ivan Damjanov - I would accept your diagnosis, simply because I do not know how to call it otherwise. Looking forward to comments of our colleagues who know more about such lesions in the lung.

Goran Elmberger - Don't know what it is. Microcalcifications. HHV8? Would be a bit cautious to call it pseudotumor given the atypical multinucleated virocyte like spindle cells. Follow-up! Multiple lesions? Odd metastasis?

Giovanni Falconieri - Very difficult. I cannot add much to your case assessment. In real life, I'm afraid I would overreact due to the excess of pleomorphic, sometimes multinucleated cells.

Franco Fedeli - Inflammatory pseudotumor/inflammatory myofibroblastic tumor. Agree.

Jeronimo Forteza - A very interesting case in which, no doubt, the most solid diagnosis is inflammatory pseudotumor. I think T-cell lymphoma could be discarded, but it is still possible that the cells can be dendritic cells instead of myofibroblastic. It would be interesting to increase a panel of markers for dendritic cells and, if there were the possibility of an ultrastructural study, even if it were in formalin, it could be interesting.

Maria Pia Foschini - I do not know exactly what it is. Probably reactive lymphoid proliferation. Several psammoma-like bodies of questionable aetiology, surrounded by macrophage-like cells are present through the lesion.

Masaharu Fukunaga - It looked like a lymphoproliferative lung lesion; however, it is very difficult to make a diagnosis.

Ondrej Hes - I see frequently inflammatory myofibroblastic tumor/inflammatory pseudotumor in the urinary bladder (mostly as second opinion cases). They are usually more spindle with less inflammation. In the urinary bladder they are usually misdiagnosed as sarcomatoid urothelial carcinoma thanks to frequent cytokeratin positivity. Anamnesis of instrumental examination or lithiasis could be helpful in some bladder cases.

Jason Hornick – I find this case very challenging - I don't think I would have come to a specific diagnosis. As you mentioned, there are lots of lymphocytes and scattered pleomorphic cells; some unusual dendritic cell neoplasm seems possible, though I don't think it fits with a recognized type.

Thomas Krausz - I would consider also the possibility of solitary fibrous tumor with secondary inflammatory changes.

Janez Lamovec - This is a very unusual type of pulmonary lesion and I don't know how I would call it. I am not sure whether it is reactive or neoplastic.

Michal Michal - It reminds me of pulmonary tumors that we saw years ago (Michal M. et al.: Epithelial plasma cell granuloma-like tumors of the lungs. *Pathol Res Practice* 2002;198:311-316).

Thomas Mentzel - Given the negativity of myogenic markers and the cytomorphology of the non-lymphocytic cells, I found the diagnosis of inflammatory myofibroblastic tumour quite difficult.

Markku Miettinen - Agree on mesenchymal neoplasm with prominent lymphoid infiltrate. Not typical of IMFT. Thought about an unusual PEComa (HMB45, MelanA?), other mesenchymal tumor, not specified.

Liz Montgomery - Hmm. I have no idea what this is and IMT seems OK but was the belly/pelvis imaged to look for something (dediff liposarcoma with lots of inflammation – the only inflammatory MFH – crossed my mind)?

Fredrik Petersson - This a very confusing field. What is an adult ALK-negative inflammatory myofibroblastic tumor? I read up in Markku's book, where it is stated that: "The designation of inflammatory pseudotumor was previously widely used for IMTs at different sites, but it has also been applied to unrelatedtumefactions..., and therefore can not be considered synonymous with IMT." I am very much looking forward to the comments from the soft tissue specialists in the group. What is the relation to calcifying fibrous pseudotumor (Van Dorpe et al. Is calcifying fibrous pseudotumor a late sclerosing stage of inflammatory myofibroblastic tumor? *Am J Surg Pathol.* 1999 Mar;23(3):329-35) and to tumefactive IgG4 sclerosing disease ?? (Bhagat P et al. Pulmonary inflammatory myofibroblastic tumor and IgG4-related inflammatory pseudotumor: a diagnostic dilemma. *Virchows Arch.* 2013 Dec;463(6):743-7).

Brian Rubin - I can't really "buy" this as an example of IMT but I don't have any idea what it is. Looks like an inflammatory nodule with scattered weird multinucleate cells. Could it just be inflammation?

Dominic Spagnolo - I can't think of an alternative to inflammatory pseudotumour. In the H&E I was thinking an FDC tumour. Thanks for the case.

Saul Suster – This is a strange lesion – it certainly doesn't look like a conventional inflammatory myofibroblastic pseudotumor of the lung. At first glance I thought we were dealing with an intrapulmonary lymph node. There are numerous scattered polykaryosomes resembling Whartin-Finkelday giant cells, some containing intranuclear pseudoinclusions, and with scattered calcifications. There is also focal stromal sclerosis with a sparse bland-appearing fibroblastic proliferation. I do not know what this is and myofibroblastic pseudotumor (even if myofibroblasts cannot be demonstrated on IHC) seems as good a name as any other. I favor benign!

Bruce Wenig - Not the typical histology of IMT that I have seen relative to the head and neck. Mixed inflammatory infiltrate including multinucleated cells; not much in the way of identifiable myofibroblasts. I guess "inflammatory pseudotumor" is appropriate. Scattered concretions, some psammomatoid, are present but not sure of their significance.

CASE NO.17 – QUIZ CASE: CONTRIBUTED BY SAUL SUSTER

Abbas Agaimy - Impressive "sickling" of erythrocytes (drepanocytes), thanks Saul for sharing this fine case. Died of sickle crisis?

Phil Allen - Pulmonary fat embolism associated with sickle cell disease, uncontrolled diabetes, obstructive sleep apnoea and possible obesity.

David Ben-Dor - Usually in the context of these seminars when a slide looks mostly normal I assume that there is probably something very subtle beyond my capabilities. This case would fit into that category. Are there sickled red blood cells in the alveolar spaces?

Alberto Cavazza - I think this is acute chest syndrome in a patient with sickle cell anemia, with some acute thrombosis and probably fat embolism.

Thomas Colby - Changes consistent with Sickle cell disease (so-called "acute chest syndrome") with recent and old thrombi, stasis of (probably sickled) red cells in vessels, and capillary dilatation. Lovely case (assuming I am right).

Kum Cooper - Capillary hemangiomatosis. Focal thromboemboli. Focal ventilation lung injury. The capillary dilatation was striking and it reminded me of a case that John Chan showed some years ago with fat emboli but I could not see any intra-luminal material (?fat). So I showed the case to my pulmonary pathologist who very confidently diagnosed this as capillary hemangiomatosis.

Ivan Damjanov - Sickling in the blood vessels, with some microthrombi. A small bone marrow embolus, due to resuscitation. Unusual dilatation of alveolar capillaries.

Hugo Dominguez Malagon - Lung parenchyma, the blood vessels contain thrombi with sickled erythrocytes.

Goran Elmberger - Subtle changes. Few thrombosed vessels. Bone marrow embolism. Diabetic microangiopathy. Lymphangiomatosis-like changes or possibly agglutination of emulsified fat (Sudan black). Possibly would perform Congo red to rule out or in amyloidosis and silver stains due to some granularity. What did I miss?

Giovanni Falconieri - Not sure whether the capillary network is just artifactually dilated. My guess here is fat embolism.

Franco Fedeli - Quiz case: Although one can well see the sickle cell morphology of intraalveolar extravasated red blood cells, I believe that the main pathologic findings herein is represented by the innumerable apparently empty holes in the alveolar capillary lumina. Is this the effect of air/fat pulmonary embolism?

Jeronimo Forteza - What I see in this case must not be the problem that the case presents, since its diagnosis is not difficult, and the issue would be in another area. What I see is a pulmonary microembolism with recent microthrombi that in some occasions slightly adhere themselves to the vascular wall and can be fatal. Embolism and coagulation alterations are related to Sickle Cell Disease. As I said, I think this case shows no problems but I have little doubt that this patient died due to pulmonary microembolism.

Maria Pia Foschini - This is a section of lung parenchyma with preserved alveolar architecture. Vessels are dilated, filled with blood and thrombi. Some small organized thrombi are present through the section. In addition small clusters of glomeruloid capillaries are seen. These features suggest a veno-occlusive lung disease, related to the long standing sickle cell disease.

Masaharu Fukunaga - Fat emboli?

Jason Hornick – The interstitium of the lung is full of vacuoles - I have no idea what this is!

Thomas Krausz - Intraalveolar hemorrhage with sickling of red blood cells and distended/"empty" alveolar capillaries ? fat embolism or alternatively only "vacated" by sickled red blood cells.

Janez Lamovec - Fat embolism?

Thomas Mentzel - Sorry, but I have no idea! It looks like diffuse intravascular coagulation?

Michal Michal - It looks like capillary hemangiomas.

Markku Miettinen - Alveolar septal vacuolization, in vascular lumina – lipid embolization, other embolization?

Liz Montgomery - Clueless. The lungs look weird but I am too obtuse to see whatever glaring finding everyone else does.

Fredrik Petersson - Air containing lung tissue with large empty vacuoles in the interstitium, ?vessels. Can not see any convincing large thrombi. Some sickling or artifact ??

Brian Rubin - I don't think I've gotten any of the quiz cases right yet and this one isn't going to be an exception. I was happy that I noticed that the RBCs were sickled in some instances. However, this doesn't look to me like the lung of a dead person. I can't figure out why he was in acute respiratory distress. Is it a PE?

Dominic Spagnolo - Looks like fat embolism. The sickle cell disease and diabetes are well-recognized associations. Perhaps the back pain indicates the presence of marrow necrosis, with consequent fat embolism. Similar appearances may occur in debilitated patients through agglutination of any intravenous fat emulsions that may have been administered. There is a small recent thrombus in a medium-sized vein in my section, and there appears to be some sludging or fibrin thrombi in a few venules, but I don't think there is any good evidence for pulmonary veno-occlusive disease (which may also occur in patients with sickle cell disease). The severe capillary congestion in the alveolar walls is reminiscent of capillary angiomas but I don't think this is the main issue here.

James Strauchen - No idea. There is something "bubbly" in the pulmonary capillaries. ?Embolic.

Paul Wakely - Pulmonary capillary hemangiomas?

Saul Suster – My case: this is a case of diffuse **pulmonary fat embolism**. There is indeed sickling of RBC's in capillaries and scattered microthrombi, but the immediate cause of acute lung failure was the extensive replacement of the lung microvasculature by fat (the multiple tiny empty vacuoles seen in the alveolar walls), which were positive with oil-red-O. This finding can be very subtle and readily confused for capillary hemangiomas or air embolism but is actually due to fatty embolism and is a known complication of sickle cell disease. It is believed that the release of lipid due to fat embolism occludes the microvasculature leading to symptoms of disseminated intravascular coagulation. In capillary hemangiomas the small capillaries will contain RBC's and should not be empty/vacuolated. Dr. John Chan submitted a virtually identical case to this in the seminars many years ago (AMR#26, Case 4). I thought the members might enjoy this case of classical autopsy pathology.

Bruce Wenig - Not sure but given the presence of a capillary proliferation I thought this could be pulmonary capillary hemangiomas (a lesion I have not previously seen/diagnosed).

CASE NO.18 – CONTRIBUTED BY SAUL SUSTER

Abbas Agaimy - There is prominent lymphoid reaction at the periphery, nerves are also closely associated but distinct from the tumor. I would think of some type of "epithelioid!" peripheral nerve sheath tumor (but SOX10 unexpectedly negative). Unusual is some clear "sebaceous-like" differentiation, would think to stain for NUT??? Was SYT-FISH done? Maybe also stain for SMARCB1 so we are now at "one million-five hundred dollar" Saul.

Phil Allen - Undiagnosed, A1/3, CD99, EMA, HBME1, glypican-3, S100 and CA-IX positive round cell tumour, presumably malignant, retroperitoneum. Sorry Saul. I have not seen a similar one before and I have no ideas that are any brighter than yours.

David Ben-Dor - This is a case for "Super-pathologist". Maybe cases such as this should be placed in a time capsule to be unearthed in 100 years to see if some future pathologist would have the tools to figure it out. Even if I very rarely see any cases the thought of thymoma popped up. Did anyone try and figure it out on an FNA or needle biopsy specimen prior to surgery?

Alberto Cavazza - If you do not know..... I like the idea of a peculiar low-grade epithelial tumor arising from ectopic pancreas, maybe acinar cell carcinoma, but it is really a guess.

Thomas Colby - Don't know. Shared around with colleagues and neuroendocrine was suggested, although NE differentiation would just be one more descriptor to a tumor that is still an enigma. Very solid variant of solid/papillary was suggested but wrong sex and peculiar site.

Kum Cooper - I like the extra-pancreatic idea Saul. Nuclear beta-catenin for solid-pseudopapillary neoplasm??? Also the CD99? Was it paranuclear in distribution? This was shown in SPN of the pancreas by a Japanese group.

Ivan Damjanov - Epithelial tumor, probably from some "developmental rest". Did not look very malignant, but the size is impressive.

Hugo Dominguez Malagon - Sorry I have not seen anything like this before.

Goran Elmberger - Is it possible to get any further info on location?? Lateralized? Cranio-caudal level. Location! Location! If primary, basically three epithelial organs to consider; adrenal, pancreas and kidney.. Teratoma – midline?? Ip12? Or metastasis. Skin adnexal? History! History! Markers do not seem to help much. There seem to be some vesiculation in tumor cell cytoplasm. Fat stain? Also xantogranulomatous tissue reaction around. If fat confirmed possibly strange adrenal gland cortical tumor? Or metastasis sebaceous tumor. Don't know. Never seen this.

Giovanni Falconieri - Just climbing mirrors, Saul. Due to the large mass size was it possible to rule out any anatomical relationship with pancreas? My idea was of a solid/papillary tumor, which may be cystic.

Franco Fedeli - Don't know. "Low-grade epithelioid neoplasm of undetermined histogenesis"? Can't help you, but agree on your diagnosis.

Cyril Fisher - I agree with Dr. Suster's diagnosis as "Low-grade Epithelioid Neoplasm of undetermined histogenesis".

Maria Pia Foschini - This is a very unusual tumor, composed of sheets of poorly differentiated cells. Cells have basophilic cytoplasm, round to ovoid nuclei with small nucleolus. Areas of necrosis and hemorrhage are present. Mitoses, even if not frequent are easy to find. These features suggest an aggressive tumor. The location is unusual, but I would like to add, to the list of immunostains, the NUT specific antibody.

Masaharu Fukunaga - Round cell tumor, probably malignant. It is very difficult to classify this tumor.

Jeronimo Forteza - When we run a definite number of antibodies for the diagnosis of a tumor, the more antibodies you run, the more difficult is to diagnose. This also happens in clinical cases when patients take 8 or more different medicines, they neutralize their effects and the doctor ends up not knowing who they are treating nor the way the patient is going to evolve. When these polymedicated patients start to have evolve in a bad way, the best thing is to withdraw all the medicines, many of them improve. If we forget about immunohistochemistry and focus on histology, we see it is an epithelioid tumor, probably malignant of with a low degree of malignity.

Jason Hornick – The morphology reminds me of a myoepithelial neoplasm - keratin and S100 protein would fit. Otherwise, I don't have any great insights! I don't think it's a pancreatic tumor...

Thomas Krausz - Not sure. I would consider the possibility of soft tissue myoepithelial carcinoma.

Janez Lamovec - Strange retroperitoneal tumor, basaloid type. Reminds me of some kind of skin adnexal tumor in unusual extracutaneous location.

Thomas Mentzel - It looks like a cellular, epithelioid neoplasm containing numerous vessels and in some areas a perivascular growth is seen. Some of the tumour cells contain a clear or vacuolated cytoplasm. Given the coexpression of S-100 protein and cytokeratin, an unusual form of solid low-grade myoepithelioma? However, I've never seen a lesion like this and also the stromal changes do not fit.

Markku Miettinen - Carcinoma, unclassified. Xanthoma cell change resembles changes in postchemotherapy tumors (often seen in germ cell tumors) although this does not look like germ cell tumor.

Liz Montgomery – Clueless.

Fredrik Petersson - Tumor, vacuolated cells. Sebaceous ca ? Adrenocortical ca ? Epithelioid liposarcoma ???

Murray Resnick - Very confusing IHC panel. There is focal perivascular dense hyalinization, although not clearly "waxy" might be worth performing a congo red stain to rule out amyloid. Along these lines would probably add neuroendocrine markers to exclude an odd pancreatic neuroendocrine tumor.

Brian Rubin - I guess I'd go with myoepithelial carcinoma. The lesion is positive for both keratins (AE1/AE3) and S-100. It reminds me of adnexal carcinomas of the skin. You might do an actin stain to see if there is any immunoreactivity.

Dominic Spagnolo - Haven't a clue Saul. I agree with your notion of atypical thymoma-like features. It also evoked a cutaneous adnexal carcinoma. ?? Basaloid squamous features. I guess there is no prior history of relevance. I am not sure this is necessarily low grade.

James Strauchen - No idea. Has a vague squamoid/cutaneous adnexal look.

Saul Suster - My case. I still don't know what this is. There has been no significant development or follow-up on this patient since submission of the case. To address some of your comments we performed some of the additionally suggested stains on the tumor. The following are the results of the stains and comments regarding some of the suggestions that were raised: 1) Sebaceous carcinoma (?metastatic, ectopic): adipophilin stain was negative; 2) Neuroendocrine carcinoma: chromogranin/synaptophysin were negative; 3) Solid and papillary neoplasm of the pancreas: Beta-catenin was strongly positive in all the tumor cells with a membranous granular pattern but no nuclear staining. I've re-reviewed the CD99 stain and it is also membranous and granular, identical to the B-catenin (no paranuclear or nuclear staining seen); 4) Adrenal cortical tumor: Inhibin negative; also, keratin was strongly positive in almost all the tumor cells, which would be very unusual for an adrenal cortical carcinoma; 5) Myoepithelial neoplasm: p63 and calponin were negative; original staining for actin was also negative; 6) Squamoid cutaneous adnexal carcinoma: p63 negative (majority of cutaneous adnexal carcinomas are all p63+); 7) Epithelioid pleomorphic liposarcoma: MDM2 was negative; besides, liposarcomas are not generally positive for keratins, EMA, HBME-1, CD99, glypican 3 and CA IX. So far of all the suggestions proposed solid and cystic/papillary tumor of the pancreas seems like the most likely possibility, although not a perfect match. There was no relation of the tumor with the pancreas according to the surgeon and I don't know if an extrapancreatic version of this tumor has yet been described (which would not necessarily mean they cannot exist). Histologically I think it could fit well for this diagnosis. The problem is this tumor has such a crazy staining pattern and can stain with so many antibodies that it is very difficult outside of its classical context to rely on immunostaining for diagnosis. The beta catenin staining is supposed to be nuclear in these tumors and it is membranous in this case. Besides, beta-catenin can stain a very large catalogue of tumors. I'm not aware of any studies showing positivity of solid and papillary tumor of the pancreas for HBME1, EMA, glypican-3, S-100 or CA IX, but perhaps it's time that we started studying them for these markers. I'm still uncertain about what this tumor is!

Paul Wakely - If those vacuolated cells contain lipid, I would consider the epithelioid variant of pleomorphic liposarcoma.

Bruce Wenig - I do not know what this tumor is either but I agree with a diagnosis of malignancy (i.e., carcinoma). I do not recognize it as pancreatic related (ectopic or otherwise). Some features are a little reminiscent of some H&N cancers. Might be worthwhile doing p16 and EBER although yield likely low. Sorry I cannot be of any assistance.

CASE NO.19 – CONTRIBUTED BY PAUL WAKELY

Abbas Agaimy - Thanks you for sharing this pretty case of intravenous leiomyomatosis.

Phil Allen - Intravenous leiomyomatosis with intra-cardiac extension. I agree whole heartedly with Paul's interpretation. Intravenous leiomyomatosis is closely related to stromal endometriosis and conventional endometriosis. Indeed mixtures of endometrial stroma, smooth muscle and endometrial glands can be found in some combined tumors. For a long time, I have argued that so called low grade Mullerian stromal "sarcoma" has more in common with intravenous leiomyomatosis than with genuine sarcomas, but my view has been out of favor for about 40 years, although it was acceptable thinking before 1970.

Carlos Bacchi - Fascinating case.

David Ben-Dor - Very interesting slide. In the pathology paragraph it is stated that there is "branching ribbon-like proliferation of cytologically bland, monotonous cells emanating from a focus in the smooth-muscle tunica media of this dilated vein. These snake-like ribbons of tissue are covered by CD31-positive endothelial cells." Are you implying in this passage that the lesion originates in the smooth muscle in the vein? Because later on the connection with the uterine myoma is developed and seems most logical. The lesional cells I see are very small and remind me of the article written by RH Young on the differential diagnosis between "very hypercellular leiomyomas" and endometrial stromal sarcomas. In the case of a uterine mass you have the characteristics of the mass itself to go on but here you're supposed to make a judgment based on material taken from a focus of supposed spread or extension so I don't know what rules apply. The immunos of uterine leiomyomas and endometrial stromal proliferations can overlap but caldesmon is supposed to be positive only in smooth muscle tumors. If endometrial stromal tumors behave like granulosa cell tumors then maybe 20 years from now this thing will reappear and except possibly for the medical student no one who was involved in the care of the patient will be available to recall this chain of events.

Alberto Cavazza - Very nice case. I agree with your interpretation: I favour an area of cellular leiomyoma in the context of intravascular leiomyomatosis.

Thomas Colby - Agree with diagnosis. Spectacular case. Without any history I would have thought about metastatic endometrial stromal sarcoma based on the cytology and some of the distinctive sclerosis.

Kum Cooper - Thanks you Paul. I interpreted the morphology as IV-low grade endometrial stromal sarcoma. Both the hyalinization and smooth muscle differentiation would fit. Beta-catenin is also a useful marker to distinguish SMT from ESS (as is H-caldesmon). I saw a similar case some months ago that was treated as IV thrombosis for over many months with anti-coagulants. Eventually the entire lesion was removed and it turned out to be LG-ESS.

Ivan Damjanov - Agree. Difficult diagnosis. Unusual.

Hugo Dominguez Malagon - Agree with diagnosis of intravenous leiomyoma, the differential include ESS.

Goran Elmberger - Extraordinary case. Your interpretation is reasonable.

Giovanni Falconieri - Quite bizarre, Paul. I have not seen this before.

Franco Fedeli - Intravascular/intravenous leiomyomatosis with intracardiac extension. Spectacular case.

Cyril Fisher - Intravascular leiomyomatosis but I agree there are features (morphology, paucity of h-caldesmon) suggestive of low grade endometrial stromal sarcoma. PCR for JAZF1-SUZ12 transcripts might be of interest.

Jerónimo Forteza - This is a very educational case of clinicopathological correlation. Intravascular leiomyomatosis with intracardiac extension and clinical behavior similar to pulmonary embolism. It is also interesting the publication of the case as endometrial stromal sarcoma with intracardiac and pulmonary extension by Dr Coganow et al. (J Ann Thorac Surg 2006; 82:1517). I have had electronic access to this paper, which offers a very interesting presentation of radiological images as well as of pathology, macro and immunohistochemistry but lacks an HE. I guess clinical thoughts that if it was intravascularly invasive, it would be a sarcoma. For years I have had similar experiences of peculiar publications showing clinical-pathological correlation, forgetting the pathologist. I take the liberty to hint that clinicians should be suggested to rewrite the paper.

Maria Pia Foschini - Very interesting case of cardiac location of intravascular leiomyomatosis. I agree with the interpretation that the present lesion is not a sarcoma.

Masaharu Fukunaga - A wonderful case. It is very difficult to make a diagnosis solely with this slide. Thank you Paul.

Jason Hornick – I agree with your diagnosis Paul. Many cases of intravenous leiomyomatosis show a compact/blue appearance with limited cytoplasm (somewhat resembling an endometrial stromal neoplasm). CD10 is variably positive in quite a large subset of pure smooth muscle neoplasms.

Thomas Krrausz - Very instructive case.

Janez Lamovec - To me this neoplasm appears like cellular leiomyoma.

Thomas Mentzel - A fascinating case of huge intravascular leiomyomatosis with extension into the heart.

Markku Miettinen - Agree on intravascular leiomyomatosis.

Liz Montgomery - This is really pretty.

Fredrik Petersson - Spectacular case. My thought process was: bland hypercellular tumor that is not primary. Sex? ok female - endometrial stromal sarcoma? But the typical vascularity was not there. Completely agree. Those hypercellular foci are characteristic of cellular leiomyoma.

Brian Rubin - Agree with your diagnosis of intravascular leiomyomatosis. Intravascular leiomyomatosis is definitely different than a leiomyoma that has run amok. They're an entity and I think they do have features that are not entirely akin to those of run of the mill leiomyomas and leiomyosarcomas. They are distinct. It would be interesting to study a series but I've only ever seen a couple of them.

Dominic Spagnolo - Spectacular case Paul. I agree with your diagnosis of intravascular/intravenous leiomyomatosis.

James Strauchen - Intravenous leiomyomatosis. Very nice!

Saul Suster – Based on the circulated slide I would have thought of an endometrial stromal sarcoma, but putting all the information together I have to agree with your conclusion.

Bruce Wenig - Agree with intravascular/intravenous leiomyomatosis.

CASE NO.20 – CONTRIBUTED BY BRUCE WENIG

Abbas Agaimy - Very rare and unusual presentation of metastatic prostate cancer. I have seen at least one case per year of HCC metastatic to the adrenal the last few years. Here I initially also thought of this possibility. A huge adrenal mass in addition to cytological mimicry can be quite misleading. Thanks Bruce for this teaching case.

Phil Allen - Metastatic prostatic adenocarcinoma to the left adrenal gland. It is comforting to learn that Australia is not the only place where clinical histories can be either less than optimal, or overlooked.

Carlos Bacchi - Great example of a mimicker (clinically and somewhat morphologically) of primary carcinoma of the cortex adrenal.

David Ben-Dor - If we were in puritan times you would want to put the surgeon in a stockade for not providing the essential clinical history. Shame on him for making the pathologist go through this roundabout workup to make a diagnosis which even if not cut and dried from the beginning would have been much easier if the history was available. In this circumstance hats off to the pathologist for thinking of the possibility and going through the trouble in the first place to figure this out. If this came to me in the absence of the complete history I don't know what I would have done. Cytokeratins can be focally positive in adrenal tumors and the "patchy" positivity demonstrated for pan keratin may not have been enough to rule out adrenal tumor; the positivity for calretinin to whatever extent it was may have been enough for a lesser practitioner to "hang his hat on" and assume that it was adrenal. But it was appropriate that the absence of any positivity for other markers expected to be positive in adrenal tumors led to circumspection and a more extensive work up which eventuated in the correct diagnosis. In my own experience I have often found that low molecular weight keratin (8/18) is sometimes more helpful than the pan keratin we use here (MNF).

Alberto Cavazza - The lack of clinical information can render very difficult a case that otherwise would be not so difficult. Very educational case!

Thomas Colby - Agree with the diagnosis. Easy trap to fall into. An elderly VA pathologist said to me once: "Think prostate cancer when an old man has a retroperitoneal mass." I guess the adrenal might qualify.

Kum Cooper - My initial impression was metastatic large cell neuroendocrine carcinoma. There are also areas which resemble rhabdoid differentiation too. Off the penny of drops with the history of prostate cancer. Thank you for this instructional case Bruce.

Hugo Dominguez Malagon - The cells have eosinophilic granules like Paneth cells.

Goran Elmberger - Great case. Agree fully. Metastatic poorly differentiated prostatic carcinoma can be a great mimicker. The often noted neuroendocrine differentiation can further complicate issues not least in an adrenal mass. Adrenal gland is one of those organs prone to metastasis together with the liver and lung but for rather unknown reasons. It's a very small organ but yet often the site of metastasis. Anyone heard a good explanation? Probably one need to take that into consideration when approaching a diagnosis. Always remember to rule out metastasis just the way you did in the present case. I recently had a tricky testicular mass where we ultimately diagnosed a metastasis of prostate carcinoma. The history was there in our LIS system but neither surgeon or our resident picked on it. Fortunately we have good IHC markers for prostatic carcinoma.

Giovanni Falconieri - Weird metastatic pattern of prostatic carcinoma, yet it may happens even to distant sites such as the breast. Just remaining around the theme, in these cases metastatic implants occurred in gynecomastic breasts following diethylstilbestrol treatment for prostatic carcinoma.

Franco Fedeli - Metastatic prostatic adenocarcinoma to the adrenal gland. An absolutely rare event.

Jeronimo Forteza - Interesting case that highlights the importance of immunohistochemistry typically applied to adrenal carcinomas. Inhibin and Melan-A as well as endocrine markers are good to ensure the adrenal origin of carcinomas located there. Thank you for this case.

Maria Pia Foschini - Thank you for sharing this interesting case of metastatic adenocarcinoma of the prostate to the adrenal gland. Metastases from prostatic adenocarcinomas are now rarely seen, and the adrenal location is even more rare.

Cyril Fisher - Metastatic prostatic carcinoma in unexpected location!

Masaharu Fukunaga - It is a very educational case. It looked like a neuroendocrine carcinoma. Thank you very much, Bruce.

Jason Hornick - Very nice case. We've had a few similar cases recently for which metastatic prostatic adenocarcinoma was not a clinical consideration; the monomorphous histology and prominent nucleoli were clues for the astute surgical pathologist. We really like the relatively new marker NKX3-1 (see publications by the Hopkins group), which is more sensitive than the conventional prostate markers (and shows diffuse and strong nuclear staining in the vast majority of cases, including the recent examples I mentioned).

Thomas Krausz - Great case. Metastatic prostate cancer is a diagnostic challenge when it presents at unusual sites without clinical history. I haven't seen it in the adrenal before.

Janez Lamovec - The morphology of this tumor is quite suggestive of adrenal cortical carcinoma and no wonder that you primarily thought of it. I would certainly do the same. This is most instructive case.

Thomas Mentzel - The neoplasm looks like a poorly differentiated carcinoma and congratulation for staining the neoplasm with PSA!

Markku Miettinen - Even if it is very strange to have a large (13.5 cm) adrenal metastasis of prostate cancer, the special studies support this and histology is consistent with this also. Would be very difficult to come up with this by histology only.

Liz Montgomery - So amazing. I have had similar experiences – have diagnosed met prostate carcinoma to the appendix and colon many times with the help of clueless general surgeons who live to cut rather than think for a moment. It's all good.

Fredrik Petersson - Great mimic! Very educational case. Never forget your prostate... We have published a spectacular case of a prostatic carcinoma which presented (sic!) with a metastasis to the sphenoid sinus giving rise to diplopia and headache (Metastasis of occult prostatic carcinoma to the sphenoid sinus: Report of a rare case and a review of the literature. Petersson F et al. Head Neck Pathol. 2012 Jun;6(2):258-63).

Murray Resnick - Would not have thought of prostate initially. There are some areas of the tumor with striking oncocyctic changes.

Brian Rubin - Interesting case with a couple of great teaching points: 1. Prostate CA doesn't metastasize as an unknown primary, at least not very often. I do a lot of bone pathology and I'm always amazed how many residents, fellows and clinicians will want me to exclude metastatic prostate CA as a metastatic carcinoma of unknown primary to bone. I don't think I've ever actually seen it. 2. The adrenal gland is a common site for metastasis.

Dominic Spagnolo - Crazy metastatic prostatic adenocarcinoma in the adrenal gland. A very instructive case and diagnostic trap. Thanks for the case.

James Strauchen - In retrospect, some of the more cribriform areas are reminiscent of prostate!

Ady Yosepovich - A classic teaching case for the importance of clinical history. I am going to share this case with all our residents. It looks like clinicians are trying to hide the major clues for diagnosis and we have to find them out.