COMMENTS TO AMR SEMINAR #68

CASE NO. 1 – CONTRIBUTED BY: Carlos E. Bacchi, M.D.

Abbas Agaimy – Very well illustrated finding with potential confusion if sampled alone, I have seen previous case which metastasized to lung and were pretty identical to this nodular lymphoid pattern and I believe such findings might herald dedifferentiation and hence ability to metastasize in well diff liposarcoma. It is for me a matter of controversy how to call tumors with such extensive areas that are well diff? Thanks for the interesting case.

Phil Allen – Agree. Inflammatory (lymphocyte rich) well differentiated retroperitoneal liposarcoma. I too think that the lymphocytes and plasma cells are reacting to something produced by the sarcoma, possibly a cytokine.

David Ben-Dor – in pulling the slide out of the box I noticed the nodule which is where I assumed the money was. I examined it carefully and realized that it was composed mostly of small lymphocytes intermixed with a few plasma cells and eosinophils, and laying in the background there are a few enlarged atypical cells largely obscured by the inflammatory component. My conclusion at that point would be that classical lymphocyte rich Hodgkin disease would need to be ruled out. I then started to read the handout and did a double take when I read the description of the adipose component which I hadn't paid much attention to. Even after reading the text I can't say I was impressed by irregularity in the size of the adipocytes and didn't see any lipoblasts, but there are fibrous septa containing not only enlarged atypical dystrophic cells but also inflammatory cells. The immunostains are convincing for a well differentiated liposarcoma with an inflammatory component. In the most recent AFIP fascicle on soft tissue tumors (pg. 242) the entity inflammatory liposarcoma is described as having a "heavy inflammatory component which is composed of lymphocytes and plasma cells which often obscures the adipocytic nature of the neoplasm, suggesting alternative diagnoses such as Hodgkin lymphoma, Castleman disease, and or inflammatory myofibroblastic tumor". The relevant images (pg 247) show adipose cells separated by the inflammatory component which focally form small nodules. What is interesting about this case is that the inflammatory component forms a discrete eye-catching nodule devoid of fat and seemingly separated from the adipose tumor, bringing up the question of a hematopoietic tumor (though how can one justify the excision of an apparently large retroperitoneal mass for a nodule turning out to measure at the end 1.5x1 cm.?). I assume that Carlos also did the expected stains for Hodgkin and found the atypical cells in the nodule to be negative for CD30 and CD15. My two cents is that this is inflammatory liposarcoma with the inflammatory component forming a nodule containing entrapped sarcoma cells (as evidenced by the immunostains) which can be confused with Reed Sternberg cells. This is one of the seemingly endless scenarios in pathology which can trip up the unwary pathologist. Congratulations on the pickup.

Gerald Berry - I have not encountered this degree of an inflammatory component in LPS. I can see how the fatty component could be overlooked if you focused only the inflammatory region. An FNA or core biopsy sample would be a nightmare!

Ira Bleiweiss - Agree. I can't recall ever seeing such a lymphoid response in a liposarcoma.

Alberto Cavazza – I saw the case quickly and at a first glance I missed the lipomatous component, but in retrospect it is there. I have seen some well differentiated inflammatory liposarcomas but never with such an exuberant lymphoid tissue. Very nice case, thanks for sharing.

Thomas Colby - Agree with diagnosis. I believe I submitted one of these 12 or 13 years ago (right after 1997 reference), but it was not as "lymphoid" as this lovely case.

Kum Cooper - Thank you Carlos. Agree with WDLS, inflammatory variant. This is one of the most florid examples I have seen. And a needle biopsy into the lymphoid area would have caused diagnostic nightmares. Interestingly the atypical cells are morphologically similar to those seen in the immediate fibrous periphery! But the IHC is most helpful.

Hugo Domínguez Malagón – Very interesting case of retroperitoneal well differentiated liposarcoma, I agree that the "lymphoid" tissue represents the inflammatory component but I was fooled by the Hodking-like appearance similar to myxoinflammatory fibroblastic sarcoma.

Goran Elmberger – Very interesting case and easy to understand how the first pathologist overlooked the LPS. As stated, ALT/WDLS in retroperitoneum usually demonstrate more than one morphological pattern as in this example with classical lipoma-like, sclerotic and as beautifully shown inflammatory component. IHC seems very supportive and I believe MDM2 FISH would reveal amplification. Good case!

Giovanni Falconieri - This is very challenging, Carlos. Indeed, when I looked at the case at first I thought I picked up the wrong slide or a mislabeled case inasmuch as what I (superficially!) saw seemed to me pretty much a reactive lymph node. Period. Going over and over again I could barely recognize clues to a well diff LPS although neoplastic cells beautifully stand out like heroes in the enclosed IHC photos. Parenthetically, a few years ago I have seen a couple of examples of retroperitoneal inflammatory LPS, both confirmed by Chris Fletcher. In these particular cases, though buried within a mixed inflammatory background (including well-formed sarcoid-like granuloma) lipoblasts could be readily recognized. Thanks for the case.

Franco Fedeli - I agree with you, it might be a very challenging case to sign out correctly if the biopsy had represented only the lymphoid component. In addition, I remember a paper edited by Rosai et al. in which the authors described a group of well-differentiated liposarcoma with foci simulating the appearance of malignant lymphomas, including that of Hodgkin lymphoma (Am J Surg Pathol. 1997 Aug;21(8):884-95. Lymphocyte-rich well-differentiated liposarcoma: report of nine cases. Argani P, Facchetti F, Inghirami G, Rosai J.)

Cyril Fisher - Nice example of inflammatory WDL. As indicated, it can be hard to spot the neoplastic cells and immunohistochemistry is very useful here, as is the finding of a lipoma-like component (that can be overlooked as normal fat). The retroperitoneal location is also a good clue.

Andrew Folpe - Inflammatory WDL.

Jerónimo Forteza Vila - This is a lymph node with a pseudoinflammatory lesion. Hodgkin lymphoma and other neoplasias can be ruled out. The liposarcoma seems to be originating in the pseudocapsule of the lympoid infiltrate.

Maria Pia Foschini - This case of liposarcoma with prominent lymphoid infiltrate is very difficult. Indeed, the similarities of the lymphoid tissue with Hodgkin lymphoma are very prominent. Even if the presence of dense inflammatory reaction in liposarcoma has been described, in this case, the patients should undergo accurate staging to clearly exclude the presence of lymph-node involvement.

Masaharu Fukunaga - Thank you very much for sharing this case and detailed discussion of this type of lesion. The hematolymphoid infiltrating area may represent dedifferentiation of liposarcoma. Recently I encountered two cases of dedifferentiated liposarcoma with inflammatory myofibroblastic tumor-like or atypical lymphoid hyperplasia-like features in the retroperitoneum, which expressed CDK4 and MDM2.

Ondrej Hes – I came across a similar tumor around the kidney: lipoma, lymphocyte rich….we have several cases, no one is so nice as this tumor. All were lipomas, no atypical features besides lymphocytic infiltrate were present (of course, can't 100% rule out possibility that I've missed lipoblasts).

Jason Hornick - Beautiful example of inflammatory well-differentiated liposarcoma, Carlos. Indeed, on a biopsy the diagnosis can easily be missed!

Thomas Krausz – I agree, that there is a well differentiated liposarcoma. However, I did not find it easy to determine whether the "central" lymphoid tissue in the section is a reactive lymph node where the capsule and subcapsular region is "eaten up" by the liposarcoma or an exuberant lymphoid tissue representing the "inflammatory" component of well differentiated liposarcoma. Highly educational case, thank you very much.

Janez Lamovec - Although we have seen some cases of inflammatory liposarcoma, the lymphoid infiltrate was less massive, and usually lymphoplasmacytic. The admixture of large multinucleated cells, some of RS type is a tricky feature though on closer inspection morphologically similar or almost identical to those in fibrous septa.

Thomas Mentzel – The rare inflammatory variant of atypical lipomatous tumour shows a rather diffuse inflammatory and lymphatic reaction making it sometimes difficult to detect the lipogenic component. The presented case shows an unusual solid growth of the nonlipogenic cells.

Michal Michal - Lymphocyte rich liposarcoma (P.Argani, F.Facchetti, G.Inghirami, J.Rosai. Lymphocyte rich well differentiated liposarcoma: report of nine cases. Am J Surg Pathol 1977:21:884-895)

Markku Miettinen - Agree on atypical lipomatous tumor/well-differentiated liposarcoma. Atypia is also seen outside the lymphoid infiltrate in fibrous septa and fat enabling one to reach the diagnosis even if dismissing the lymphoid component as reactive.

Delia Perez Montiel - Well differentiated liposarcoma, important to mention and to have in mind when making the diagnostic process is that all the inflammatory reaction really distracts from the rest of the lesion.

Kyle Perry - Wonderful case. Out of my own interest I ran this by one of our hematopathologists and they were (based only on the H&E) also concerned for Hodgkin lymphoma.

Fredrik Petersson - Agree. The atypical stromal cells are there; both in the fibrous and lymphoid areas I could not see any lipoblasts. If the lymphoid component only would have been sampled, as you say, difficult, probably impossible (at least for me) to reach the correct dx.

Santiago Ramón y Cajal - Very nice case. Agree with the diagnosis.

Murray Resnick - Fascinating case. The demarcation between the nodular hematolymphoid area and the rest of the tumor is quite striking. One wonders how this evolved biologically. The liposarcoma cells must be secreting some sort of chemokines or something may have targeted a local immune response to the tumor.

Juan Rosai - Very nice case, similar in all regards to the tumors that Fletcher et al reported as "well differentiated inflammatory liposarcoma" (quoted in the Discussion) and which we published as "lymphocyte-rich well-differentiated liposarcoma" (not quoted !) Interestingly, one of our patients developed a true lymphoma at the site.

Brian Rubin – Excellent example of atypical lipomatous tumor / well-differentiated liposarcoma, inflammatory subtype. The inflammatory nodule in this case is very unusual/solid, I've only rarely seen similar cases. These types of cases are very easy to confuse with a hematolymphoid neoplasm. Great case!

James Strauchen - An interesting case of well differentiated liposarcoma/atypical lipomatous tumor.

Saul Suster – Pretty spectacular case! Thank you Carlos for sharing this with us; I've never seen such a florid lymphoid response in cases of "inflammatory liposarcoma".

Paul Wakely – We had a similar case to yours just recently Carlos, where the pathologist thought it was a lymphoma, and was going to send it to the hemepath division before I pointed out to him the atypical non-lymphoid cells being obscured by a florid lymphocytic population. MDM2 by IHC and FISH were positive in our case. As you state, the key to this diagnosis is recognition of the markedly atypical cells lying in the fibrous septa surrounding the nodule full of lymphocytes.

Ady Yosepovich - Agree with liposarcoma, a very peculiar variant, thank you for sharing this unusual case.

CASE NO. 2 CONTRIBUTED BY: David Ben-Dor, M.D.

Abbas Agaimy – Pretty slide David. I started to think of analogy to what Dr. Cubilla did for penile lesions so this variant might be something like warty-basaloid in the spectrum of HPV-related genital SCC?

Phil Allen – High grade cervical intraepithelial, papilloma virus positive, squamous carcinoma in collision with a non-invasive, papilloma virus negative verruciform squamous carcinoma. David has covered more possibilities than I could think of. Despite the failure to demonstrate any viruses in the verruciform component, I suspect that both lesions have been induced by papilloma viruses.

Gerald Berry - Based on the HPV phenotype patterns I would have to conclude that a "collision" event occurred!

Ira Bleiweiss - Agree. CIN III

Alberto Cavazza – I am not an expert, my untrained diagnosis would be CIN III / HSIL extending to the margins.

Thomas Colby - I probably would have called this a non-invasive papillary squamous carcinoma arising in the setting of CIN and not doing much GYN pathology any more I am not really conversant with the subtleties of the variable p16 staining. Technically, one could call this all CIN 2 and 3, but the papillary squamous lesion is distinctly unusual. To me it is frankly carcinomatous.

Kum Cooper - Thanks David for this exciting case. Firstly, I would have called the keratinizing component a papillary squamous cell carcinoma (with no stromal invasion). I think both the morphology and cytology warrants this interpretation (especially in a 61 year old). Secondly, recent publications have shown more than one HPV type occurs fairly frequently in the cervix. Lastly, the papillary tumor is likely associated with an HPV type not probed for with the ISH. Broad spectrum PCR may reveal another type.

Hugo Domínguez Malagón – Another possibility is pagetoid spread of the CIN III into the condilomatous lesion

Goran Elmberger – Important case. I have seen cases with multiple infection/tumors using combination of p16 IHC, H/L-R HPV in situ and HPV genotyping after LCM. Could be case now alternatively intratumoral heterogeneity with regards to HPV integration and p16 activation.. (GE)

Giovanni Falconieri - Thank you David. GYN pathology has become almost a neglected area in my practice in the third millennium so I may not add or comment on your outstanding considerations,

Franco Fedeli - Very challenging case. I was wonder if the "condylomatous" lesion had an infiltrative aspect?

Andrew Folpe - HGSIL. I guess I would have ignored the other areas.

Jerónimo Forteza Vila - Attending to morphological findings, the first impression is that one of a unique lesion. Nevertheless, the different expression of p16 makes me consider two different lesions.

Maria Pia Foschini - This case is quite interesting. I agree that the two components have different morphologies, but I am not completely persuaded that this is enough to consider them as a collision tumor. The two components could belong to the same neoplastic proliferation simply showing areas with different degree of keratinization. Even the area showing higher keratinized features shows cytological atypia, suggestive of malignant transformation. The apparent absence of HPV infection, searched with in situ hybridization, could be a false negative result.

Masaharu Fukunaga – Microinvasive squamous cell carcinoma. Thank you very much for the detailed discussion, David.

Ondrej Hes – I would have a problem to not call such lesion squamous, well-differentiated exophytic carcinoma-I am not sure about invasion. I would rather prefer to call it early invasion (at least in my slide)…..

Jason Hornick - Very interesting case. It seems most likely that the exophytic/verrucoid lesion is also HPV-driven (as you suggest, perhaps an HPV type that is not detected by the probes?)...but this is outside of my area of expertise!

Thomas Krausz – I agree, that the two architecturally and phenotypically different components are puzzling. I find it easier to conceptualize that there is one lesion with two faces (flat primitive and warty differentiated) than two independent high grade CIN colliding. I have no firm explanation for the molecular result though.

Thomas Mentzel – An interesting and unusual case, I was thinking on CIN III with focal keratinization, but it is true, that there is less atypia and maturation. A problem is the lack of HPV in this area for what I have no sensitive explanation.

Markku Miettinen - High-grade dysplasia is clearly present.

Delia Perez Montiel - I think that the explanation for the absence of the expression of the virus could be that the number of copies is too low and cannot be detected in these areas.

Kyle Perry - This is a great case. Thanks for including the genotyping information.

Fredrik Petersson - Non-invasive, obviously malignant, keratinizing squamous proliferation with spindle cell areas towards one of the margins. Doesn't look like conventional CIN to me. Per continuitatem growth from " north" or "south" was my thought? Searched the literature and found this: Recent case report: Primary Endometrial Squamous Cell Carcinoma In Situ: Report of a rare disease. Jetley S et al. Sultan Qaboos Univ Med J. 2015 Nov;15(4):e559-62, where 5 other cases in the literature is referred to. Thanks for educated discussion on HPV and keratinizing HSIL.

Santiago Ramón y Cajal - Very interesting. The CIN-3 and intraepithelial carcinoma as well as the condylomatous dysplasia are clear. The histological features and the p16 supports that there could be two different tumor clones. It could be interesting to perform p53 as some HPV-negative tumors have been reported positive for p53.

Juan Rosai - Very thoughtful discussion of a rare phenomenon. I like the idea of a "collision" tumor.

Brian Rubin – Very interesting case and discussion. It's great that you chased down the case in such detail and proved once again that our eyes and brains are very powerful discriminators of these kinds of subtle histological distinctions.

James Strauchen - CIN 3 and atypical condyloma.

Ady Yosepovich – these are very nice observations, thank you for sharing this illustrative case.

CASE NO. 3 CONTRIBUTED BY: Kumarasen Cooper, M.D.

Abbas Agaimy – Spectacular case that is not to be solved without history! The skin damage patterns with regard to the diverse agents and medicines used is an emerging challenge to skin pathologists in particular. Great case Kum, thanks!

Phil Allen – Proliferative myofibroblastic lesion after black salve agent application, anterior leg. Both the clinical picture and the histology are spectacular. I have not seen one like this before. I hope that I don't confuse it with a desmoid if I see another.

David Ben-Dor – the slide looked to me like a large and deeply penetrating keloid. The lesion as depicted in the clinical photo looks dreadful and I'm not sure how this could correspond to a "spot" that the patient tried to remove. The article embedded in the submission didn't show up well on my computer but I could vaguely make out that in some cases there may be an intense cellular reaction bringing up the issue of panniculitis-like lymphoma. Was the clinician aware of the history of use of this salve and did he bring it to your attention? Was a biopsy performed prior to excision? I presume that even if the correct diagnosis could be established on biopsy the tumor would have to have been removed surgically in any case since it would be unlikely to heal on its own. Unfortunately, if the "spot" wasn't biopsied prior to application of the salve it may be difficult to know prove what it really was. I don't need any convincing that use of such materials is ill advised and dangerous.

Gerald Berry - The accompanying images are striking. I agree that the lesion is reactive. I was not aware of these corrosive salves. Extraordinary.

Ira Bleiweiss - Ouch, really ouch.

Alberto Cavazza – I agree. Very interesting case, particularly for the macroscopic features and for the clinical history.

Thomas Colby - Agree with diagnosis. I believe Kum discussed this case at a prior meeting.

Kum Cooper - My case. The lesion has healed very well in recent follow-up.

Hugo Domínguez Malagón – Very interesting phenomenon, the overall picture is of an exuberant granulation, reparative response and foreign body reaction.

Goran Elmberger – Good to know. Glad he didn't suffer from venereal disease.

Giovanni Falconieri - Great teaching case, Kum. I do not know if black salve is employed somewhere in this country.

Franco Fedeli - That is an example of clinico-pathologic correlation. I didn't know about these "self-treatment" medications and their consequences, but seeking in the literature I found a review of cases in which the authors describe the histopathological features associated with application of these agents to cutaneous lesions (Pathology. 2013 Dec;45(7):670-4. Histopathological features associated with application of black salve to cutaneous lesions: a series of 16 cases and review of the literature. Leecy TN, Beer TW, Harvey NT, Kumarasinghe SP, McCallum D, Yu LL, Wood BA.).

Cyril Fisher - What an unusual case, Kum. It looks like a reactive proliferation but I have not seen this before in relation to a corrosive salve.

Andrew Folpe - Interesting clinical story. I'm just seeing scarring on the slide, though.

Jerónimo Forteza Vila - Thank you for sharing this amazing case, and the historical reference.

Maria Pia Foschini - I agree with the diagnosis of reactive myofibroblastic proliferation, basically a giant keloid lesion.

Masaharu Fukunaga - A very unusual but education lesion. The photos are very impressive. The vascular proliferation is unique and looks reactive. Thank you Kum for the detailed discussion.

Ondrej Hes – Great case!!!! Great story … ☺ Sanguinaria canadensis ☺ just for illustration:

Jason Hornick - Wow. I have never seen such a case!

Thomas Krausz – The gross picture is frightening. I agree that histologically this is a reactive condition. I did not know about the "corrosive cancer salves". I enjoyed listening to your presentation on this case at an earlier occasion.

Janez Lamovec - This is a fascinating lesion; it appears reactive with extensive vascular proliferation and myofibroblastic proliferation with little chronic inflammatory cells. I was not aware that escharotic agents may cause such an extreme reaction.

Thomas Mentzel – An impressive clinical picture in this reactive proliferative myofibroblastic lesion.

Michal Michal - I think this is a nice case of "acroangiodermatitis pseudokaposi Mali" (a nice term devised and used by dermatologists).

Markku Miettinen - Reactive, exuberant vascular proliferation resembling that seen in leg ulcers (sometimes also called acroangiodermatitis).

Delia Perez Montiel - Exuberant reparative response, very impressive.

Kyle Perry - Interesting case. To my knowledge we have not seen changes from these "escharotics" in Manitoba. It will be helpful to look out for this in the future.

Fredrik Petersson - Pretty non-specific histology as you described. Jumped when I saw the clinical picture, puzzled. Went back to the slide to find something "exciting", to no avail. No black salve for me.

Santiago Ramón y Cajal - Agree with the diagnosis and interpretation.

Murray Resnick - Striking case. Thanks for including the enlightening attachment.

Juan Rosai - Remarkably florid stromal reaction, predominantly vascular, with ill-defined vascular lobules

Brian Rubin – I love pseudotumors and this one has such a crazy and interesting history.

James Strauchen - Never seen a "black salve" lesion before!

Ady Yosepovich - Amazing case – thank you.

CASE NO. 4 CONTRIBUTED BY: Manuel Sobrinho Simões, M.D.

Abbas Agaimy – Widely invasive, oncocytic (Hürthle cell) carcinoma, NOS, with abundant lymphoid infiltration and prominent angioinvasion; good teaching case, agreed with diagnosis before reading the PS. Initially I felt some subtle similarity to oncocytic PTC and I wonder if poorly differentiated oncocytic PTC does exist or is even diagnosable??? Having now read the postscriptum, I would suggest looking at the kidneys or history, any Hürthle-like non-Hürthle makes me think of some odd eosinophilic RCC metastatic to the thyroid. What about PAX8? It is of course expected in both.

Phil Allen – This looks rather like a Warthin's tumour to me. Could it be a primary Warthin-like variant of papillary thyroid carcinoma that happens to be TTF-1 and thyroglobulin negative? They are said to have a prognosis similar to papillary thyroid carcinoma? I would be interested to hear what Juan thinks.

David Ben-Dor – clinically I would expect this to be an anaplastic carcinoma but the histology is not typical for that entity. Histologically it looks to me like a Hurthle cell carcinoma which is behaving aggressively (like an anaplastic carcinoma?). I would call it high grade but in doing so I'm not sure if this is merited by the cytology alone or if I'm impressed by the behavior including the obviously invasive pattern seen on the slide. Histologically it doesn't look typical for the poorly differentiated thyroid carcinoma referred to as "insular carcinoma" – I'm not sure if this was your intention. I'm looking now in the latest thyroid AFIP fascicle where on pg 172 it is stated that besides those tumors which easily fit into the category of insular carcinoma there is a "heterogeneous" group of tumors which share some features with that entity but which differ from it in certain aspects and can show features of other types of thyroid tumors, including follicular and papillary and also oncocytic; the author concludes that it may be futile to assign these tumors to a definite category and that it may have to suffice to leave it as "poorly differentiated". Calling this a "poorly differentiated carcinoma composed of Hurthle or oncocytic cells" would make sense. I also didn't see many mitoses but I could find a few small foci of necrosis, maybe less than what would be expected in insular or poorly differentiated carcinoma. I was intrigued by your point that a high mitotic rate wouldn't be expected in a Hurthle cell tumor since the cells wouldn't have time to accumulate mitochondria if they were reproducing rapidly. But in that case how do they proliferate and metastasize? I thought this activity would result from a high proliferation rate. Until proven otherwise for me this looks like a thyroid carcinoma. If not thyroid then it would have to be an oncocytic carcinoma coming from elsewhere. Anaplastic carcinomas can be negative for usual thyroid markers though admittedly this case doesn't show the histological features typical of that. If this were metastatic I would be fascinated to know where it's coming from.

Gerald Berry - Based on the clinical history and pathologic findings I would have called this widely invasive oncocytic carcinoma.

Ira Bleiweiss - Oncocytic carcinoma for sure, but where is the primary if not thyroid? Did I miss something?

Alberto Cavazza – I thought of an oncocytic, aggressive thyroid carcinoma and I completely missed the possibility of a metastasis. Really a great case, and very educational! Just a couple of guesses about the origin: kidney? Liver (or hepatoid carcinoma from somewhere)?

Thomas Colby - Agree with diagnosis. It is nice once in a while to see bona fide cancers occurring in the thyroid rather than all of these follicular variant cases that inundate us these days.

Kum Cooper - Interesting discussion! Assuming that MCT has been ruled out, could this be of renal origin?

Hugo Domínguez Malagón – Sorry, 'am afraid I cannot be of help. The oncocytic appearance is a phenotype that can be found in many neoplasms inside and outside the thyroid; even medullary carcinoma has an oncocytic variant.

Goran Elmberger – Still think oncocytic carcinoma is relevant classification even if it might be metastatic. Clinicopathological correlation! More IHC? If no other primary tumor is found maybe still thyroid carcinoma?

Giovanni Falconieri - Another lesson from oncocytic tumors in the thyroid! I felt distressed after looking at the slide and reading your critical evaluation of the case. My consideration here would be the same as yours: tumor cell nuclei do not fit for PTC, and overall it looks pretty much alike a follicular oncocytic/Hurtle cell carcinoma. Were this my case I would probably be twice-wrong and sign it out as such without resorting to immuno stains. I think that clinicopathologic correlations may be more revealing, though I would want to rule out a primary in the kidney first.

Franco Fedeli - Challenging case. Despite the absence of all of the nuclear features of papillary carcinoma of the thyroid, I guess that the overall morphologic aspect of this neoplasm could be compatible with a papillary carcinoma, especially in the setting of an oncocytic lesion.

Cyril Fisher - Very instructive case and good advice! And useful discussion regardless.

Andrew Folpe - Oncocytic carcinoma. I can't help but think it is probably most likely primary in the thyroid, despite the IHC (unless another obvious primary turns up).

Jerónimo Forteza Vila - This case have been studied exhaustively. In my opinion the lymphoid infiltrate is an immunologic response.

Maria Pia Foschini - This is a very aggressive tumor, showing oncocytic features. I agree that the morphology and clinical presentation point toward a primary thyroid origin, even if TTF1 and thyroglobulin are negative. However, it can also be a metastasis of oncocytic carcinoma arising in another body site. The patient should undergo extensive search, nevertheless, in case no other primary is detected I would suggest two possibilities: loss of markers in oncocytic thyroid carcinoma or oncocytic carcinoma arising from intra-thyroid parathyroid.

Masaharu Fukunaga - I favor the diagnosis of oncocytic carcinoma, NOS. Thank you very much for the interesting comments

Ondrej Hes – Very nice case, I would be curious to check any association with Lynch syndrome. Lymphoid stroma is abundant, I would stain at least mismatch proteins. Just out of curiosity. Really great case for me (as thyroid gland tumor ignorant).

Jason Hornick - I would have gone down the same trap...I don't know what this tumor is. Was PAX8 also negative?

Thomas Krausz – Yes, after looking at the slide and considering something within the oncocytic neoplastic world of the thyroid, I was shocked to read the "postscript". Is the tumor PAX8 positive? I would consider a metastasis from kidney. I would also stain for GATA3. I am puzzled. Thank you very much for the highly educational discussion.

Janez Lamovec - To me, with all your results, I wouldn't be surprised if the primary tumor could be somewhere in the kidney (oncocytic RCC). Let's wait to hear what Ondra will say.

Thomas Mentzel –Given the postscriptum we have to discuss a metastatic disease (which would "explain" also the prominent angioinvasion).

Markku Miettinen - Hurthle cell carcinoma. Without clinical correlation it could be difficult to rule metastatic carcinoma, such as an unusual type of kidney cancer. With TTF1 negativity, might still be difficult to rule thyroid origin unless primary is found elsewhere (kidney, lung, salivary gland?).

Delia Perez Montiel - Nice discussion, I agree with the diagnosis.

Kyle Perry - Difficult case. If I were to start considering potential other primary sites, renal would be a consideration.

Fredrik Petersson - Infiltrative, oncocytic, a bit "Warthin-like", no PTC nuclear features. IHC strongly argues against primary. Other immune-stains ? Metastasis ? Breast? Kidney?

Santiago Ramón y Cajal - This is a very difficult case and after the great discussion of Dr. Sobrino little more is left to say. To me, I was surprised to see in the epithelial cells the presence of cilia. Because it seems to be a non-thyroidal tumor according to the immunos !!, I wonder if it could be a carcinoma derived from thyroglossal duct or other local structures.

Murray Resnick - Interesting case. Intrigued as to what the follow-up IHC and molecular studies revealed. One factor to keep in mind is that TTF is not always positive in Hurthle cell neoplasms (Bejerano et al AIMM 8: 189-94, 2000). In this study 2/6 Hurthle cell tumors were positive for TTF albeit all were positive for TG. One should also consider an oncocytic parathyroid tumor.

Juan Rosai - Too many difficult questions ! Let's try:

1. I think it is an oncocytic variant of papillary carcinoma
2. Probably a reaction to the tumor
3. "Moderately" invasive (more than "minimally" but not enough for "widely")
4. I agree. Very good point
5. I agree again
6. And again

Brian Rubin – Cool case and great discussion – very educational for me. Could it be metastatic renal cell carcinoma? I'm not sure about thyroid but most metastatic carcinomas of unknown primary to bone and soft tissue turn out to be lung (more common) and then kidney. The histology looks more like renal than lung to me.

James Strauchen - Oncocytic carcinoma!

Saul Suster – Fascinating case and great discussion! Again, the immunohistochemical results are confounding and inconclusive, raising more issues than they resolve! Although I agree that the tumor looks very oncocytic, the clinical presentation and evolution smacks strongly of anaplastic thyroid carcinoma. Not all anaplastic carcinomas are spindle and pleomorphic, and epithelioid/oncocytic variants arising in preexisting Hurthle cell tumors have also been described. The absence of TTF1 and thyroglobulin would be consistent with an anaplastic thyroid carcinoma. Why not an oncocytic variant of anaplastic carcinoma? Have any additional stains been done since submission of the case? Were keratins strongly positive in the tumor cells (ATC are most often negative)? Were renal cell markers tested? How about MIB-1; in ATC nearly ALL nuclei are strongly positive, unlike RCC or Hurthle cell carcinoma. Is there any follow-up clinical history and has a distant primary been identified? If not, I would definitely consider an unusual variant of anaplastic carcinoma.

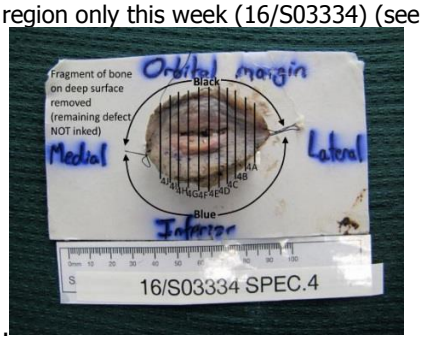
Paul Wakely – What fascinating story and lesion! In reading your discussion, there is a disconnect between the clinical scenario (acting like ATC) and the histopathology lacking necrosis, readily identifiable mitoses, and negative nodes. I was wondering if you had performed a PAX-8 stain. If an extrathyroidal primary is not found, and a PAX-8 stain is positive, I would vote for this being an anaplastic thyroid carcinoma with oncocytic features. Most unusual.

Ady Yosepovich - what a case!!! It appears we need to use more immunos in every thyroid tumor that is not a classical thyroid carcinoma. Thank you for this great lesson.

CASE NO. 5 CONTRIBUTED BY: Phil Allen, M.D.

Abbas Agaimy – Nice case of skin squamous cell carcinoma arising from epidermoid cyst, in addition a peculiar basal proliferation throughout, superficially Pinkus-like but likely reactive. Thank you for sharing this beautiful case.

Phil Allen – Squamous cell carcinoma arising from an epidermoid cyst (my case). I had another one in the infraorbital region only this week (16/S03334) (see picture below)



Photograph of the infraorbital tumour with superimposed block key. The slit-like central opening overlying the tumour is most unusual and gives the impression that the area has previously been surgically incised. However, the sections 4C to 4I show an epidermoid cyst opening onto the skin with squamous carcinoma apparently arising from the wall of the cyst on the deep and side aspects. Sections 4A and 4J from the sides showed the cyst with no tumor.

David Ben-Dor – I agree with your observations. This is a squamous cell carcinoma arising in a cyst which is otherwise lined by a keratinizing hyperplastic epidermis not of the type usually seen in a garden variety "epidermal inclusion cyst", though maybe it started out its career as an infundibular cyst lined by orthokeratotic epithelium which due to the above average life span of its bearer just kept on growing and thickening and accumulating keratin. By papilloma virus I presume you mean the type associated with verruca; this would then be an unexpected type of inverted growth. I don't see any koilocytosis. My thought in looking at the slide before reading the history was a carcinoma arising in a fistula related to osteomyelitis; of course for that you would need the right history. In my own collection there is a case of benign fibrous histiocytoma of the buttock associated with an epidermal inclusion cyst, the second presumably representing surface epithelium pinched off by the tumor. I was given to understand that this can happen with FH which I don't see in the slide submitted.

Gerald Berry - I have not seen SCCA arise in an epidermoid cyst but have had a couple of cases of the chronic draining sinus-related SCCA.

Ira Bleiweiss - Squamous cell carcinoma.

Alberto Cavazza – I agree with the interpretation but I have never seen a similar case before.

Thomas Colby - Agree with diagnosis. I have not seen a carcinoma arising in a cyst. Was there any history of a chronic sinus at this site?

Kum Cooper – Phil, it is highly unlikely to be HPV associated. I took the liberty of sharing this case with Dr David Elder (your fellow Australasian countryman) who thought that this was more likely to be a SCC arising in a previous scar (Marjolin's).

Hugo Domínguez Malagón – Could it be a case of the so called "carcinoma cuniculatum"??

Goran Elmberger – Would be of interest to perform HPV analyses. After reviewing your case 3 days later I got one case of my own! Thanks!!

Giovanni Falconieri - Great case, Phil. I agree with your assessment and interpretation. To the best of my memory I have seen a case of multicentric squamous carcinoma occurring within trichilemmal cysts in a young man suffering from innumerable trichilemmal tumors since adolescence reflecting a genetic defect and microscopically exhibiting a broad spectrum, from banal trichilemmal cysts, to proliferating trichilemmal cysts and frank invasive carcinoma. He undergoes periodically excision of these tumors and over the last 20 years he had countless tumor resections.

Franco Fedeli - Thank you for sharing such a rare case. Presence of multiple cysts could let me think about a syndromic condition? (J Dermatol Case Rep. 2015 Dec 31;9(4):103-6. doi: 10.3315/jdcr.2015.1215. eCollection 2015.

Multifocal squamous cell carcinoma arising in a Favre-Racouchot lesion - report of two cases and review of the literature. Leeuwis-Fedorovich NE, Starink M, van der Wal AC.)

Cyril Fisher - Invasive SCC arising in epidermoid cyst, a rare event and very nice slide.

Andrew Folpe - Squamous cell CA.

Jerónimo Forteza Vila - Very interesting case. It is important the expression of p16 in head and neck tumors.

Maria Pia Foschini - Squamous cell carcinoma arising in epidermal cyst is a very rare event. It has been reported in several cases of intracranial epidermoid cyst (review. J Neurooncol 74: 187-194, 2005).

Masaharu Fukunaga - Thank you very much for the beautiful case of SCC arising from epidermal cyst. I had an autopsy case of SCC arising from epidermal cyst, in which marked inflammation might trigger the cancer.

Jason Hornick - I have not seen such a case previously. Beautiful section. I suspect not HPV-associated.

Thomas Krausz – I did see a case, similar to this, long time ago. I don't know whether HPV is pathogenetically important in a case like this or not.

Janez Lamovec - Squamous cell carcinoma in the epidermoid cyst. Heard of it but never seen one; most convincing example. Thank you.

Thomas Mentzel – A nice case that belongs probably in the spectrum of follicular cutaneous squamous carcinoma as described in Br J Dermatol 2013; 169: 384-388.

Markku Miettinen - Squamous carcinoma arising in a cyst or sinus formation. Cannot see pre-existing cyst in the section.

Delia Perez Montiel - This is an excellent case to show residents the importance of ample sampling even in a case of epidermal inclusion cyst.

Kyle Perry - Agree with the diagnosis. I've personally never seen this before.

Fredrik Petersson - Overlying skin and part of the cyst showing syringofibroademoatus-type hyperplasia and subjacent fibrosis and elastosis. Clearly malignant squamous proliferation arising from the cyst. Never seen this before.

Santiago Ramón y Cajal - Thank you very much for the case. I was wondering if you could stain with p16. Of course, at your disposal, if you want to send the block for the molecular study of HPV.

Juan Rosai - Very impressive. It reminds me of the well-differentiated squamous cell carcinomas developing in the fistulous tracks of chronic osteomyelitis.

Brian Rubin – Interesting case. I see many epidermal inclusion cysts and I've never seen one develop into squamous cell carcinoma. I would imagine that it's not HPV related.

James Strauchen - SCC arising in epidermoid cyst vs. epithelioma cuniculatum.

Paul Wakely – Have not encountered such a lesion with squamous carcinoma arising in an epidermal inclusion cyst.

Ady Yosepovich - thank you for this case. I just had a case of cystic squamous cell carcinoma in a cardiac transplanted patient. Some of these tumors are attributed to SV 40 virus or HPV virus. These tumors are present in immunocompromised hosts.

CASE NO. 6 CONTRIBUTED BY: Hugo Domínguez Malagón, M.D.

Abbas Agaimy – A very rare and well-illustrated case of myoepithelial carcinoma of bone. Thanks.

Phil Allen – Histologically malignant, multinodular myxoid tumour with definite squamous differentiation and clear cells with keratin and S-100 positivity and a mesenchymal appearance, apparently primary in the right fifth rib, male aged 49. I do not recognise this tumour. It somewhat resembles an ossifying fibromyxoid tumour but the squamous differentiation is unequivocal and I have never seen that in an ossifying fibromyxoid tumour. I doubt that it is the same tumour described as a myoepithelioma of soft tissue.

David Ben-Dor – The tumor looked epithelial but something bothered me about calling it "carcinoma" though the presence of a squamous island depicted in the image but not found in the slide would deepen the confusion. Myoepithelial carcinoma makes sense though I would have thought that the cytokeratin and S100 stains would be more prominent. For this case you need to be familiar with the tumor and raise the suspicion on the basis of the histology. I regret saying that I don't think I would have thought of the possibility.

Ira Bleiweiss - Never seen this before.

Alberto Cavazza – I agree, very nice and unusual case.

Thomas Colby - I was struggling with the H&E, but agree with the diagnosis after reading the discussion. The X-ray pictures are lovely. I did not find squamous nests in my slide.

Kum Cooper - Thank you Hugo. Agree with your assessment of myoepithelial neoplasm of bone.

Goran Elmberger – Thanks for sharing rare case. Based on morphology and IHC seems to be a good example of myoepithelial carcinoma of bone. Squamous differentiation can be seen and supports diagnosis. Translocation analysis is golden standard but can be difficult/impossible on decalcified specimens.

Giovanni Falconieri - Beautiful and instructive case, Hugo. Thank you. I completely agree; I have seen a similar case in the same location yet with a preponderant involvement of soft tissue rather than the rib, with a more pronounced myxoid background.

Franco Fedeli - Very interesting case.

Cyril Fisher - The S100 protein/CK immunophenotype and clear cells are convincing for myoepithelial tumor (presumably malignant). EM would be of interest if you have material. Thanks Hugo for nice images.

Andrew Folpe - Agree with myoepithelial CA of bone.

Jerónimo Forteza Vila - Are the epithelial cells from a periferic origin or mesenchymal transformed cell?

Maria Pia Foschini - The present tumor is composed of epithelioid, polygonal cells, focally with clear cytoplasm and focal squamoid differentiation. The diagnosis of myoepithelial carcinoma of bone is plausible, if no other possible sources of primary tumor have been excluded. The diagnosis of myoepitheliomas arising in the soft tissues is becoming more frequent, and the criteria are not always uniform. I personally still have some doubt on the real existence of these tumors.

Masaharu Fukunaga - Recently I have encountered a case of myoepithelioma in small bone in the index finger. Hugo, thank you for sharing a beautiful case of myoepithelioma of bone. It is also similar to adamantinoma.

Jason Hornick - Very nice example!

Thomas Krausz – Agree with diagnosis. I haven't seen myoepithelial tumor in bone before.

Janez Lamovec - This is obviously epithelial (myoepithelial) tumor, with relatively uniform small mostly clear cells with scattered dyskeratotic cells and relatively rare mitoses. When primary and in the bone or soft tissues I always have problem to understand their histogenesis (?carcinoma).

Thomas Mentzel – Thanks for the nice case of a myoepithelioma of bone; did neoplastic cells show loss of INI1 expression what is the case in a number of cases?

Markku Miettinen - Good for myoepithelioma (malignant). Bone seen is reactive new bone formation. Metaplastic metastatic carcinoma would be in the differential.

Kyle Perry - Very nice case of malignant myoepithelioma of the bone.

Fredrik Petersson - Low-grade round cell neoplasm with clear cytoplasm, few mitotic figures and rather hypocellular edematous stroma. Bone invasion - malignant. Reading the IHC – Ha! Istanbul man. However, no extracellular material commonly encountered in salivary glands. Michal published a recent study (AJSP)on clear cell salivary gland carcinomas and EWSR1 rearrangement was detected in 20 of 51 (39%) cases of Clear cell myoepithelial carcinoma, in 5 of 21 (24%) cases of Clear cell myoepithelial carcinoma exPA, in 1 of 11 (9%) cases of epithelial-myoepithelial carcinoma, and in 4 of 5 (80%) cases of hyalinizing clear cell carcinoma!

Santiago Ramón y Cajal - A fascinating case, especially when you do not think about this diagnosis. Initially, we thought in Synovial sarcoma and even in other types of small cell sarcomas. Once you note the squamous component and with immunohistochemical profile that you describe, the diagnosis is very conclusive.

Juan Rosai - Myoepithelioma and myofibrosarcoma have become very fashionable diagnoses. I hope they don't suffer the fate of hemangiopericytoma and malignant fibrous histiocytoma.

Brian Rubin – Nice example of a myoepithelial neoplasm of bone. I think the diagnosis of myoepithelial carcinoma is warranted in this case due to the high level of mitotic activity and nuclear atypia.

James Strauchen - Myoepithelioma of bone. Never seen this before!

Saul Suster – Agree with your diagnosis of myoepithelial carcinoma. First time I see this arising in bone – has this presentation been described in the literature? Given the rarity of this presentation, I would want to rule out first a metastasis from another organ. If no primary tumor is found elsewhere, then I think this case is reportable. There is certainly a precedent for primary epithelial tumors of bone (adamantinoma of bone).

Paul Wakely – Fascinating case Hugo. First time I see.

Ady Yosepovich - Wow…. Did not know that myoepithelial carcinomas can arise in bone. The Ewing translocation is a big pitfall. Thank you for this case.

CASE NO. 7 CONTRIBUTED BY: Jerónimo Forteza Vila, M.D.

Abbas Agaimy – CLL presenting as bilateral cauliflower ears, impressive clinical images, never saw before or heard of, thanks for teaching me.

Phil Allen – Bilateral cauliflower ears caused by leukemic infiltrates presenting two years before the patient developed haematologically apparent chronic lymphatic leukaemia. Thanks for the case. I was not aware of this unusual presentation of a common disease.

David Ben-Dor – I would call these prolymphocytes or paraimmunoblasts. When I see them as sheets as would be the case here I confuse them with large lymphoid cells. Is the patient 40 years old now and if so and the cauliflower ears were present in 1997 the disease began at the age of 20? In any case unless there is a typo he has shown pretty good survival.

Gerald Berry - I think the term "cauliflower ear" is appropriate although I thought it was restricted to boxers after many years in the ring!

Alberto Cavazza – Nice case for the peculiar clinical presentation, that I ignored.

Thomas Colby - Agree with diagnosis. CLL with a distinctly unusual manifestation as "cauliflower ear". Cauliflower has become an in-vogue food along with kale. Where is Mike Tyson when we need him?

Kum Cooper - Thank you for this interesting case. I have only read about the "cauliflower-ear" presentation.

Hugo Domínguez Malagón – Nice case of cauliflower ear skin infiltration by CLL, I was unaware of the phenomenon.

Goran Elmberger – Highly unusual presentation. Good to know. Good work-up!

Giovanni Falconieri - I cannot add a single word, Jeronimo. A great case and an outstanding presentation, as always.

Franco Fedeli - Really a peculiar presentation of a common pathologic process. In my experience, one of the most common extra nodal sites of CLL is the prostate.

Cyril Fisher - Lymphoma of the pinna! Not seen this before.

Andrew Folpe - Interesting clinical presentation of CLL.

Maria Pia Foschini - The present case is interesting as the "cauliflower" lesions of the ear appeared about 12 years before the diagnosis of CLL! I wonder if the correct diagnosis had been performed or suspected at the time of initial diagnosis and what was the patient management.

Masaharu Fukunaga - Thank you for the beautiful case of B cell type CLL with detailed analysis.

Jason Hornick - Remarkable presentation.

Thomas Krausz – Amazing, what strange things nature can do.

Janez Lamovec - CLL infiltrate in the skin of ears. Strange location.

Thomas Mentzel – A nice example of cutaneous involvement in CLL.

Markku Miettinen - Looks good for small B-cell lymphoma infiltrate.

Delia Perez Montiel - A beautifully documented case of this strange phenomenon.

Kyle Perry - Wonderful case. Agree with the diagnosis.

Fredrik Petersson - For the lymphoma people.

Santiago Ramón y Cajal - Agree with the diagnosis. Thank you very much, Jeronimo.

Juan Rosai - Very exotic and thoroughly convincing.

Brian Rubin – Very interesting. I never heard of this before.

James Strauchen - Did not receive a slide. Sounds interesting though!

CASE NO. 8 CONTRIBUTED BY: Masaharu Fukunaga, M.D.

Abbas Agaimy – Beautiful benign multicystic mesothelioma, clinically mimicking ovarian mass, thanks Masa.

Phil Allen – Benign multicystic mesothelioma of the uterus. This disease has some features in common with endometriosis, although the occasional male case is a point of difference between the three generally accepted endometriosis-like proliferations, endometriosis, endosalpingiosis and endocervicosis. I doubt that it is a different morphological manifestation of an adenomatoid tumor, although both are unequivocally mesothelial proliferations.

"Mesothelial inclusion cyst" is a much safer name then "mesothelioma" because many clinicians think anything called "mesothelioma" is a highly malignant and rapidly fatal tumour.

David Ben-Dor – Thanks- very interesting. The surgeons simply excised it and left the uterus in without a frozen to confirm it was benign? The hobnailing in places is prominent- I wonder how this would look on a frozen. I wouldn't think of the diagnosis especially in that circumstance but I wouldn't be surprised if you did.

Gerald Berry - Agree

Ira Bleiweiss - Agree. Benign and cystic and mesothelial (BACAM- a new acronym I just made up)**.**

Alberto Cavazza – Nice example of benign multicystic mesothelioma. I have seen a few examples in the pleura, a rare location as you mentioned.

Thomas Colby - Essentially agree with diagnosis. I would probably be somewhat descriptive here since I believe the term multicystic mesothelioma is used primarily for peritoneal lesions. Although, as pointed out in the reference from John Chan, overlap with uterine involvement (and adenomatoid tumors) is something that occurs, although not something I personally have seen.

Kum Cooper - Thank you, Masa for this interesting case. Not seen an example in the subserosal location before.

Hugo Domínguez Malagón – Excellent example of BMCM. The microvilli are visible by light microscopy. EM is nice in these cases.

Goran Elmberger – Given cited IHC results should be of mesothelial origin. Ciliated cells perhaps somewhat unusual in mesothelial derived lesions. Sometimes hard to differentiate at light microscopical level. Perhaps long microvilli. Perhaps primary cilia seen in EM and sometimes in light microscope in mesothelial derived lesions and many unexpected tissues. Reference: Mesothelial primary cilia of peritoneal and other serosal surfaces. S.D. Bird / Cell Biology International 28 (2004) 151–159 (GE)

Giovanni Falconieri - I agree with your interpretation, Masa. A very useful teaching example of a classic in surgical pathology. My impression is that this kind of lesion is most often underestimate or rubricated under other heading, due to other, frequently concurring pelvic diseases.

Franco Fedeli - Thank you for sharing such a rare variant of adenomatoid tumor. A paper about this topic has been published recently in literature (J Cancer Res Ther. 2015 Oct-Dec;11(4):967-9.Cystic adenomatoid tumor of the uterus. Manucha V1, Azar A, Shwayder JM, Hudgens JL, Lewin J.)

Cyril Fisher - Nice example of benign multicystic mesothelioma.

Andrew Folpe - Multicystic mesothelioma, very nice case.

Jerónimo Forteza Vila - Nice and interesting case. No other diagnosis to add.

Maria Pia Foschini - Thank you for sharing with us this case of multicystic benign mesothelioma. In addition to all the condition that you mentioned in the report, it can also be found in acute appendicitis (Occhionelli et al. Journal of Medical Case Report 2016;10:44).

Ondrej Hes – Fantastic case, never seen such nice example. Interesting are inconspicuous areas of cells in "cambium" mesothelial layer. Seems to me, they resembling bridging strands in adenomatoid tumor. However I think this lesion should be called BMCM, not adenomatoid tumor.

Jason Hornick - Nice case - I have not seen an example within the myometrium.

Thomas Krausz – As it is in myometrium, I prefer the terminology of cystic adenomatoid tumor.

Janez Lamovec - Twenty years ago we described a case of a multilocular peritoneal inclusion cyst in the pelvic cavity (Histopathology 1996; 28, 466-469) that in addition to well- known characteristics also showed several areas of microcystic pattern of growth, a prominent intramural mesothelial cells proliferation and innumerable intracellular hyaline globules; the referring pathologist entertained a possibility of yolk sac tumor.

Thomas Mentzel – A beautiful example of a rare lesion, many thanks.

Markku Miettinen - Looks convincing for multicystic "mesothelioma". Have not seen this in uterus before.

Delia Perez Montiel - Very nice example of BMCM.

Kyle Perry - Agree with this case. Great summary.

Fredrik Petersson - Great case. Cannot argue with the immunoprofile – mesothelial. The background looks "myoid" any IHC ?

Santiago Ramón y Cajal - Agree with the diagnosis.

Juan Rosai - I like Bob Scully's nomenclature (mesothelial inclusion cyst) better than benign multicystic mesothelioma.

Brian Rubin – Nice example of a very rare tumor. Thanks

James Strauchen - Multicystic peritoneal mesothelioma

Ady Yosepovich - thank you for this illustrative case.

CASE NO. 9 CONTRIBUTED BY: Thomas Krausz, M.D.

Abbas Agaimy – Great slide Thomas, thanks, expect the unexpected! Might be quite misleading if no history or not considered in the DDx as IHC is significantly overlapping.

Phil Allen – Clear cell endometrial adenocarcinoma metastatic to the kidney six years after excision of the primary. I assume the primary tumour exhibited the same immunohistochemical phenotype as the metastasis.

David Ben-Dor – this would be an extremely difficult diagnosis without clinical history. I don't know why clinicians can be so recalcitrant about providing clinical history unless they themselves aren't aware of it (presumably the kidney resection was performed by a urologist but wouldn't the absence of the uterus be apparent to him somewhere along the line?). In my own practice I've recently seen two cases of clear cell carcinoma arising in the cervix with no uterine involvement; the diagnosis was confirmed by positivity for Napsin A which was recently described in clear cell carcinomas of the gynecological tract by Allen Gown. According to the recent WHO blue book on urinary tract tumors (pg 29) the cells of collecting duct carcinoma are "cuboidal although columnar and hobnail cells are commonly found", and the cytoplasm is usually "pale eosinophilic or clear", so there may be some cytological overlap between CDC and clear cell endometrial carcinoma aside from the prominent desmoplastic stroma expected in the former case.

Ira Bleiweiss - OMG. I certainly would have erred and called this renal cell ca.

Alberto Cavazza – A further example of the importance of clinical information and accurate morphology. Very nice case, thanks for sharing.

Thomas Colby - Agree with diagnosis. I was initially favoring collecting duct carcinoma and probably would have continued to do so without a history of "endometrial carcinoma", but certainly would have been clued in if I had known about the exact subtype of her endometrial carcinoma.

Kum Cooper - Excellent teaching case, Thomas. Agree with clear cell carcinoma of Mullerian origin. Q: did you perform napsin-A (which can also be positive in this tumor)?

Hugo Domínguez Malagón – Very impressive histology, I was wrongly considering a collecting duct carcinoma in atrophic kidney.

Goran Elmberger – Tough case showing importance of history awareness. In Sweden we are now working towards a central database and registry including digitized slides of all cases accessible to all pathologists regardless of laboratory affiliation. Part of my project plan as chairman of the Swedish Society of Pathology.. Personally I always teach my residents to always start with browsing patient history in LIS system. Appreciated the references!

Giovanni Falconieri - Thank you, Thomas. A very difficult and challenging case. I believe that without clinicopathologic correlation my case assessment would be nearly impossible. Thank you also for the discussion and raising essential points for an effective differential diagnosis.

Franco Fedeli - Good case. I do not have any experience with the monoclonal antibody HNF-1beta, but the expression of AMACR in this tumor looks unusual to me.

Cyril Fisher - Another instructive example where it is necessary to think of metastasis. Tough case without knowing the history.

Andrew Folpe - Ouch- I looked at that too fast, saw the end stage non-neoplastic kidney, and thought we were going down the "renal carcinomas associated with end stage kidney" route. Of course the morphology is classical for clear cell GYN cancer once you think of it!!

Jerónimo Forteza Vila - The morphological findings of the tumor are similar to collecting duct carcinoma, so that immunohistochemistry is crucial for the correct diagnosis.

Maria Pia Foschini - This is a very interesting and difficult case. Indeed, the clinical history is essential to reach a correct diagnosis.

Masaharu Fukunaga - Very education case! My impression was collecting duct carcinoma of the kidney. The discussion is very informative. Thank you, Thomas.

Ondrej Hes – Another fantastic case for me. I believe, it would be easily misdiagnosed as unusual RCC (unclassified, Xp11, etc, etc). I have seen similar case, endometriosis with Mullerian type carcinoma infiltrating kidney.

Jason Hornick - Wow I suspect I would have come to the conclusion that the tumor was an unusual collecting duct carcinoma. Great case.

Janez Lamovec - Most instructive case.

Thomas Mentzel – An unusual metastatic pattern, many thanks.

Markku Miettinen - Agree that it is good for clear cell carcinoma of ovarian/endometrial origin. Could be easily confused with some form of renal carcinoma.

Delia Perez Montiel - Lovely case, kidney metastases are rare and morphology of uterine clear cell carcinoma is classic, this case also illustrates that differential diagnosis has to be performed in every case.

Kyle Perry - When I first looked at the case (without seeing the history), I was concerned about collecting duct carcinoma. With the clinical history uterine clear cell carcinoma would certainly be a better fit.

Fredrik Petersson - My notes before reading the description: very aggressively infiltrating carcinoma, cytologically high-grade – pleomorpgic, solid, tubular, nested – a bit of hobnailing, occasional psammoma bodies. If primary; translocation-associated ?, urothelial ?? collecting duct ??. Met from gynae ??? Challenging case !

Santiago Ramón y Cajal - A very difficult case without knowing the medical history. My first impression was of a collecting duct carcinoma.

Murray Resnick - Nice case and excellent discussion.

Juan Rosai - A typical case of what Dr. Ackerman used to call "the man from Istanbul syndrome".

Brian Rubin – Wow! Excellent diagnosis of something extraordinarily unusual.

James Strauchen - Fascinating!

Saul Suster – This is a very impressive case! I have never seen a metastasis of uterine or ovarian cancer to the kidney before! A real pitfall for diagnosis without a history.

Paul Wakely – Beautiful case. In looking at this slide, but before reading the history I was deceived into trying to push this cancer into some peculiar primary renal carcinoma – whose histologic subtypes seem to continue to expand wildly.

Ady Yosepovich - this is a teaching case that reminds us to search for the previous pathology.

CASE NO. 10 CONTRIBUTED BY: Santiago Ramón y Cajal, M.D.

Abbas Agaimy – Unusual presentation of un uncommon neoplasm with unusual gross features. Would be hard ever to think of infantile fibrosarcoma at this site. ETV6 FISH is highly appreciated. Thanks for sharing this great case.

Phil Allen – Fatal infantile fibrosarcoma of the retroperitoneum biopsied at age six weeks with death at age eight months despite therapy. I would never have made the diagnosis on the basis of the section alone but the patient's age and the demonstration of the infantile fibrosarcoma translocation firmly establishes the diagnosis.

David Ben-Dor – does the term "fibrosarcoma" have any biological relevance or is it more of a vestige from the time when many soft tissue tumors were called "fibrosarcomas" for wont of a more specific term? This would seem to be a high grade poorly differentiated malignancy distinguished by a specific genetic signature. As genetic analysis becomes more and more pre-eminent maybe some of these "old fashioned" terms will be discarded.

Gerald Berry - Agree. Nice case.

Alberto Cavazza – I agree but I am not an expert, so to me this is a diagnosis of exclusion.

Thomas Colby - Agree with diagnosis. Lovely case, and lovely discussion, and just in time for me to use this at a small pediatric pathology club that I am involved in (and I will, of course, acknowledge the source of the case).

Kum Cooper - Thank you Santiago for this interesting childhood tumor. I was unaware that these may occur in the abdomen. Could the abdominal variants arise in congenital mesoblastic nephroma?

Hugo Domínguez Malagón – Why not mesoblastic nephroma cellular type?, it is a retroperitoneal cystic mass, the age is adequate and shares de same traslocation. In addition, cases of combined mesoblastic nephroma-infantile fibrosarcoma have been described.

Goran Elmberger – Difficult case and very good diagnosis. Looks quite different than the newly recognized MASC tumor with the same driver translocation. Small and blue. Indistinguishable from cellular congenital mesoblastic nephroma on histological, immunological and genetic level. No kidney relation clinically or radiologically?

Giovanni Falconieri - An impossible case for me, Santiago. For me, pediatric pathology is far beyond the twilight zone. Cannot add any comment. Yet, I thank you for this collectible item.

Franco Fedeli - Thank you for sharing this case. In my opinion this tumor represents a good example of a pathologic process in which morphologic features alone are no longer sufficient, but we need to deepen the molecular profile to reach the correct diagnosis. In addition, the same translocation is the molecular signature of mammary analogue secretory carcinoma of salivary glands, an entity introduced by doctor Skalova in 2010, which shares morphologic, immunohistochemical and molecular aspects with its mammary counterpart.

Cyril Fisher - The appearances are possibly modified by chemotherapy but difficult to diagnose if SMA negative and without the molecular findings. ETV6-NTRK3 fusion has been reported in supposed inflammatory myofibroblastic tumors (more common in pediatric abdomens) though no inflammation is seen here. However, these might be infantile fibrosarcomas with inflammation, provoking a circular argument about what are the defining diagnostic features for each tumor type.

Andrew Folpe - Infantile fibrosarcoma.

Jerónimo Forteza Vila - The translocation is definitive for the diagnosis.

Maria Pia Foschini - Thank you for providing this case together with a review of the possible differential diagnoses.

Masaharu Fukunaga - This is my first time to see infantile fibrosarcoma in the abdominal cavity. Aggressive behavior compared with those of other locations!

Jason Hornick - Extraordinary case - I have never seen an example in the abdominal cavity.

Thomas Krausz – Without the positive ETV6-NTRK3 molecular result, I would have had a differential diagnostic dilemma. The few infantile fibrosarcomas I seen before were all solid. The cystic alteration confused me.

Janez Lamovec - Retroperitoneal location of infantile fibrosarcoma is relatively rare, and if morphology is not very typical the differential diagnosis may include several entities. However, typical translocation and immune results are helpful.

Thomas Mentzel – A difficult diagnosis, and as stated, usually the prognosis of infantile fibrosarcoma arising on the limbs is much better.

Markku Miettinen - Difficult to histologically link with infantile fibrosarcoma but with genetic confirmation looks ok for that. We have been doing ETV6 rearrangement studies, for example in infantile intestinal tumor candidates, but so far finding none.

Delia Perez Montiel - A very well supported case; in some areas reminded me of a clear cell sarcoma of the kidney, was the kidney affected?

Kyle Perry - Agree. This case nicely illustrates the degree to which cystic/necrotic changes can sometimes take place in this tumour.

Fredrik Petersson - On the very primitive/"immature" cyto-morphological spectrum of infantile fibrosarcoma. Very high proliferation despite not so high mitotic activity. As you say, unusual site. Molecular nails it. Thanks for educational case.

Juan Rosai – Nothing to add.

Brian Rubin – Excellent example of infantile fibrosarcoma. Sad case but instructive.

James Strauchen - Infantile fibrosarcoma. Didn't appreciate the abdominal presentation

Ady Yosepovich - a very nice diagnosis, thank you.

CASE NO. 11 CONTRIBUTED BY: Alberto Cavazza, M.D.

Abbas Agaimy – Thank you for sharing this spectacular case, I missed that paper and thus never heard of this finding before, thank for the great teaching.

Phil Allen – Chickenpox granuloma, lung. Some 50 years ago, the Royal Australasian College of Physicians used to test their specialist candidates with a plain x-ray of a chickenpox lung. I do not think they had any supporting science

behind their diagnosis but the cream of the Australian consultant physicians could not possibly be wrong, even in those distant times. As a result, I had heard of the condition but had never seen a section until this case. Many thanks for the contribution.

David Ben-Dor – you seem to have the monopoly on this topic. Congratulations for having thought of the correct diagnosis. Would this be considered as parallel to the hypersensitivity reaction to tuberculosis? Has this phenomenon been described only in people who contracted the disease in adulthood and never had it in childhood? Would you expect to see this phenomenon in children? My impression is that you think that in "your part of the world" varicella would be at the top of the list of differential diagnosis for lesions such as this, but to me it would appear to be highly unusual. Why would an immunocompetent adult come down with varicella? I thought we all caught this as kids and became immune for life but in the era when children were widely vaccinated for viral infections those that didn't (maybe because of political or ideological objections on the part of the parents) didn't have from whom to contract the disease but remained susceptible.

Gerald Berry - History is indeed helpful in this case.

Ira Bleiweiss - Wow. Never heard of this.

Thomas Colby - Agree with diagnosis. Alberto, I think I have actually seen this case before, haven't I? These lesions are rather underwhelming pathologically until one gets the history (and, if possible, can perform the PCR for varicella zoster) and then they become quite interesting.

Kum Cooper - Wow I have read about this many decades ago; but never thought I would see a case. Thank you for sharing this unique feature of Varicella.

Hugo Domínguez Malagón – A new one for me, thanks.

Goran Elmberger – New to me. Sounds plausible. Great to know!

Giovanni Falconieri - I must congratulate with you, Alberto, for your diagnostic sharpness. I might just say that this is a necrotic granuloma, and would definitely miss the interpretive points. Great teaching case!

Franco Fedeli - Great Alberto! Really intriguing case and helpful comment.

Cyril Fisher - How interesting. This must be very rare to see in a biopsy. New to me.

Andrew Folpe - Chickenpox-related pulmonary nodules. Never heard of this. Thanks for educating me.

Jerónimo Forteza Vila - In this case, clinical data are very important to determine the etiology of the granulomas. The anamnesis and PCR are essential in this case.

Maria Pia Foschini - Thank you for sharing this interesting case! Is the present case one of those previously published (Am J Surg Pathol 2012: 36:1497-1502; Chest 2014;145:433-34)?

Masaharu Fukunaga - Welcome, Dr. Cavazza! Chickenpox-related pulmonary granulomas, I have never seen before. This is very educational to me.

Ondrej Hes – Just thinking, how many chickenpox-related pulmonary nodules I´ve missed/misdiagnosed during frozen section service.

Jason Hornick - Thank you for sharing the case - I have not (knowingly) seen this phenomenon before.

Thomas Krausz – Highly educational case, thank you very much for submitting it. I was not aware that chickenpox can cause necrotizing pulmonary nodules with features overlapping with those of necrotizing granulomas of other etiology.

Janez Lamovec - A teaching case. I have never seen this.

Thomas Mentzel – Many thanks and I was not aware that these necrotic granulomas may be related with previous chickenpox infection.

Delia Perez-Montiel - Because of the high incidence of tuberculosis in my country, we ask PCR for mycobacteria in every granulomatous lesion, We rarely suspect chickenpox. Again, this case illustrates the need for differential diagnosis and the use of the new armamentarium in order to get to the final diagnosis. Thanks for the teaching.

Fredrik Petersson - Wow! Did not know about this. One wonders where the virus resides within the necrotic nodules, in the peripheral macrophages??

Santiago Ramón y Cajal - Thank you very much for the case. It is the first time I see a nodule of these characteristics.

Murray Resnick - Great case. Was not aware of this entity.

Juan Rosai - Another green dragon.

Brian Rubin – Never seen this before. Very educational case.

James Strauchen - Chickenpox of the lung! Fabulous! Severe disease is more common in adults!

Saul Suster – Was not even aware this was a "thing"! Thanks for sharing this educational case.

Paul Wakely – I must admit that I was unaware of chickenpox-related pulmonary granulomas before.

Ady Yosepovich - what a tricky case, I once had this on frozen section in the middle of the night taken in a harvesting procedure for heart transplantation. The surgeon noticed small nodules in the lung parenchyma of the donor. The slide showed non-caseating granulomas, I deferred the diagnosis. The stains for microorganisms were negative. I don't remember if they used the organs.

CASE NO. 12 CONTRIBUTED BY: Brian Rubin, M.D.

Abbas Agaimy – Thanks Brian for sharing this beautiful slide and for the good discussion, we hope to have some adjunct molecular tests in the future to facilitate diagnosis as this is as you pointed out a diagnosis of exclusion. Without typical areas and at metastatic sites might be impossible to diagnose so we just might have called many "high grade epithelioid cell neoplasm" in the past.

Phil Allen – Fatal epithelioid variant of myxofibrosarcoma (myxoid malignant fibrous histiocytoma), deep soft tissues of the left lower leg with left inguinal nodal and pulmonary metastasis. How come this fellow dresses in pseudo-epithelial drag while his former partner has only become an undifferentiated pleomorphic sarcoma?

David Ben-Dor – all I can say is that this is a hypercellular tumor with solid and looser myxoid areas, showing the curvilinear vessels which are the hallmark of myxofibrosarcoma. From what I understand solid areas are seen in the high grade variant of these tumors which can resemble myxoid fibrous histiocytomas, or may actually be the same thing. If my understanding is correct than the presence of solid areas may be enough to put this tumor in the high grade category, regardless of the presence of epithelioid cells. Sometimes when I see large tumors in accessible areas such as the limb in this case and especially with a highly visible metastasis I wonder how the patient permitted it to grow to such an extent, but this can be explained in this case by the highly aggressive nature of the tumor.

Gerald Berry - I saw a case a year or so ago and went down the myoepithelial carcinoma path before recognizing this diagnosis. Now I am always on the lookout for it!

Ira Bleiweiss - – An aptly titled lesion.

Alberto Cavazza – An entity I have never seen before. I missed the diagnosis, but in retrospect the multinodular growth and the curvilinear vessels may be characteristic enough at least to think of this possibility. Thanks for educating me.

Thomas Colby - Agree with diagnosis. I hope I recognize the next epithelioid variant of myxofibrosarcoma, but I fear my ignorance will continue to get the better of me. This appears to be a lovely example.

Kum Cooper - Read the paper…awaited my first "live" case. Thanks Brian. The lobulated myxoid areas on low power is useful. Also there are nice "pseudolipoblasts" and even "signet-ring cells"!

Hugo Domínguez Malagón – The cells also have a "rhabdoid" phenotype, was the expression of INI1 explored?

Goran Elmberger – Difficult to a general pathologist. No specific markers or molecular findings… Very peculiar intracytoplasmic vacuoles described as pseudolipoblasts in the Nascimento paper.

Giovanni Falconieri - Thank you Brian for submitting this unusual variant of MFS, never seen and (I believe) heard of before.

Franco Fedeli - Thank you for this exciting case. Since the extension of the epithelioid component could be focal, I think it could be necessary grossing extensively this tumor, in order to avoid missing such diagnosis.

Cyril Fisher - Epithelioid variant of myxofibrosarcoma, nice example. I suspect (and in my own experience) this is more common than the number of publications suggests.

Andrew Folpe - Epithelioid myxofibrosarcoma. Very nice example.

Jerónimo Forteza Vila - A very interesting case, thank you for sharing it.

Maria Pia Foschini - Thank you for sharing this interesting case. Myxoid features can be present in several different tumors (as shown also by case 23 of the present slide seminar). Differential diagnosis is important to reach a correct therapeutic planning.

Masaharu Fukunaga - This is my second time to look at epithelioid variant of myxofibrosarcoma. Differential diagnoses include conventional high grade myxofibrosarcoma, myoepithelial carcinoma and proximal type epithelioid sarcoma.

Jason Hornick - Very nice example, Brian.

Thomas Krausz – Clearly a differential diagnostic challenge. Since the original publication of this subtype/variant of myxofibrosarcoma, I was hoping to get a beautiful example in my collection. Brian, thank you very much for submitting it. Focally the cells appear rhabdoid. I assume both INI1 and BRG1 are retained?

Janez Lamovec - We only saw one case of this type of myxofibrosarcoma; we were not sure of a diagnosis and sent the case to Chris Fletcher. Morphologically, our case was very similar to this one; interestingly, quite a few tumor cells were positive for α- SMA.

Thomas Mentzel – Many thanks Brian for the wonderful case, it's so rare.

Michal Michal - I think it is a typical example of **myxoinflammatory fibroblastic sarcoma**. Increased atypical mitoses raise a question, whether not to consider it as a high grade variety of myxoinflammatory fibroblastic sarcoma. (Michal M., Kazakov D.V., Hadravský L., Kinkor Z., Kuroda N., Michal M.: High grade myxoinflammatory fibroblastic sarcoma. Report of 23 cases. Annals of Diagnostic Pathology, 19, 157-163, 2015.)

Markku Miettinen - Agree on myxofibrosarcoma with epithelioid features.

Delia Perez Montiel - Some cells look as rhabdoid cells, is this rhabdoid component considered and described as part of the tumor?

Kyle Perry - Very nice case of epithelioid variant of myxofibrosarcoma. In my (limited) experience, I've seen one other case. Your comments on lymph node metastasis (particularly the possibly increased likelihood in this variant) are particularly interesting.

Fredrik Petersson - Very aggressive clinical course indeed. Yet another good educational case from Dr. Rubin. I wonder how these tumors relate to high-grade variants of myxo-inflammatory fibroblastic sarcoma?

Santiago Ramón y Cajal - A difficult case. My first impression was to rule out a rhabdomyosarcoma and a rhabdoid tumor. I understand that the myogenin, myoD1 and the INI1 were inconclusive.

Juan Rosai - Will we ever run out of new entities in the soft tissue sarcoma field? A long time ago I heard Dr. Ackerman saying, coming back from the AFIP, "I think Franz Enzinger is running out of entities" The only time I saw LVA making a wrong prognosis.

Brian Rubin – My case – my slide had bubbles! I hope all of your slides are ok. We've been having trouble with our coverslipper.

James Strauchen - Epithelioid variant of myxofibrosarcoma. Knew it was the epithelioid variant of something!

Saul Suster – Nice case! As is often the case with soft tissue tumors, terminology for a lesion like this can be challenging. We've all experienced the merry-go-round of overlapping and repetitive descriptive terms in soft tissue tumors, which at times can get very confusing. This tumor, first described by Drs. Nascimento and Fletcher, certainly has very distinctive morphologic features that could merit a more original or distinctive name. "Epithelioid" is rather counterintuitive for any type of fibrosarcoma (fibroblasts are not round!). Perhaps we will not fare any better in the future when these are termed according to their molecular signatures (pX^2/17-p-INH-3 tumor….)

Ady Yosepovich - thank you for contributing this rare variant.

CASE NO. 13 CONTRIBUTED BY: Paul E. Wakely, Jr., M.D.

Abbas Agaimy – Impressive reactive atypia in parathyroid adenoma. One year ago I had a case at frozen section but atypia was very focal and less extensive than in your case; thanks Paul.

Phil Allen – Apparently non-functioning, 2 gram parathyroid adenoma with bizarre cells in a patient with concomitant medullary thyroid carcinoma. I have never seen such atypia in a parathyroid adenoma, although I do not think I have ever previously seen a non-functioning parathyroid adenoma found incidentally during thyroid surgery. It is certainly a fearsome case.

David Ben-Dor – the atypia is impressive. Given the size was there parathyroid hyperfunctional clinically? Is this part of an MEN syndrome?

Gerald Berry - Nice example.

Ira Bleiweiss - Very bizarre cells indeed.

Alberto Cavazza – Really a striking example of benign endocrine cytological atypia! This phenomenon can also occur in pulmonary carcinoid tumors, where it can be misleading particularly in small biopsies and frozen sections because the overall bland organoid appearance can be missed and a wrong diagnosis of higher grade carcinoma can be made.

Thomas Colby - Agree with diagnosis. Beautiful example of "endocrine anaplasia".

Kum Cooper - Thanks Paul. Cannot recall seeing such marked cytological atypia in a parathyroid adenoma. Has the term "symplastic" adenoma been used?

Hugo Domínguez Malagón – Beautiful case of non-malignant "endocrine atypia", it seems restricted to the chief cells, the oxyphil cell population has small nuclei, thank you Paul.

Goran Elmberger – Enjoyed bizarrely! Adenoma with atypical cells ≠ atypical adenoma.

Giovanni Falconieri - Great case, Paul. This is one of the lessons that my mentors over the years have tried to plug into my brain: never overestimate nuclear atypia in endocrine proliferations, the prototypical example being the (quasi-monster) nuclei of pheochromocytoma. An instructive case.

Franco Fedeli - Very peculiar case. In Italy we are used to calling this kind of atypia "caricatural".

Cyril Fisher - Striking example, very nice slide, thanks Paul.

Andrew Folpe - Very nice example of "endocrine atypia".

Jerónimo Forteza Vila - The bizarre cells are spectacular.

Maria Pia Foschini - Bizarre cells are quite frequent in parathyroid adenomas, but such a high degree of atypia as seen in the present case is quite rare and unusual. The presence of bizarre cells can be troublesome especially in fine needle aspiration cytology.

Masaharu Fukunaga - Thank you, Paul, it is a very impressive case. Nuclear pleomorphism indicates parathyroid adenoma.

Jason Hornick - Beautiful case Paul. I have not seen such a 'scary' example previously.

Thomas Krausz – Agree with diagnosis. Very nice example.

Janez Lamovec - Pleomorphic cells in parathyroid adenomas are often seen but to be present to such an extent is really very unusual.

Thomas Mentzel – So it´s an "ancient parathyroid adenoma", very nice.

Markku Miettinen - Nice atypia in parathyroid adenoma. Ironically the parathyroid carcinomas we see do not have that atypia (just clear cells).

Delia Perez Montiel -This kind of bizarre cells are very similar to leiomyoma with bizarre nuclei which have a degenerative origin.

Kyle Perry - Thanks for sharing this case. This is a helpful illustration of just how atypical cells can become in these parathyroid adenomas.

Fredrik Petersson - Spectacular case of endocrine atypia. Typical morphology and very extensive. Excellent to scare residents with.

Santiago Ramón y Cajal - Agree. Thank you very much.

Murray Resnick - Beautiful case. Showed the slides to Dr. DeLellis who also thought this was a great example.

Juan Rosai - "Bizarre" is all right for these monstrous cells. My first mentor, Dr Eduardo Lascano, commented about them that they are "grandes pero boludas".

Brian Rubin – Great case of wild, but clinically insignificant cytological atypia in a parathyroid.

James Strauchen - Endocrine atypia in the parathyroid! Great example!

Saul Suster – This is certainly one of the most florid examples of this phenomenon I've ever seen! Thank you, Paul, for this collector's item.

Ady Yosepovich - I always wonder what's the meaning of the "bizarre" cells. The features are striking, thank you for sharing this case.

CASE NO. 14 CONTRIBUTED BY: James A. Strauchen, M.D.

Abbas Agaimy – A true pitfall case, I indeed thought of IPT of lymph nodes but knowing the setting of case presentation I assumed some hidden aspects and tricks before reading the text and seeing the images, thanks Dr. Strauchen for a beautiful case.

Phil Allen – ALK positive anaplastic large cell lymphoma mimicking an inflammatory lesion in a right axillary lymph node. The lymph node superficially appears to be benign but the infiltration of the hilar fat by atypical mononuclear cells does look malignant. If it were not for the fatty infiltration, I think I would have called this benign.

David Ben-Dor – This is indeed very scary. There is an evident perinodal infiltrate with features of granulation tissue and, though albeit a little on the cellular side, there is no way I would have thought of lymphoma. Trying as hard as I can I can't make out anything atypical, though the immunos show that the node is full of tumor. We're getting more and more needle biopsies of axillary lymph nodes taken in mammography which in this situation would be a disaster.

Alberto Cavazza – I agree the large cells are there, but they are subtle and the lesion can be easily confounded with an inflammatory pseudotumor of lymph node.

Thomas Colby - Agree with diagnosis: This is a VERY SUBTLE case and I went down the inflammatory route even knowing that there was something there that I should be seeing. Knowing the diagnosis, I think I can pick out the cells, but I would probably be most convinced if I could put the CD30 and the H&E side by side.

Kum Cooper - Thank you for this diagnostically challenging case. I was not aware of this variant. The IHC is convincing too.

Hugo Domínguez Malagón – Anaplastic lymphoma, I thought the population corresponded to antigen-presenting or endothelial cells.

Goran Elmberger – Difficult but important case for non-hematopathologist. When looking for some suggestive hallmark cells, understand why our hemepath staff always run a lot of immunos whenever consulted. Translocation screening with NGS next step?

Giovanni Falconieri - Another impossible, yet educational case for me. Thank you for your submission.

Franco Fedeli - Underhand case! I've never met one like this. From a morphologically point of view it is very difficult to distinguish from an inflammatory pseudotumor of lymph node.

Andrew Folpe - I think my slide may have been less subtle, since I am not a very good hematopathologist, and my first thought was "ALCL".

Jerónimo Forteza Vila - This is an interesting case in which immunohistochemistry is essential.

Maria Pia Foschini - thank you for sharing this interesting and difficult case. In daily routine practice it can be easy to overlook the neoplastic cells and interpret the features as non-specific, possibly viral lymphadenitis!

Masaharu Fukunaga - It is very difficult to make a diagnosis. My first impression was dedifferentiated liposarcoma with inflammatory myofibroblastic tumor-like features.

Jason Hornick - Remarkable case - very easy to miss!

Thomas Krausz – The lymph node is certainly not normal. Purely on H&E I was not sure between reactive versus lymphoma. Thank you very much for the highly educational discussion.

Thomas Mentzel – Very difficult cases, and very easy to overlook!

Markku Miettinen - Very stealthy tumor and nice reminder to do the immunostain panels in atypical lymphoid infiltrates. Should be caught by CD30 in screening, followed by ALK.

Delia Perez Montiel - That lymph node looks very reactive to me, I'll have to be more careful when viewing nodes.

Fredrik Petersson - I had to back to the slide to see the large cells. Initially I was struck by the vascular proliferation in conjunction with some granulocytes. Was thinking HHV8. Bartonellosis… was not aware of this. Scary.

Santiago Ramón y Cajal - Thank you very much for the case. Very difficult with the hematoxylin and eosin. It is quite polymorph with a reactive background. The Interfollicular expansion and especially a thickened capsule with infiltration by blast cells plus the Immuno seems conclusive. I was wondering if you had also conducted a molecular study.

Murray Resnick - I would more than likely have missed this one. As nicely stated in the comment one would need an extremely high index of suspicion to make this diagnosis.

Juan Rosai - Very tricky case, nicely documented.

Brian Rubin – I think I would have missed this diagnosis and that scares me, which I guess is the point of seeing this type of case. Alright, I'm scared and hopefully I won't miss this diagnosis.

Saul Suster – I would have missed the diagnosis completely! Without identifying the surprisingly large number of CD30+ cells this would be a major pitfall. I noticed one of the co-authors of the only paper on this entity is Dr. Bacchi. Very astute observation! Congratulations, Carlos.

CASE NO. 15 CONTRIBUTED BY: Franco Fedeli, M.D.

Abbas Agaimy – Pretty SEF, thanks Franco. Just signed out an identical in-house case this week with extensive bone formation.

Phil Allen – Sclerosing epithelioid fibrosarcoma, supraclavicular soft tissues. I was seeing about one of these a year until our administration started to levy a charge for consultations. This is the first case I have seen since the administrators smelt the money. In practice, they received hardly any because nearly all the referrals immediately dried up.

David Ben-Dor – Along with the previous case of myxofibrosarcoma this seminar is turning into a mini-soft tissue pathology course (and who knows what other cases I'll find further on). I'm taking advantage of this to brush up on these entities. Histologically it looks very typical of the entity diagnosed but interestingly according to the authors of the latest soft tissue tumor AFIP fascicle (2014- pg 185) MUC4 positive lesions are categorized as low grade fibromyxoid sarcoma. I wonder what the biopsy showed.

Gerald Berry - Nice example of a very difficult diagnosis.

Ira Bleiweiss - VERY sclerosing – another aptly titled lesion.

Alberto Cavazza – I agree, nice example and discussion

Thomas Colby - Agree with diagnosis. One of the few soft tissue tumors that I can (sometimes) recognize.

Kum Cooper - Nice example Franco of SEF. Thank you.

Hugo Domínguez Malagón – Nice case of SEF thank you Franco.

Goran Elmberger – Good case. Differential with other epitheloid fibrosing sarcomas pertinent. MUC4 should be helpful. SEF also important to recognize as mimicker of metastatic breast cancer. IHC and FISH helpful. Claimed to

be clear cells but I wonder if not merely retraction artifacts. EM literature does not show clear (!) explanation for cytoplasmic clear features.

Giovanni Falconieri - I agree with your interpretation, Franco. SEF is also on top of my differential. Just seen it only in slide seminars, not too much to add.

Cyril Fisher - Nice example of SEF, thank you Dr Fedeli.

Andrew Folpe - Very nice example of SEF. Interesting ddx in that location with clear cell salivary gland tumors.

Jerónimo Forteza Vila - An interesting and difficult case.

Maria Pia Foschini - Sclerosing epithelioid fibrosarcoma is a difficult lesion that should be differentiated from other tumors. Immunohistochemistry for MUC4 is important. More recently EWSR1-CREB3L1 gene fusion has been reported as a diagnostic aid (Arbajian E. et al. Am J Surg Pathol 2014;38:801-808).

Masaharu Fukunaga - A beautiful and classical case of sclerosing epithelioid sarcoma, thank you Franco.

Jason Hornick - Very nice example.

Thomas Krausz – Agree with diagnosis. We have just seen a rare primary example of sclerosing epithelioid fibrosarcoma of bone, which was originally misdiagnosed as osteosarcoma.

Janez Lamovec - Epithelioid fibrosarcoma; a very characteristic appearance.

Thomas Mentzel – A wonderful example of a rare but distinct entity.

Markku Miettinen - Very good for sclerosing epithelioid fibrosarcoma, probably representing a progression form of low-grade fibromyxoid sarcoma.

Delia Perez Montiel - Very nice example of this difficult lesion.

Kyle Perry - Agree. This is a great example of sclerosing epithelioid fibrosarcoma. Thank you so much for sharing this case.

Fredrik Petersson – Beautiful case.

Santiago Ramón y Cajal - Agree with the diagnosis. Thank you very much.

Murray Resnick - Great example. Very interesting that these tumors have no specific immunophenotype and that they are negative for such a long list of immunostains. It is my understanding that there is no known genotype suggesting that these rare tumors are likely a mixed bag biologically.

Juan Rosai - Another new type of soft tissue sarcoma, but one which I have learned to recognize (the hard way).

Brian Rubin – This is a beautiful and prototypical example of sclerosing epithelioid fibrosarcoma with a very nice summary.

James Strauchen - Sclerosing epithelioid fibrosarcoma. Have never seen one on the hoof! Thank you!

Paul Wakely – Beautiful example of SEF Franco. Thank you.

Ady Yosepovich - A rare variant of fibrosarcoma, thank you for this illustrative case.

CASE NO. 16 CONTRIBUTED BY: Göran Elmberger, M.D.

Abbas Agaimy – Myoepithelial carcinoma seems to be increasingly recognized (two cases included in this seminar¸ one of bone, case 6). Many such cases might have been merely called poorly diff carcinomas or SCC in the lung if not thought of or no ME markers included. Thanks Göran for the teaching discussion.

Phil Allen – Peripheral carcinoma with a myoepithelial phenotype, presumably primary, upper lobe of right lung. I wonder how many different tumour entities are now being posted to the myoepithelial carcinoma address.

David Ben-Dor – This is another remarkable case, and the second one of myoepithelial carcinoma in this seminar. The write up was masterful. As Goran pointed out so well, making the correct diagnosis depends on thinking about it in the first place, something not so easily done since at least to a certain extent this process goes on in the "sub" or "pre" conscious (Freudian terminology which may be antiquated in this age of fMRI brain scans). To make things more complicated, also as Goran points out, the immunohistochemistry panel required in some cases may be involved, since once you get beyond the cytokeratin positivity the immunos can be variable (in Hugo Dominguez' s case also part of this seminar the actin was negative). Cases such as this are submitted to the seminar from time to time and I never think of the correct diagnosis. So should every lung tumor biopsy which is p63+ positive be further worked up for myoepithelial carcinoma? In recent years the use of p40 has gained popularity in lieu of p63 for diagnosis of pulmonary squamous cell carcinoma, as the former is purported to be more specific since p63 positivity may be seen in lung adenocarcinomas. Is p40 positive in myoepithelial tumors? In a cursory examination I didn't see any literature on this; if not then positivity for this marker in a lung tumor could be assumed to rule out MEC and put the mind of the pathologist at ease.

Gerald Berry - Thank you for the detailed discussion.

Ira Bleiweiss - Another new entity for me.

Alberto Cavazza – I agree, and myoepithelial differentiation may be underrecognized in lung cancers. I think Dr. Yousem reported similar cases as "Pulmonary adenosquamous carcinomas with amyloid-like stroma" (Mod Pathol 1989;2:420-426).

Thomas Colby - Agree with diagnosis. I fear that on a busy day, I might simply call this poorly-differentiated non-small cell carcinoma, do the appropriate immunostains for squamous and glandular differentiation and then call it a day. I hope I would be able to recognize the subtle features that suggest that this is not a routine carcinoma including the vague myxoid change associated with the epithelioid cells and focal reticular pattern. It would be easy for me to overlook the plasmacytoid cells and the relative paucity of the stroma. Nevertheless, once one considers it and does the appropriate immunohistochemical panel, I think myoepithelial carcinoma is the right diagnosis.

Kum Cooper - Goran this is truly the "man from Istanbul". I thought this was going to be a metastasis from the breast; and did not consider MECA of the lung. Thanks for the education and discussion.

Hugo Domínguez Malagón – The histology is of a high-grade poorly differentiated carcinoma; in my slide there is comedo type necrosis and nuclear atypia and up to 3 mitosis per HPF, the immunos are essential to make a diagnosis of MEC.

Giovanni Falconieri - Beautiful and instructive case, Goran. As you said, another lesson from the man of Istanbul. Your case description and comment are superb as well. I have not experience with pulmonary myoepithelial carcinoma, I am afraid that this lesion might be easily confused with squamous carcinoma.

Franco Fedeli - Thank you for sharing this "man from Istanbul" and for your detailed discussion about this topic. In addition, I've recently read a paper about this tumor, edited by doctor Travis and doctor Antonescu (Am J Surg Pathol. 2016 Feb;40(2):212-23. Thoracic Myoepithelial Tumors: A Pathologic and Molecular Study of 8 Cases With Review of the Literature. Leduc C1, Zhang L, Öz B, Luo J, Fukuoka J, Antonescu CR, Travis WD.)

Cyril Fisher - Myoepithelial carcinomas are being increasingly recognized in unexpected locations. Thanks for the very useful discussion.

Andrew Folpe - Interesting. I do not think I would have thought of a myoepithelial CA, although the IHC looks convincing.

Jerónimo Forteza Vila - Lung origin cannot be ruled out because of TTF1 negativity.

Maria Pia Foschini - I agree with the diagnosis of myoepithelial cell carcinoma of the lung. The morphology is similar to what is observed in salivary gland cases. The number of atypical mitoses in high, and nuclear atypia is prominent, all these features are indicative of aggressive behavior in salivary glands. I wonder if they have the same prognostic significance in lung cases.

Masaharu Fukunaga - Myoepithelial carcinoma of the lung. I have never seen this before. Thank you Goran for the detailed discussion and differential diagnosis.

Jason Hornick - Interesting case.

Thomas Krausz – Before reading the discussion I was considering poorly differentiated/non-keratinizing squamous cell carcinoma or solid adenocarcinoma. We started to use p40 for squamous differentiation because of better specificity than p63. Thank you for the comprehensive discussion and congratulations on your myoepithelial carcinoma diagnosis.

Janez Lamovec - I must admit that I did not recognize this tumor as a myoepithelial carcinoma but thought of a poorly differentiated non-keratinizing squamous cell carcinoma. The tumor cells are quite uniform, there is no heterogeneity of cellular population and pseudoglandular spaces with mucoid type of interstitial fluid may also be seen in squamous cell carcinoma.

Thomas Mentzel – Many thanks for this difficult case and for the detailed discussion. Probably the presence of many growth patterns and different cell types is a helpful clue for thinking of myoepithelioma.

Markku Miettinen - Agree that evidence supports myoepithelial carcinoma, with S100 and SMA present. Difficult to catch this histologically.

Delia Perez Montiel - It looks like very similar to breast carcinoma, immunohistochemistry is very helpful.

Kyle Perry - This case is very instructive. It makes one wonder how many of these tumors are correctly identified.

Fredrik Petersson - Agree. Got a "myoepithelial feeling" when I saw the slide. On my sections focal presence of basement-type material within some tumor nests and limited, but even so, some bluish myxoid substance.

Santiago Ramón y Cajal - Another fascinating case of myoepithelial carcinoma. Goran, thank you very much.

Juan Rosai - See comments to Case 6.

Brian Rubin – Excellent case and wonderful discussion.

James Strauchen - Myoepithelial carcinoma of the lung. Great case!

Saul Suster – Agree with diagnosis. This is very rare in the lung. We recently had an in-house case that also caused problems for initial diagnosis (on frozen section was called poorly-differentiated carcinoma). The review cited by Goran that was written by Dr. Rosen (Appl IHC Mol Morphol 2014) cites only 8 previous case reports.

Paul Wakely – Thank you Goran for such a lucid and erudite discussion of myoepithelial neoplasia.

Ady Yosepovich - Thank you for this unusual case again stressing out always to expect the unexpected.

CASE NO. 17 CONTRIBUTED BY: Maria Pia Foschini, M.D.

Abbas Agaimy – Brain metastasis of nodular mesothelioma with sarcomatoid features, highlighting the importance of clinicopathological correlation, thanks for sharing this case.

Phil Allen – Metastatic sarcomatoid malignant mesothelioma to the brain from a right pleural epithelioid malignant mesothelioma. I initially thought this would be a glioblastoma multiforme but the tumour is GFAP negative. Sonja Klebe (reference 2) agrees with the diagnosis. Doug Henderson (reference 3) is away for the next two days so I will have to show it to him later.

David Ben-Dor – So I looked at the slide, read the brief description, and was prepared for a malignant meningioma or, given the history of "lung nodule" metastatic spindle cell squamous cell carcinoma, which this turned out not to be. Given the terse description given in the short summary ("lung nodule") I consoled myself by thinking that if I had been informed that the lung nodule was peripheral I would have had a fighting chance, but to my consternation reading further on in the case presentation it turned out to be a central lung nodule. I always used as a rule of thumb that mesotheliomas usually don't metastasize but here again my ignorance was revealed. At least the immunos were on the right side of the truth. Another case providing much food for thought. I note in the references that Giovanni Falconieri described this chain of events 25 years ago- must have used EM since I don't know what immunostains were available then.

Ira Bleiweiss - Wow!. Mesothelioma can do anything.

Alberto Cavazza – A nice case, with a combination of rarities! Metastases as the first clinical presentation of mesotheliomas are quite rare: I remember I have seen a few cases in lymph nodes, in the lung and in the skin.

Thomas Colby - Malignant sarcomatoid neoplasm. Morphologically, I think this could be compatible with a (somewhat poorly-differentiated) mesothelioma with spindling. Since this appeared to present as a lung nodule, I would also be concerned about a metastatic sarcomatoid lung carcinoma and I would probably have done some additional immunostains including more mesothelial markers and more carcinoma markers. Calretinin by itself is not all that specific.

Kum Cooper - Thank you for this very interesting case. Mesothelioma was not in my differential given the pulmonary nodule. In fact I thought that this represented a metastatic spindle cell squamous cell carcinoma. Thank you for the reminder that mesothelioma may present as a parenchymal nodule.

Hugo Domínguez Malagón – Sarcomatoid mesothelioma, I agree with the diagnosis.

Goran Elmberger – Tricky case. A bit unusual age and sex. Any history of asbestos exposure?

Giovanni Falconieri - Great case, Mariapia. Agree with your interpretation. My experience still remains that of >25 years ago when I reappraised the autopsy mesothelioma repository at the University of Trieste, still one of the largest available.

Franco Fedeli - Rare clinical presentation of mesothelioma. In addition to your discussion, I think that despite the growing number of reports about the recognition of gene translocation in mesothelioma, the best and most helpful molecular signature of this tumor is the homozygous deletion of p16, especially useful in differential diagnosis with benign mesothelial proliferations, along with the assessment of BAP1 immunohistochemically.

Cyril Fisher - Rare presentation of intracranial metastasis of mesothelioma. It would not have been my first thought on the brain tumor biopsy alone. It seems that mesothelioma can metastasize to almost any location.

Andrew Folpe - Without IHC, this is just a malignant spindle cell tumor. I don't know that I have ever seen a mesothelioma presenting with brain mets.

Jerónimo Forteza Vila - The invaginated tumor is unusual.

Maria Pia Foschini - I hope that you find this case interesting. On presentation we missed the correct diagnosis, and interpreted it as a metastasis from lung sarcomatoid carcinoma.

Masaharu Fukunaga - Welcome Dr. Foschini**.** The HE histology of the brain tumor seemed to be leiomyosarcoma. Thank you for the interesting case.

Jason Hornick - Amazing presentation.

Thomas Krausz – I agree that the clinical is unusual for malignant mesothelioma. I also agree that this sarcomatoid neoplasm is consistent with metastasis from the sarcomatoid component of biphasic mesothelioma. Calretinin can be positive in squamous cell carcinomas including sarcomatoid ones. I assume WT1 was positive in the epithelioid component of mesothelioma.

Janez Lamovec - It is impossible to diagnose this malignant spindle cell tumor correctly without history and immunostains.

Thomas Mentzel – Impossible case without the lung lesion and immunohistochemistry.

Markku Miettinen - Very good for sarcomatoid mesothelioma (geographic necrosis, spindle cells).

Delia Perez Montiel - Mesothelioma is clinically very symptomatic tumor, generally, as Maria said, initial presentation as brain metastasis is very rare. From now on I must include mesothelioma in the differential diagnosis of unknown primary.

Fredrik Petersson - As you say, most likely metastasis from a "pseudocarcinomatous mesothelioma".

Santiago Ramón y Cajal - Agree with the diagnosis. Without knowing the story my diagnosis was metastatic sarcomatoid carcinoma. With the clinical history, sarcomatoid mesothelioma.

Juan Rosai - We have also seen cases of malignant mesotheliomas presenting as lymph node metastases (Sussman J et al Am J Surg Pathol 1990, 14:819-828).

Brian Rubin – Very interesting presentation of mesothelioma presenting as metastasis of unknown primary to brain. When I looked at the slide I thought it might be gliosarcoma with metastasis to lung. Not sure if this is real but I've noticed that when mesothelioma metastasizes to bone, it is sarcomatoid in the few cases I've seen.

James Strauchen - Sarcomatoid malignant mesothelioma. The intraparenchymal presentation is fascinating!

Saul Suster – Very difficult case! I'm not sure I would have been prepared to call this mesothelioma based on the calretinin positivity alone. The clinical setting is quite wrong for mesothelioma (young age, no pleural mass, heavy smoker with lung nodule). Epithelioid mesotheliomas do not show an inverse pattern of growth (i.e., they don't generally start as an intraparenchymatous lung nodule that then secondarily invades the pleura). I think under the circumstances a more logical alternative would be a poorly-differentiated lung carcinoma with sarcomatoid features which happens to be calretinin positive. I think sometimes we put too much stock on spurious results of immunohistochemistry or in single-positive stains in an effort to make a correct diagnosis while losing sight of the clinicopathologic context.

Ady Yosepovich - OK – this is unusual, again a great lesson for including all the possibilities in the differential diagnosis. Thank you for this case.

CASE NO. 18 CONTRIBUTED BY: Giovianni Falconieri, M.D.

Abbas Agaimy – This is for me likely some type of basaloid salivary-analogue lung carcinoma. Has some superficial similarity to the anaplastic myoepithelial carcinoma reported by Fred Petersson but it is not clearly high-grade. Not fitting for a solid-pattern adenoid cystic carcinoma as well. I would favor a basal cell "adeno" carcinoma given the prominence of p63 and some central CK7 expression as well as the low-grade cytology. Thanks Falco for sharing this nice case.

Phil Allen – Endobronchial basaloid squamous cell carcinoma, left upper lobe of left lung. I have not seen one like this before. I showed it to Sonja Klebe who also had not seen one before. She thinks it is predominantly basaloid and raised the possibility of a radiation induced tumour. Did the patient receive any radiotherapy for the previous breast cancer?

David Ben-Dor – Maybe a basaloid carcinoma arising in a bronchial salivary gland?

Gerald Berry - I think the term "basaloid squamous carcinoma" is appropriate.

Ira Bleiweiss - Basaloid squamous cell carcinoma certainly fits.

Alberto Cavazza – A very strange tumor indeed. As you mention, the biphasic appearance, the fibrous stroma that seems to be part of the lesion and the relatively bland-looking cytology with low mitotic activity, are all peculiar. I think this tumor may be less aggressive than the classical lung cancer: if it is primary of the lung I would consider it as a peculiar low-grade malignancy, but I suggest to carefully exclude clinically the possibility of a metastasis. In particular, this tumor reminds me an ameloblastoma/adamantinoma; any positive pertinent clinical history?

Thomas Colby - A very peculiar tumor indeed. Despite the relative low-grade/bland appearance of the cells, it does appear to be infiltrative into the lung, and I agree that it is a carcinoma, and basaloid squamous carcinoma is not an unreasonable diagnosis. Without any history, I wondered about peculiar metastatic carcinoma, from the skin, adenxae, or salivary gland. Falco, I have not seen a case exactly like this.

Kum Cooper - Initially I too wondered about a cutaneous BCC!!! However, my final thought is whether this could represent a salivary-gland carcinoma given the endobronchial location, low grade and non-aggressive nature e.g. basal cell adenocarcinoma.

Hugo Domínguez Malagón – Never seen a similar case. The neoplasia is by histology an endobronchial basaloid squamous cell carcinoma with desmoplastic reaction and invasion to the periphery. Differential diagnosis includes solid type adenoid-cystic carcinoma, adamantinoma and NUT+ carcinoma.

Goran Elmberger – Unusual histology. Don't recall seeing his before. A bit curious if further IHC staining might disclose a subtle biphasic salivary gland myoepithelial pattern since I submitted what I believe is a SGT in lung in this seminar. Sometimes ME phenotype is hard to appreciate and for that reason I usually do even more markers. Admittedly S100 and caldesmon negativity is not very promising.

Franco Fedeli - Great case. I've never seen one like this. Have you ruled out a salivary gland origin of this cell proliferation?

Cyril Fisher - That seems a good diagnosis in keeping with the morphology.

Andrew Folpe - I don't have a better name than that.

Jerónimo Forteza Vila - Very interesting case.

Maria Pia Foschini - It is a polypoid lesion, with an epithelial and stromal component. The epithelial component shows basaloid features, with the classical peripheral palisaded features, but the cells have bland nuclear features, mitoses are present, but very rare. Some inflammatory cells are present. In addition, there are small areas of typical, invasive squamous cell carcinoma. I wonder if this invasive squamous cell carcinoma can arise in a benign endobronchial papilloma.

Masaharu Fukunaga - I have never seen this type of tumor in the lung. I would call it basosquamous cell carcinoma.

Ondrej Hes - Never seen, but we have 2 cases in registry, both diagnosed by Michal Michal.

Jason Hornick - I have not seen a tumor quite like this previously.

Thomas Krausz – I agree with the diagnosis of basaloid squamous cell carcinoma of the bronchus. Lin O et al. Arch Pathol Lab Med 1995; 119:1167-1170. The fibromatous stroma is somewhat unusual.

Janez Lamovec - To me this carcinoma is predominantly basaloid and, except for some foci with only an abortive squamous cell differentiation, basaloid-squamoid?

Thomas Mentzel – It looks like basal cell carcinoma (have you stained it for BerEP4?).

Markku Miettinen - Has an ameloblastoma-like look, but the diagnosis of squamous cell carcinoma is appropriate, looks low-grade.

Delia Perez Montiel - In cervix I have seen some cases like this with basaloid and squamous appearance and desmoplastic change in the stroma. I don´t know if it is described in other organs.

Kyle Perry - I've never seen a case like this, although I can appreciate the basaloid qualities of the tumor.

Fredrik Petersson - Why is this not a salivary-gland type, low-grade basal cell adenocarcinoma?

Santiago Ramón y Cajal - Agree with the diagnosis. Thank you very much.

Juan Rosai - I like very much Saul's diagnosis of endobronchial basaloid-squamous cell carcinoma.

Brian Rubin – After looking at the first 17 cases in this seminar I was thinking that this might be an unusual metastatic cystosarcoma phyllodes! I haven't seen a similar case but I don't look at a lot of pulmonary pathology. I shared the case with one of our pulmonary pathologists and he has not seen anything similar either.

James Strauchen - A most unusual intrabronchial squamous cell carcinoma!

Saul Suster – Falco, given the comment from Dr. Hes that they have 2 similar cases in their files I would urge you to get together with him and put your cases together for a publication!

Paul Wakely – I'm afraid I am of little help Falco since I cannot do better than the diagnosis you have issued.

Ady Yosepovich - There is some resemblance to the basaloid type of adenoid cystic carcinoma, can be studied by specific translocation.

CASE NO. 19 CONTRIBUTED BY: Anais Malpica, M.D.

Abbas Agaimy – Thank you for sharing this pretty case, Anais. Initially I thought of the myxoid nodular changes of myometrium associated with NF1 but your case is more cellular. I agree with ESS, but would think of molecular confirmation due to the unusual pattern as some nodules seem as if merging with adjacent myometrium.

Phil Allen – CD10 and progesterone receptor positive endometrial stromal sarcoma with myxoid features, uterus. The recent changes in the classification of endometrial stromal sarcoma based on the presence or absence of the YWHAE-NUTM2 gene rearrangement is outlined in Histopathology 2015; 67:1-19. I do not know what this recent change implies for this patient, who has only had a myomectomy. Should she receive progesterone therapy alone, or a hysterectomy with or without bilateral oophorectomy, with or without egg preservation?

David Ben-Dor – this is a myxoid tumor obviously dissecting through the myometrium. The tumor cells themselves look rather bland and overall there is a "tissue culture" look. I've seen a few cases of endometrial stromal tumor nodule in which the cells looked smaller and were closely packed together than in this case and of course they had the spiral arterioles which I didn't find here. My cases were nodules and I remember struggling to see if I hadn't overlooked any possible small area of invasion, but in rereading the old AFIP fascicle on uterine tumors (IIIrd series, 1991, pg 100) it is clearly stated that in cases of low grade endometrial sarcoma, "the infiltration is never subtle but is almost always extensive at the microscopic level". Here the existence of invasion obviously isn't an issue but in general apparently one doesn't need to get too obsessive, neurotic or paranoid over this issue.

Ira Bleiweiss – Agree.

Alberto Cavazza – A variant of endometrial stromal sarcoma I always feared to encounter in my routine! Thanks for sharing this beautiful case.

Thomas Colby - Agree with diagnosis.

Kum Cooper - Thank you Anais, I cannot recall seeing an ESS with such extensive myxoid change. I too would have done the stains.

Hugo Domínguez Malagón – Very good case of myxoid endometrial stromal sarcoma, thank you.

Goran Elmberger – Interesting variant.

Giovanni Falconieri - Thank you for this contribution, Anais. I may not comment since I have little experience with Gyn path, yet I find this of outstanding educational value.

Franco Fedeli - Interesting case. In my opinion, just the immunohistochemical stains can help differential diagnosis with myxoid muscular lesion.

Andrew Folpe - Agree. Excellent case.

Maria Pia Foschini - The present case of endometrial stromal sarcoma shows focal but well evident myxoid stroma. Oliva published recently a comprehensive review on mesenchymal tumours of the uterus (International Journal of Gynecological Pathology 2014; 33:374-384), and underlined that the myxoid and fibroblastic feature are unusual.

Masaharu Fukunaga - Thank you for sharing the interesting and rare case. I agree.

Jason Hornick - Very nice case.

Thomas Krausz – Great case. The myxoid feature in this case is striking. I am so pleased to have a copy in my teaching collection. Thank you very much.

Janez Lamovec - A very tricky lesion with such a myxoid appearance. I wonder whether surrounding myometrium is O.K.; somewhere there seem to be eosinophilic cytoplasmic inclusions present.

Thomas Mentzel – A quite difficult case and the differential diagnosis includes a number of myxoid mesenchymal neoplasms.

Markku Miettinen - Agree on low-grade stromal sarcoma.

Delia Perez Montiel - This case is very rare, mixoid change in low grade ESS, when present are usually focal. I have never seen a case with this extensive myxoid pattern.

Kyle Perry - This is an interesting variant of endometrial stromal sarcoma.

Fredrik Petersson - Some areas slightly reminiscent of extraskeletal myxoid chondrosarcoma. Convincing IHC. Would have been interesting to see IHC for CD31; the typical vascular pattern of low-grade stromal sarcoma is not obvious on H&E.

Santiago Ramón y Cajal - A very interesting case. Thank you very much. I was wondering if after myomectomy will be indicated a hysterectomy. Myxoid areas show epithelioid cells, partially rhabdoid.

Juan Rosai - I guess every type of soft tissue deserves to have a "myxoid variant".

Brian Rubin – Interesting case of myxoid ESS. Seems like the cases I've seen before had more focal myxoid stroma than the current case. I wonder if it might contain an unusual gene fusion.

James Strauchen - Myxoid endometrial stromal sarcoma. Fabulous!

Ady Yosepovich - very nice case, thank you for sharing.

CASE NO. 20 CONTRIBUTED BY: Anais Malpica, M.D.

Abbas Agaimy – Very rare case of MST of ovary, indeed same morphological and genetic spectrum as pancreatic SPN and some testicular stromal tumors (we reviewed and discussed these aspects in a recent paper on beta-catenin in Adv Anat Pathol, 2016). Thanks again Anais for this great case. Looking to reading Michal's comments on this case?

Phil Allen – Microcystic stromal tumour, right ovary. There is very little microcystic tumour in my slide.

David Ben-Dor – I see an atrophic ovary in keeping with pt age with foci of dense fibrosis containing a few hemosiderin granules, and with discrete bland cellular infiltrates. One surface painted with ink looks like the surface of a cyst with underlying sclerosis. I don't see a mass so I presume that the tumor described is represented on this slide by these infiltrates which have a few tiny cysts.

Alberto Cavazza – Thanks for showing this rare tumor. In the ovary, β-catenin positivity is shared with solid pseudopapillary neoplasm, but if I understood correctly the majority of the experts think mycrocistic stromal tumor is a different entity.

Thomas Colby - Agree with diagnosis, but I probably will not recognize the next one of these that I see.

Kum Cooper – Wow, another treat! Thank you. Read about this entity but not seen one.

Hugo Domínguez Malagón – Microcystic stromal tumor. Sorry I did'nt get this one. In my slide no microcysts are present, under the surface there is a thin layer of hyalinized material (almost like osteoid) and above that polygonal cell in a myxoid stroma with pink vacuolated cytoplasm.

Goran Elmberger – Only small areas of recognizable tumor left in my sections but truly microcystic pattern. Diagnostic challenge for many reasons.

Giovanni Falconieri - Again, Anais, another impossible case for me. I feel so frustrated, but thank you for the submission

Franco Fedeli - Very rare case. I've never seen one like this.

Andrew Folpe - Fascinating. I was not aware of this. I'm ready for the next one!

Jerónimo Forteza Vila - I agree with the diagnosis.

Maria Pia Foschini - Thank you for showing this interesting and rare case.

Masaharu Fukunaga - A beautiful case of ovarian microcystic stromal tumor, thank you, Dr. Malpica.

Jason Hornick - Beautiful case - thank you for sharing.

Thomas Krausz – Anais, thank you very much for another special treat. I assume the FOXL2 is not mutated in these tumors.

Janez Lamovec - In my slide, there are only a few foci in which microcystic pattern could be appreciated; however, this is the first example of this recently described tumor that I've seen.

Thomas Mentzel – There are scattered enlarged cells with enlarged nuclei, what represents most likely a degenerative phenomenon.

Delia Perez Montiel - Thank you very much for this nice example of microcystic stromal tumor.

Kyle Perry - Great case of microcystic stromal tumor. The psammomatous calcifications present appear to have been reported in a minority of cases

Fredrik Petersson - Was not aware of this. Thanks Anais.

Santiago Ramón y Cajal - Thank you very much for the case. Very enlightening.

Juan Rosai - I presume most of these tumors were called "ovarian microcystic stromal tumors, not otherwise specified" by the solons of this field before 2009.

Brian Rubin – Thanks – very educational. I never saw a case of this before.

James Strauchen - Never even heard of this one! Thank you!

Paul Wakely – Fascinating case Anais. I have just a small focus of this tumor on my slide.

Ady Yosepovich - thank you for sharing this unusual case.

CASE NO. 21 CONTRIBUTED BY: Volkan Adsay, M.D.

Abbas Agaimy – Great case of herpes colitis, very impressive, some time ago I stopped staining IBD cases with unexplained exacerbation or therapy resistance for HSV as I never have seen a positive case, now I have to rethink of this and look for some morphological "clues" again!!! Thanks Volkan for great case.

Phil Allen – Herpes associated massive ulceration in a total colectomy specimen from an ulcerative colitis patient undergoing intensive immune suppressive treatment. In the absence of an elixir of youth that would allow me to perform like the exceptionally skilled young colleague who spotted the virocytes, I will have to stain all future ulcerative colitis specimens from immune suppressed patients for herpes virus. Thanks for the reminder of my age, which must have made me miss the virocytes.

David Ben-Dor – knowing that as a seminar case there should be something unexpected and not simply colitic ulcers covered with fibrinopurulent debris, I initially searched the debris very carefully thinking that maybe I'll find an amoeba. I vaguely remembered seeing something big and darkly staining, but after reading the comment I went back and couldn't find anything that would make me think of a virus. I agree with everything said in the comment, including the importance of morphology, and also with your young colleague being "highly skilled" (as stated).

Gerald Berry - A nice reminder to consider other viral etiologies besides CMV!

Ira Bleiweiss - In all honesty I would not have picked this up and left it as U.C.

Alberto Cavazza – Spectacular case! The degenerative-looking cells reminded me adenovirus more than herpes, but I submit myself to immunostains. Also to me, the character of the necrosis (and I suspect also the number of the infected cells) suggest that the virus plays a significant role in the present disease.

Thomas Colby - Agree with diagnosis. I, too, thought the pattern of ulceration here suggested viral-type ulceration and necrosis, and, in fact, found one cell that appears to have an inclusion (not perfect, but close) after going back following reading the description and looking very carefully. This does not look like usual-type ulceration as one sees in CUC.

Kum Cooper - Nice case Volkan. Yes my case viral inclusions in lymphocytes and macrophages too. I presented that case at the first International AMR seminar in Italy.

Hugo Domínguez Malagón – viral-type inclusions in the degenerative cells are very difficult to pick upiiii

Goran Elmberger – Interesting and potentially important given antiherpetic drugs. I have difficulties seeing viral cytopathogenic signs in my levels. Perhaps focal finding or I need the help of young colleague of yours.

Giovanni Falconieri - Nice case, Volkan. I must confess that I have had hard time in recognizing viral CPE. A great contribution. Thank you

Franco Fedeli - It's really insidious this "man from Istanbul". In my opinion, this case suggest to think about herpes virus infection in any case with eosinophilic necrotic nuclei.

Cyril Fisher - Excellent observation. I expect I would have missed this.

Andrew Folpe - Thanks for the nice teaching case.

Jerónimo Forteza Vila - The morphological findings are insufficient for diagnostic. The case is difficult without immunohistochemistry.

Maria Pia Foschini - In this case I found very difficult to detect the viral changes on H&E. It is interesting to know, as most of the viral lesions in treated ulcerative colitis are CMV related, and these HSV related modifications can easily be undetected.

Masaharu Fukunaga - This is my first time to see the herpes infection with ulcerative colitis. Finding virus-inclusions are very difficult to point out. Thank you very much the excellent case and inviting us to the reception in Seattle, Volkan.

Jason Hornick - Great observation Volkan - I fear I would have entirely missed the infection.

Thomas Krausz – Volkan, your young pathologist deserves not only a bonus but also promotion.

Thomas Mentzel – Congratulations to your young colleagues, I`m totally missed these scattered purple cells…

Markku Miettinen - Fulminant colitis, Herpes is difficult to see and I wonder how many are missed by not doing immunostains.

Delia Perez Montiel - With so much inflammation is difficult to suspect viral inclusions and as you say in a context of inflammatory colitis not suspected Herpes, congratulations to your young colleague.

Fredrik Petersson - Saw those degenerative cells, reflected on virus (CMV, adeno..), but dismissed them – never got the "herpes feeling".. Then read the text. Wow. Lesson: Can never rest and "just because you're not paranoid, it doesn't mean they are not out to get you" !

Santiago Ramón y Cajal - A very illustrative case. I wondered if you could discern whether the herpes virus was type 1 or type 2.

Murray Resnick - Fascinating case. Have to start paying more attention to atypical cells in the ulcer bed… The discussion raises an important question as to whether Herpes contributed to the ulceration or whether the virus is merely colonizing IBD ulcers. As many of you are aware there is a significant literature on CMV infection in IBD patients and much discussion as to the contribution of CMV to refractory disease and the role of IHC in its detection. I also wonder whether the atypical cells were epithelial or stromal in origin. Extrapolating from the esophagus one typically sees the inclusions in the intact epithelium at the ulcer edge. Was serology performed?

Juan Rosai - Nice case. It reminded me of a case I saw in 1974, shortly after having moved to the U. of Minnesota (Foucar E. et al, Am J Clin Pathol 1981; 76:788-801)

Brian Rubin – I of course didn't see the virally infected cells until I read Volkan's comments. Once prompted I was able to find them. It's an interesting point about whether the infection is incidental or pathogenic. I thought about it and not sure how to prove it outside of an animal model or similar model.

James Strauchen - An interesting phenomenon in steroid treated UC patients!

Paul Wakely – Virally infected cells are very easy to overlook among all this necropurulent debris. In fact, I was not convinced they were there till you told me the immunostain was positive.

CASE NO. 22 CONTRIBUTED BY: Saul Suster, M.D.

Abbas Agaimy – Spectacular case, thanks Saul for sharing the slide, this must be vanishingly rare and the non-thymologist would otherwise never see such a case.

Phil Allen – Atypical thymoma with rhabdomyomatous differentiation. I reckon I saw one of these about 45 years ago at the AFIP, courtesy of Lisa Hochholzer, who worked in the pulmonary and mediastinal section. I have not seen any more until this case. The rhabdomyomatous differentiation is unequivocal.

David Ben-Dor – I see the small spindle cells, the squamous islands, and the rhaboid cells. Taken on their own I could see where the squamous cells would look atypical and in a small needle biopsy without the benefit of context could be misinterpreted as malignant. The rhabdoid cells could be misinterpreted as dyskeratosis furthering the confusion.

Gerald Berry - Wow! I will now be on the lookout for "rhabdoid cells" in my next thymoma.

Ira Bleiweiss – Agree.

Alberto Cavazza – I can just say that I enjoy very much this case.

Thomas Colby - Agree with diagnosis. What a spectacular case. I was surprised that Saul mentioned the WHO classification in his discussion of the tumor. I guess we all mellow.

Kum Cooper - Thank you Saul. Much enjoyed. Never thought that I would see a case.

Hugo Domínguez Malagón – Rhabdomyomatous thymoma, spectacular case, thank you Saul.

Goran Elmberger – Great case. Thanks for sharing.

Giovanni Falconieri - Great case, Saul. Another beautiful collectible example. I think I have a recut from your series, when we shared Sinai cases at times.

Franco Fedeli - Thank you for sharing this rare case. Have you ever seen a malignant transformation of the rhabdoid component in this neoplasm? In addition, it seems to me that the rhabdoid component is associated with squamous cells. What do you think about my thought?

Cyril Fisher - What a rarity, but very distinctive appearance. Very nice slide.

Andrew Folpe - Wow!! I remember reading that paper, but I did not think I would get to see a case of one. Spectacular.

Jerónimo Forteza Vila - A beatiful, spectacular and unusual case.

Maria Pia Foschini - This interesting case of rhabdomyomatous thymoma, remembers the presence of cells with striated muscle differentiation in the fetal thymus.

Masaharu Fukunaga - Rhabdomyomatous thymoma. I have never seen this type of tumor, thank you for sharing case.

Jason Hornick - Wow - beautiful case Saul.

Thomas Krausz – What a fantastic case. I certainly enjoyed looking at it.

Janez Lamovec - I have never seen one before. Thank you, Saul.

Thomas Mentzel – What a case! Many, many thanks.

Markku Miettinen - Nice rhabdomyomatous thymoma. Immuno is convincing. Without doing it could even dismiss those rhabdoid cells of squamoid epithelial origin.

Delia Perez Montiel - Agree, beautiful case.

Fredrik Petersson - Nice case! Was not aware that Mib-1 index now impacts thymoma classification.

Santiago Ramón y Cajal - A case seminar. Thank you very much.

Juan Rosai - Spectacular case of the entity first described by Kristin Henry in 1972 (Br J Dis Chest, 1972; 66:291-299).

Brian Rubin – Very beautiful case. However, are you sure those "rhabdomyomatous" cells are benign? I've seen embryonal rhabdomyosarcomas with very similar to identical appearing cells and also in MPNST. They look different than the cells of the average rhabdomyoma which are bigger and have more abundant cross-striations.

James Strauchen - Fabulous myoid cells!

Ady Yosepovich – Thank you for this illustrative case

CASE NO. 23 CONTRIBUTED BY: Bruce M. Wenig, M.D.

Abbas Agaimy – Very unusual and great case Bruce. I would consider a primary thyroid neoplasm a diagnosis of exclusion in this case and suggest whole body imaging + history. The pattern is similar to grade 3 MFH. So this might be a thyroid metastasis of a soft tissue sarcoma of the extremities or from the neck soft tissue. Some metastatic pleomorphic liposarcoma might be pretty identical without lipogenic features.

Phil Allen – High grade myxoid sarcomatous thyroid neoplasm, probably an anaplastic carcinoma, in a male aged 47. I agree with Bruce's interpretation but have taken a slightly stronger line, replacing the "possible" with a "probable".

David Ben-Dor – Since I've already come across a case of myxofibrosarcoma in this seminar I can't help but see some resemblance. Here the myxoid areas look deceptively bland but there are solid areas that are high grade malignant. I don't know whether in tumors such as these where the cells run amok and break all the rules it pays to seek any logic.

Gerald Berry - I agree that this likely represents a thyroid neoplasm and I think your designation is optimal.

Ira Bleiweiss – Agree.

Alberto Cavazza – I have not a firm opinion. It is not clear to me if some follicles have nuclear features sufficient to qualify as papillary carcinoma, maybe not. Maybe there are focal areas more epithelioid-looking, but again I am not sure. In any case, I favour an anaplastic/sarcomatoid carcinoma, probably of thyroid origin.

Thomas Colby - Agree with diagnosis. In my blissful ignorance, I simply lump all high-grade tumors at this site under anaplastic carcinoma of the thyroid.

Kum Cooper – Bruce, I interpreted this as a high grade myxofibrosarcoma involving the thyroid gland. Another "man from Istanbul"?

Hugo Domínguez Malagón – Sarcomatoid (myxoid MFH-like) carcinoma. As you stated, the lymph node metastasis and the keratin positivity favor carcinoma over sarcoma.

Goran Elmberger – No better idea. Support from molecular data including mutations and translocations specific for thyroid malignancies?

Giovanni Falconieri - I agree with you, Bruce. As a knee-jerk reflex I would also go for anaplastic carcinoma of the thyroid exhibiting remarkable myxosarcomatoid features. Great contribution.

Franco Fedeli - Very challenging case. As you, I guess that your case could represent a weird example of undifferentiated (anaplastic) thyroid carcinoma, especially because of the presence of nodal metastasis and the focal expression of thyroglobulin. Could be useful to perform molecular testing in order to verify the presence of the most common molecular alterations of well-differentiated thyroid carcinoma?

Cyril Fisher - It does look like myxofibrosarcoma but given the IHC findings as well as the features described, myxoid spindle cell carcinoma seems a better fit.

Andrew Folpe - Probably anaplastic thyroid CA. If ever there was a diagnosis that needed a specific molecular finding, it is anaplastic thyroid CA.

Jerónimo Forteza Vila - Maybe Ki-67 should be higher in an anaplastic carcinoma.

Maria Pia Foschini - I agree with the diagnosis of a highly malignant neoplasm, with myxoid sarcomatous features. In the absence of any other possible primary, and in light of positive immunostaining for thyroglobulin and cytokeratins, the possibility of a primary thyroid carcinoma seems plausible. The presence of myxoid stroma is unusual. Many years ago we reported on three cases of sarcomatoid carcinomas arising in the breast, larynx and cervix uteri, showing similar strong myxoid stroma (Hum Pathol. 1990 Aug;21(8):859-65.). Therefore, it seems that these spindle cells immersed in myxoid stroma can be a feature in the morphological spectrum of sarcomatoid carcinomas.

Masaharu Fukunaga - High grade malignant tumor, anaplastic carcinoma is most likely. Thank you Bruce for the unusual tumor.

Jason Hornick - Agree with your interpretation - seems most likely to be anaplastic carcinoma.

Thomas Krausz – Yes, I was considering some kind of sarcoma first; however, given the immunoprofile and the overall morphology, I agree this is more consistent with a variant of anaplastic carcinoma.

Janez Lamovec - To me this tumor looks more like a sarcoma (?myxofibrosarcoma); of course I cannot explain the presence of thyroglobulin and keratin positive cells, however, in epithelioid variant of myxofibrosarcoma keratin and desmin positive cells were described in a few cases.

Thomas Mentzel – Despite the age of the patient the diagnosis of poorly differentiated, metaplastic carcinoma (sarcomatoid carcinoma) is the best in my opinion.

Markku Miettinen - Agree that anaplastic sarcomatoid thyroid carcinoma is the best diagnosis.

Delia Perez Montiel - Anaplastic carcinoma seems to be the best diagnosis rather than a sarcoma; clinical behavior supports the diagnosis of carcinoma.

Fredrik Petersson - Looks like a very high grade myxofibrosarcoma to me. I guess the IHC points towards an epithelial origin (?).

Santiago Ramón y Cajal - Agree with the interpretation. I am in favor of a sarcomatoid carcinoma.

Murray Resnick - Very unusual case. Agree that this may represent an anaplastic thyroid carcinoma. Would be happier if there was focal TTF as opposed to focal thyroglobulin positivity.

Juan Rosai - Very thoughtful discussion and conclusions. I have nothing to add.

Brian Rubin – I agree with your logic, rationale and diagnosis. With difficult material, you have to pile up the evidence for each diagnosis and pick the one that fits the best/has the most evidence.

James Strauchen - Putative myxoid anaplastic thyroid carcinoma! Why not!

Saul Suster – I think this is an unusual variant of anaplastic carcinoma of the thyroid. Dr. Rosai used to teach that all sarcomatoid-looking tumors of the thyroid should be regarded as anaplastic carcinoma until proven otherwise. I think you've proved otherwise.

Paul Wakely – After that extensive immunostaining work-up, I have to agree with you Bruce, and call this an ATC with myxoid stroma. It would have been nice (and more convincing) had the PAX-8 been positive.

Ady Yosepovich - very exceptional, would prefer a sarcoma according to morphology.

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

Abbas Agaimy – High grade malignancy with large cells having voluminous foamy or bubbly cytoplasm and diffuse pleomorphic primitive cells dissecting between dermal collagen. Extensive necrosis. I would think of some variant of liposarcoma (such as dediff with hibernoma-like features or epithelioid/PEComa-like pleomorphic liposarcoma). Melanoma is surely always a possibility? Other less likely DDx PEComa? CK positive?

Phil Allen – High grade, diffusely infiltrating malignant tumour with multi-vacuolated cells and necrosis, subcutis and dermis, neck. The term malignant fibrous histiocytoma was invented for tumors just like this. The multi-vacuolated cells are clearly histiocytic rather than lipoblastic and there is plenty of fibroblastic differentiation for good measure. While pathologists argue over the name, I would advise the surgeon to hope that it is not a secondary and to widely re-excise the area as if it were a primary sarcoma. I think it has considerable metastatic potential.

David Ben-Dor – my immediate gut reaction is that these are malignant cells with ground glass cytoplasm. Malignant reticulohistiocytosis?

Alberto Cavazza – Sorry, I have no good ideas. A possibility could be a sort of histiocytic sarcoma. The epidermis has a minimal melanocytic proliferation, and a peculiar melanoma with desmoplastic and balloon features may be a further idea.

Thomas Colby - It is malignant, it is in the skin and soft tissue, it has balloon cells, infiltrates as single cells in the collagen, and if it isn't a balloon cell melanoma, I am bereft.

Kum Cooper - To use the old adage MFH?

Hugo Domínguez Malagón – Perhaps a form of atypical fibroxanthoma, I could not find mitotic activity.

Goran Elmberger – Difficult. Dedifferentiated LPS? Malignant granular cell tumor?? Histiocytic malignancy? Melanoma? Any help from markers?

Giovanni Falconieri - No clue whatsoever!

Franco Fedeli - In my opinion, immunohistochemical findings are essential to resolve this case. In differential diagnosis I would consider melanoma and dedifferentiated liposarcoma.

Andrew Folpe - Xanthomatous undifferentiated pleomorphic sarcoma arising in association with some sort of superficially located, fibroblastic precursor lesion.

Jerónimo Forteza Vila - Pleomorphic liposarcoma, with a lot of necrotic areas.

Maria Pia Foschini - The lesion is located in the sub-cutaneous fat. It is a malignant tumor, mainly composed of large and finely vacuolated cells, with necrotic areas. At the periphery, spindle atypical cell and areas of fat tissue with atypical cells are present. Even if the lesion is superficial, I would favor the diagnosis of liposarcoma with hybernoma-like features.

Masaharu Fukunaga - It is very interesting; I favor dedifferentiated liposarcoma.

Janez Lamovec - Very unusual, extremely pleomorphic sarcoma-like tumor with rare mitoses – we saw 2 cases of somewhat similar tumors that were excised with no additional treatment – at the last follow-up the patients were alive and well 10 and 16 years after surgery.

Markku Miettinen - Pleomorphic sarcomatous neoplasm with an unusual pseudoxanthomatous morphology. Would go intermediate grade by formal grading because of necrosis. Immunohistochemical studies to rule out PEComa (HMB45, MelanA) would be useful. Even as PEComa it would be malignant. Should be excised completely with negative margins, along with adequate follow-up.

Delia Perez Montiel - Malignant fibrous histiocytoma with atypical fibroxanthoma like features?

Kyle Perry - Dedifferentiated liposarcoma with "homologous" lipoblastic (and hibernomatous?) differentiation.

Fredrik Petersson - Could this be a funny melanoma with a desmoplastic component and a bizarre balloon cell component. (I thought I saw some melanocytic atypia in the epidermis…).

Murray Resnick - Given the age of the patient and the sun damaged skin would favor a balloon cell melanoma.

Juan Rosai - Pleomorphic sarcoma, NOS (I am ashamed I cannot go further).

Brian Rubin – Based on anatomic location (neck, subcutis) I'd wonder about a balloon cell melanoma. The overlying epidermis did not contain any in-situ lesions but there was solar damage in the superficial dermis. If S-100 / SOX10 are negative, then I'd think about a PEComa so HMB-45 and myogenic markers. If those are negative, then I'd probably end up in the undifferentiated pleomorphic sarcoma category. There are atypical spindle cells in the adjacent dermal tissues so it's probably undifferentiated pleomorphic sarcoma.

Paul Wakely – I may be way off, but this slide reminds me of the epithelioid variant of pleomorphic liposarcoma – a tumor described by Markku and Dr. Enzinger many years ago.

Ady Yosepovich - Morphologically I favor sarcoma, of course per exclusion on immunohistochemical stains.

Saul Suster – My case: I diagnosed this case as an undifferentiated pleomorphic high-grade sarcoma. Based on the pleomorphic and lipoblastic tumor cells present in the surrounding fat and connective tissue, I raised the possibility of a dedifferentiated liposarcoma in the differential diagnosis. However, MDM2 immunostains and MDM2 FISH were negative. Interestingly, p16 was strongly positive in the atypical spindle and pleomorphic cells. Stains for S-100 protein, HMB45, melanoma cocktail, SMA, and cytokeratins were negative. The most remarkable aspect of this case is the areas containing sheets of large xanthoma-like cells. There are not true xanthoma cells and I believe these are malignant cells and part of the tumor (the nuclear pleomorphism and prominence of nucleoli would be unacceptable for conventional histiocytes). The prominent perinuclear cytoplasmic vacuolization seen in many of these cells are highly suggestive of lipoblastic differentiation. I still don't know what this tumor is and "undifferentiated sarcoma" is a convenient term of desperation, but it looks so distinctive that I wish we had a better name for it!