COMMENTS TO AMR SEMINAR #63

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

Phil Allen - Inflammatory angiomyolipoma of the liver. This diagnosis seems to me to be inescapable because of the fat, blood vessels, HMB 45 positive cells and the inflammation. The questions as to whether it is a variant of angiomyolipoma of the liver, a variant of inflammatory myofibroblastic tumour or an IgG4 related disease appears to be still unresolved. Thanks very much for the contribution. Naturally, I was completely unaware of the disease.

Carlos Bacchi - Incredible case! I was very convinced by morphology only that the diagnosis was going to be IgG4-related disease. I don't know if I had this case in my hands I would have requested melanocytic markers, probably not. I was particularly impressed by the presence of medium-sized thick-walled veins within the lesion with complete lumen obliteration by inflammatory cells and fibrosis. This is a very educative case. Thanks.

David Ben-Dor - I commend you for the detailed exposition of the facts of the case and for the learned comments. I'm curious as to why HMB-45 was ordered in the first place. The cytological description of the HMB-45 positive cells as being variably spindled and/or dendritic would bring to mind the histiocytic cells which participate in reactive lymphoid follicles. Maybe these are sometimes positive for HMB-45 and no one thought to look before now? Are there really fat cells in the inflammatory infiltrate, or can these be lipid vacuoles resulting from destruction of hepatocytes and subsequent liberation of fatty cytoplasmic substances? Whatever this really is, I admire the creativity and imagination reflected in the solution proposed.

Michele Bisceglia - Inflammatory angiomyolipoma of the liver with features overlapping with IgG4-related pseudotumor. Hepatic angiomyolipoma is in of itself a rare tumor and inflammatory angiomyolipoma is even more rare and in this case almost invisible without immunophenotyping. This tumor reunites features of inflammatory angiomyolipoma with features of IgG4-related pseudotumor. An incredible case. Indeed a fully investigated case and a brilliant diagnosis!

Ira Bleiweiss - Thanks. I was unaware of this.

Thomas Colby - A very intriguing case and excellent discussion from which I learned quite a bit. To me this is a very peculiar lesion and I probably would not have thought to do an HMB-45 although perhaps when IPT did not pan out I might have done some additional immunostains. I find the changes in the adjacent liver extremely intriguing and some that might favor some peculiar inflammatory process over inflammatory AML. This case appears to just have come out as a case report in Int J Clin Exp Pathol, 2013;6:771.

Kumarasen Cooper - Thank you Abbas for the education. I had not heard of an inflammatory AML before (although I have seen a few AMLs in the liver including one with marked nuclear pleomorphism). The IgG-4 question dove-tails into the questions raised by Volkan in the last AMR seminar (chicken or the egg?). The entity I considered was the inflammatory pseudo tumor-like FDC sarcoma described by JKCC; where the cells are EBV positive (but I notice in your comment that CD 21 and EBER ISH was negative).

Hugo Dominguez Malagon - Interesting case, mi impression was of an inflammatory pseudotumor vs IgG4 related disease.

Goran Elmberger – Got the IgG4 look-alike picture but missed the underlying angiomyolipoma without the info/ihc stains/relevant differential diagnosis in my mind. The fat is obvious on second look, as well as the IHC results. Not an easy case but still very important lesson. Wonder what else is hiding under the IgG4 sclerosing disease umbrella…Thanks!

Giovanni Falconieri - Impossible. Great case to start with. Welcome to the club and thank you for this exotic contribution.

Franco Fedeli - Inflammatory angiomyolipoma of the liver with features overlapping with igG4-related pseudotumor. This is a very interesting case. Maybe I would have called it conventional inflammatory pseudotumor, after excluding inflammatory pseudotumor-like follicular dendritic cell tumor based both on negative immunos and negative EBER-ISH. In

this case one can really suspect the IgG-4 chronic inflammatory disease based on some suggestive features (such as obliterative phlebitis and the prominence of plasma cell infiltration), but the assessment of a IgG4-related pseudotumor would have distracted you even more from the underlying angiomyolipoma.

Cyril Fisher - Remarkable diagnosis of an exceptionally rare lesion.

Christopher Fletcher - This does indeed appear to be a very subtle example of inflammatory angiomyolipoma – much more difficult to recognize than the two prior examples which I have encountered and I think that the diagnosis would have been extremely difficult without immunostains. It would be interesting to know the ethnicity of this patient – most published cases of inflammatory angiomyolipoma have been from Asian countries and the only cases which I have seen have also been in Asian patients.

Jeronimo Forteza-Vila - This was a case of differential diagnosis with lymphoma, but it is inflammatory angiomyolipoma. IgG4 positivity is evidence of a disease related to IgG4 and it is logical to think that this inflammatory disease has caused the "tumour". Then it is a pseudotumor related to IgG4, although it is difficult to explain fat and vessels, since we are dealing with liver.

Masaharu Fukunaga - It is not difficult to make a diagnosis of IgG4-related liver disease, but it is very hard to find angiomyolipoma on the H&E slide. Thank you very much for the wonderful case and the detailed description.

Allen Gown - Great case! Curious what the estimated fraction of tumor cells were that were HMB45-positive. Looks like a study might be in order to sort out the relationship of the entities in the differential diagnosis, and perhaps members of the club could collaborate on this. Hepatic angiomyolipoma is in and of itself a rare tumor and inflammatory angiomyolipoma is even more rare, and in this case almost invisible without immunophenotyping. This tumor unites features of inflammatory angiomyolipoma with features of IgG4-related pseudotumor. An incredible case. Indeed a fully investigated case and a brilliant diagnosis!

Thomas Krausz - At first inspection I was considering IgG4 related pseudotumor versus lymphoma. Reading your diagnosis and discussion with the immuno-profile of the lesion, I agree with your diagnosis. It is still puzzling to see the combination of two entities. Great case, next time, hopefully, will recognize it.

Janez Lamovec - On H&E, this appears to me as an inflammatory pseudotumor, possibly IgG4 related.

Tom Mentzel - What a case! Given the prominent inflammatory infiltrate I was thinking on an inflammatory pseudotumour of the liver, however, the mentioned expression of HMB-45 as well as the presence of thick-walled vessels and scattered lipogenic cells is convincing. Although the importance of IgG4-related lesions is probably overemphasized at the moment it will be interesting to analyse more cases in this direction, many thanks!

Markku Miettinen - Reactive process with phlebitis, cholangitis, and lymphohistiocytic-plasmacytic infiltration with fibrosclerosing background. Could not connect this with angiomyolipoma (AML) although a small number or large cells with big nuclei and abundant eosinophilic cytoplasm are present; some large cells look more like histiocytes. Many previously reported examples of inflammatory AML seem to have more of the AML component. Could this alternatively be an inflammatory process that has acquired/contains HMB45/MelanA-positive cells – I agree with Abbas that these possibilities are in the differential. It would be of interest to study inflammatory lesions of liver for HMB45 and other melanocytic markers.

Liz Montgomery - This is really interesting. I did not spot the AML component. It just looked like IgG4-related fibrosclerosing disease to me. Your discussion was really great and I will think about it the next time I see what I think is IgG4-related fibrosclerosing disease.

Fredrik Petersson - Very well demonstrated and discussed case. As stated, it is difficult to get around the HMB-45 and Melan-A expression in relation to an inflammatory variant of AML (and the differential diagnoses raised) and given that IgG4-related pathology could be perceived as an inflammatory pattern rather than a disease sui generis. I think the interpretation - diagnosis is very well substantiated. I had a focus of distinct obliterative angiitis on my section.

Juan Rosai - I have to confess that the idea of an inflammatory angiomyolipoma of the liver did not cross my mind, in part because I was unaware of the entity and in part because when looking again at this slide, I have trouble in identifying the components that define that tumor. I don't see good large epithelioid cells, the amount of adipose tissue is insignificant, and the vessels do not have the features that are typical of that condition. On the contrary, some of those vessels are heavily inflamed, a feature which is said to be common in inflammatory pseudotumor of the liver (Someren et al Am J Clin Pathol 79:167-171,1978). Therefore I would favor the diagnosis of an inflammatory pseudotumor, fully acknowledging the fact that this remains an obscure process of unknown etiology and pathogenesis. I also have reservations about the currently fashionable diagnosis of IgG4-related disease.

Brian Rubin - Interesting/instructive case and discussion. I see the scattered fat cells but the spindle cells are inapparent on my slide due to all the inflammation. I would have thought IMT or IPT based on histology.

Dominic Spagnolo - This is a spectacular case. I have to say I was going down the IMT path, fat notwithstanding. The numbers of IgG4 plasma cells are not that numerous given the total plasma cell burden, and the constitutional symptoms are not typical of systemic IgG4-related disease, so I would favor that they represent a skewed IgG subclass expression in whatever this thing is (and I agree the evidence for inflammatory AML is compelling). Thanks for the case.

James Strauchen - Fabulous. I was unaware of inflammatory angiomyolipoma and would probably have called it IPT. IgG4 plasma cells are turning up now in practically everything!

Saul Suster - I would have called this inflammatory pseudotumor and gone on to the next case. Thank you for the erudite discussion and imaginative interpretation, and welcome to the Club, Abbas!

Bruce Wenig - Inflammatory appearing lesion the more I stared at it the more it reminded me of IgG4-related diseases I have seen it in head and neck sites although this case has more of a diffuse pattern of growth rather than the retention of lobular configuration especially in submandibular gland IgG4-related disease (formerly referred to as Küttner tumor). Finding phlebitis is cases I have seen has always been a challenge but there is a nice examples of phlebitis in this case. I did not pick up on the angiomyolipomatous component. Very nice discussion with images. Thank you.

Ady Yosepovich -Thank you for sharing this unusual case.

CASE NO. 2 – CONTRIBUTED BY: PHIL ALLEN, M.D.:

Abbas Agaimy - Never seen a lesion like this in intramuscular location. Reminds me of epithelioid fasciitis or proliferative myositis of childhood, particularly the good circumscription of the lesion and vague lobulation. Thanks for sharing this interesting and challenging case.

Phil Allen - My case. Chris Fletcher kindly e-mailed me the correct diagnosis as soon as he saw the slide a month or so ago. The diagnosis is pseudo-myogenic (epithelioid sarcoma-like) haemangioendothelioma, vastus medialis muscle (Am J Surg Pathol 2011; 35: 190-201). Many thanks for putting me out of my misery, Chris.

Carlos Bacchi - I see no reason why this couldn't be myxoinflammatory hyaline tumor in an unusual location.

David Ben-Dor - Allen- this is above my pay grade (even an Israeli one).

Michele Bisceglia - Possible ectopic myxoinflammatory hyaline tumour with minimal myxoid areas, vastus medialis muscle. When I looked at the slide blind, I called it proliferative myositis: but most likely I am wrong.

Ira Bleiweiss - All I can say is benign and myxomatous. I leave the name to the soft tissue gurus.

Thomas Colby - I would actually favor something in the fasciitis/proliferative myositis group but I defer to the large cadre of soft tissue pathologists on the panel.

Kumarasen Cooper - Wow is this a pseudomyogenic hemangioendothelioma? AE1/AE3 is OK. Should be FLI-1, ERG and CD31 positive. If so then I have now have a glass slide! The age, site and morphology appears to fit nicely. Defer to CDMF.

Hugo Dominguez Malagon - The nodule is well delimited, is formed by ganglion-like cells with nucleoli but no mitosis, there is inflammatory infiltrate with neutrophiles. I still consider this as belonging to the proliferative myositis group.

Goran Elmberger - Difficult case clearly outside my area of expertise. I was into proliferative myositis myself based on ganglion-like cells and inflammatory component. I believe there is slight focal extension between individual muscle fibers possibly indicating abortive checkerboard pattern. I would also include fetal rhabdomyoma in differential diagnosis even if I don't see convincing striated pattern. IHC would be interesting including desmin and myoglobin. Have no personal experience with myxoinflammatory hyaline tumor. Specific markers available?

Giovanni Falconieri - This is difficult to me as well, Phil. No good suggestion, regretfully.

Franco Fedeli - Ectopic myxoinflammatory hyaline tumour . When I saw the slide, honestly I thought it could be a variant of proliferative or nodular fasciitis (just for the presence of cells that resemble ganglion-like cells). Really, I don't have another diagnosis

Cyril Fisher - Given the positivity for cytokeratin I would also consider epithelioid sarcoma-like (pseudomyogenic) haemangioendothelioma.

Christopher Fletcher - Phil, as we discussed by email, this is a perfect example of pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma.

Jeronimo Forteza-Vila - Agreement with diagnosis.

Masaharu Fukunaga - I think it is inflammatory myofibroblastic tumor.

Allen Gown - Interesting case. The cytokeratin positivity together with the rhabdoid appearance of some cells makes me wonder if SMARB1 (INI1) studies were performed.

Thomas Krausz - Case 2 My first consideration was also proliferative myositis. Apart from AE1/AE3 were there other keratins or myoepithelial markers positive, if yes I would consider variant of soft tissue myoepithelioma? I assume S100 and GFAP were negative, so a variant of benign epithelioid nerve sheath tumor is unlikely? Unusual variant of proliferative myositis with aberrant AE1/AE3 expression. Sorry, no other ideas.

Janez Lamovec - I would rather call this lesion proliferative myositis. I don't see Reed-Sternberg-like cells, lipoblast-like cells, myxoid foci are quite indistinct, inflammatory infiltrate minimal, etc.

Tom Mentzel - Actually for me the lesion does not resemble myxoinflammatory fibroblastic sarcoma and given the cytomorphology of tumour cells and the stromal changes I would like to stain the lesion with CD31, ERG, INI1 and myogenic antibodies.

Markku Miettinen -Would consider this epithelioid sarcoma-like/pseudomyogenic hemangioendothelioma. Should also be positive for ERG and possibly CD31 and negative for INI1.

Liz Montgomery - Could this be a pseudomyogenic/epithelioid sarcoma-like hemangioendothelioma? Add CD31, CD34, INI1 and see what happens.

Fredrik Petersson - Do not know what this is. Ganglion-like cells indeed. What about additional immunohistochemical characterization of the lesional cells? On my section, there were some cells at the periphery of the lesion that had at least some hint of cytoplasmic cross striations and with nuclear features similar to the definitive lesional cells at the center (?).

Juan Rosai - This looks to me like a variation in the theme of proliferative myositis, probably the end stage of a reactive lesion. Some of the cells have the ganglion-cell like appearance that is said to be a marker of that condition. I would therefore regard this case as belonging to the same family as nodular fasciitis (an entity that the contributor knows all too well) or - to use a more generic term that Dr. Ackerman liked - a ""mesenchymal reaction to injury".

Brian Rubin - I don't recognize this is an entity but agree that it's not proliferative myositis. I think I would have ended up at unclassified spindle cell sarcoma, morphologically low-grade. The cells do look like those in MFS but I think they're non-specific. There is minimal inflammation and myxoid stroma.

Dominic Spagnolo - Phil I favor this to be proliferative myositis. I don't think it is a low grade sarcoma.

James Strauchen - Tempted to consider it a variant of proliferative myositis despite the lack of the checkerboard.

Saul Suster - Looks like proliferative myositis but the cytokeratin staining is wrong for this diagnosis. Don't know what this is but it also looks wrong for myxoinflammatory fibroblastic sarcoma.

Bruce Wenig - I do not honestly know what this lesion is but although cellular with atypical appearing cells it looks benign. Many of the cells have the appearance of myofibroblasts. I am curious what other immunostains were done and were reactive aside from cytokeratin.

CASE NO. 3 – CONTRIBUTED BY: MICHELE BISCEGLIA, M.D.:

Abbas Agaimy - Very impressive case Michele! The architecture is peculiar and many lobules have a feeding vessel. Could this be an unusual variant of soft tissue angiomatosis?

Phil Allen - Large (10cm), congenital, kaposiform (infantile) haemangioendothelioma with recurrence and lymphangiectasia, subcutis, anterior chest wall, female now aged 23. Despite the histological similarity of the cannonball foci of kaposiform haemangioendothelioma to tufted angioblastoma of Nakagawa, I doubt that this is a tufted angioma which is a relatively harmless although persistent condition, is superficial (dermis and subcutis) and does not invade deeply, is relatively small, does not exhibit kaposiform spindle cell areas or lymphangiectasia and is not associated with a consumptive coagulopathy. Based on the few cases I have seen, I believe tufted angioblastoma (Nakagawa) and kaposiform haemangioendothelioma are separate entities. Tufted angioma is relatively harmless, although difficult to eradicate, while kaposiform is often life-threatening. Incidentally, I suspect that proliferative cutaneous angiomatosis of Jack Brooks (Int J Surg Pathol 2: 68-70, 1994) is probably a variant of kaposiform haemangioendothelioma.

Carlos Bacchi – It is an unusual case!

David Ben-Dor - As usual a very learned and detailed exposition Does this lesion always present in a disseminated manner as seen here, or is this feature in this case related to its relation to the antecedent lymphangioma?

Ira Bleiweiss - Wow. Very cool case.

Thomas Colby - Agree with diagnosis of tufted angioma arising in a lymphangioma. I have not seen one of these before.

Kumarasen Cooper - Thank you Michele. Great diagnosis with EM and IHC confirmation. This is the classic "man in Istanbul".

Hugo Dominguez Malagon - I agree with the diagnosis of tufted hemangioma; nice discussion.

Goran Elmberger - Great case and interpretation. I do find the descriptive term cannon-ball pattern a bit presumptuous taking the small diameter of lesion into account. Similar pattern has been called glomeruloid lesions in the description of kaposiform hemangioendothelioma. The latter entity might be a differential diagnosis or at least a synonym.

Giovanni Falconieri - As usual with Michele this is another uncommon disease spectacularly discussed and thoroughly documented.

Franco Fedeli - I think that this case is a beautiful example of tufted angioma and is the first that I see in the context of a lymphangioma. The lesion on the whole should be placed in the rubric of so-called "tumor in tumor" lesions. The acquired "traumatic" histogenesis for the tufted angioma component of this lesion is plausible. Some authors consider this lesion as related to kaposiform hemangioendothelioma and I am aware of at least a case of kaposiform hemangioendothelioma of the skin of the leg in a young patient who underwent previous surgical operation on the ispilateral tibia.

Cyril Fisher - Tufted angioma associated with lymphangioma, very nice example.

Christopher Fletcher - This recurrent chest wall lesion is extremely unusual but I suspect that it would fit better with kaposiform haemangioendothelioma associated with lymphangiomatosis – perhaps the kaposiform elements were very scant in the original excision 20 years ago.

Jeronimo Forteza-Vila - Agreement with diagnosis. Fat component is due to its location and sometimes might be confusing.

Masaharu Fukunaga - Thank you for the interesting case and description. I agree, however, that it overlaps with hemosiderotic fibrolipomatous tumor. I wonder if the adipose tissue around the lesion is non-tumorous or tumorous? We often see adipose tissue around benign vascular lesion.

Allen Gown - Fascinating case, thank you.
Thomas Krausz – Agree with diagnosis, though on H&E it took me a bit of time to recognize the angiomatous nature of the cellular proliferation and at first, I considered lipofibromatosis in the differential diagnosis.

Janez Lamovec - This was very difficult for me, Michele. I recognized lymphangioma but didn't know what to do with these (really cannon ball!) spindle cell foci. In addition, I always thought of tufted hemangioma to be a dermal lesion. Thank you for this case and instructive discussion.

Tom Mentzel - Many thanks for this interesting case. Given the close relationship of tufted haemangioma and kaposiform haemangioendothelioma (that shows a focal expression of podoplanin) and the fact that lymphangiomatous changes may be seen adjacent to these lesions (Am J Clin Pathol 1997; 108: 450), this case nicely illustrates the position of tufted haemangioma in the spectrum of vascular lesions.

Markku Miettinen - Agree on lymphangioma with tufted angioma or kaposiform hemangioendothelioma-like foci.

Liz Montgomery - Glorious case. What a joy to behold.

Fredrik Petersson - Spectacular case. That tufted angioma may be related to an (?)ongoing causative factor is perhaps supported by the fact that the tumor may undergo "spontaneous" regression (Miyamaoto T. 1992, Br J Dermatol). Moreover, vascular malformations are frequently dynamic and sometimes progressive lesions (likely underpinned by vasculo-proliferative chemical signals) and may give rise to tufted angioma (Michel S. 1999, Br J Dermatol).

Juan Rosai - Spectacular case of tufted angioma arising in a congenital lymphangioma, accompanied by the usual scholarly discussion of the entity by the contributor.

Brian Rubin - Very nice case - agree with classification.

Dominic Spagnolo - Very nice case and comprehensive discussion Michele. Thank you.

James Strauchen - Definitely eye-catching!

Bruce Wenig - I agree with a diagnosis of tufted angioma and along the periphery of the lesion the findings support a lymphangioma so your hypothesis seems reasonable to me.

Ady Yosepovich - Very nice diagnosis, thank you for sharing.

CASE NO. 4 – CONTRIBUTED BY: IRA BLEIWEISS, M.D.:

Abbas Agaimy - Pretty case, typical lesion in atypical location! Thanks.

Phil Allen - Eccrine spiradenoma, skin and subcutis, right breast. This tumour can also be a bit of a devil in the soft tissues, where it is sometimes confused with synovial sarcoma.

Carlos Bacchi - Typical histology in an atypical location, or atypical clinical presentation.

David Ben-Dor - Looks to me like it was incompletely resected (or the specimen fell apart in surgery)- if this is correct was it necessary to go back and take everything out given the diagnosis of a benign tumor? Was there any attachment to the skin?

Michele Bisceglia - Eccrine spiradenoma of the breast**.** Agree. This breast tumor is identical to the cutaneous counterpart. A very evident feature here is represented by the intratumoral lymphocytic infiltration which occasionally may be so heavy, picturing the so-called thymoma-like variant (reported in the skin). A handful of cases of spiradenoma have been reported in the breast: two cases were classified as malignant and one recurred several times.

Thomas Colby - Agree with diagnosis; agree that sweat gland tumors in the breast represent a real trap, that I fell into at first review.

Kumarasen Cooper - Thank you Ira. The breast of course is a modified eccrine gland.

Hugo Dominguez Malagon - I agree with the diagnosis, it has some mitotic activity, but I counted only one per 10 HPF.

Goran Elmberger - Being a head and neck pathologist I would like to raise some issues here. Situation reminds me of a tumor located superficially in parotid region when discussion focused on whether we are dealing with a skin adnexal tumor or a salivary gland tumor with overgrowth into the skin. First I agree on the diagnosis, but then from a theoretical point of view we first need to decide if we are dealing with a skin adnexal tumor proper or a breast tumor. Based on the presented intratumoral sections this is impossible. The superficial location might indicate skin tumor but really sections need to prove relationship to skin and breast. If this is a breast tumor one might consider naming it benign adenomyoepithelioma or refer it to the skin-adnexal type tumors of the breast – eccrine spiradenoma… Finally, if you, like me, favour H&N pathology, one should probably give a serious consideration to labelling it salivary gland-like tumor of the breast – basal cell adenoma…Same as they say in Thailand.

Giovanni Falconieri - I agree with spiradenoma, although the biopsy site and lesion size are enough to deviate the unexpert like me to a totally wrong path and ultimately miserable wrong interpretation

Franco Fedeli - Nice case of eccrine spiradenoma, with the two cell types bordering the neoplastic tubular glands. Of note also the angiomatous component which is seen in this tumor and which was reported in some cases of spiradenoma of the skin.

Cyril Fisher - Eccrine spiradenoma in unusual location, very nice slide.

Christopher Fletcher - Eccrine spiradenoma – nice example. It seems surprising that a relatively small lesion such as this is so extensively ulcerated and inflamed – perhaps the patient had attempted some type of self-treatment.

Jeronimo Forteza-Vila - It is a very interesting case. It is a typical case of "Istambul man" (failure of recognizing a pathology for being located in a "typical location"), since it is a frequent skin tumour but rare in the breast. What is important is to know whether it is benign o malignant. I agree this case is a benign one.

Masaharu Fukunaga - Eccrine spiradenoma, I agree.

Allen Gown - Nice case, Ira. Recently saw a non breast skin eccrine spiradenoma with atypia as well, but that tumor was well circumscribed. How was this tumor upon resection?

Thomas Krausz – Very nice case. In addition to the luminal and basaloid (lymphocytoid) cells, there is also a striking lymphocytic infiltrate (often seen in spiradenoma).

Janez Lamovec - I wonder whether Michal will call this tumor a spiradenocylindroma.

Tom Mentzel - A nice case of eccrine spiradenoma.

Markku Miettinen - Eccrine spiradenoma is agreeable. It could be difficult to distinguish it from some kind of basal cell adenoma originating from breast elements although I do not see definitive ones here.

Liz Montgomery - Thanks for this. Skin appendage tumors are baffling to me.

Fredrik Petersson - On my section, the tumor shows in addition to the characterisic spiradenomatous morphology, a component of the tumor with bland, non-descript tubular morphology without the two cell types was seen. Moreover, in some small areas there is abundant basement membrane-like material where basaloid tumor cells are compressed into strands and cords reminiscent of what can be seen in some adenoid cystic carcinomas. We (including Michele Bisceglia and Michal Michal) reported such adenoid cystic carcinoma-like features in *cutaneous* spiradenomas a few years ago. (Adenoid cystic carcinoma-like pattern in spiradenoma and spiradenocylindroma: a rare feature in sporadic neoplasms and those associated with Brooke-Spiegler syndrome. Am J Dermatopathol. 2009 Oct;31(7):642-48.).

Juan Rosai - This breast tumor is clearly of salivary gland type, but my problem is whether to call it adenoid cystic carcinoma or to place it in a basaloid category. Parenthetically, this is often the situation in the other sites where this tumor occurs, such as thymus, cervix, and anal canal. The intriguing aspect is the fact that these tumors look *almost* like adenoid cystic carcinomas but not quite like the prototypical example in the major or minor salivary glands. The cylinders are not very well formed and the lymphocytic infiltrate is more in keeping with other types of adnexal tumors, including eccrine spiradenoma, as the contributor pointed out. Taking everything into consideration, I would favor a basaloid (or basal cell) adenoma, rather than carcinoma because it seems to be totally encapsulated or at least very well circumscribed.

Brian Rubin - Beautiful example.

Dominic Spagnolo - Eccrine spiradenoma of the breast – don't see this every day of the week! Thanks.

James Strauchen - Fabulous!

Bruce Wenig - Eccrine spiradenoma. Nice case.

Saul Suster - Agree, looks like eccrine spiradenoma.

Ady Yosepovich - Don't want to get this case in core needle biopsy, could have mistaken this for the basaloid variant of adenoid-cystic carcinoma, thank you for sharing this challenging case.

CASE NO. 5 – CONTRIBUTED BY: KUM COOPER, M.D.:

Abbas Agaimy - Beautiful case. Nice example of benign lesions often mistaken for malignancy and sent for consultation! Thanks, Kum.

Phil Allen - Benign endocervical polyp with exuberant gestational-associated changes. I haven't seen it before either. It looks like an Arias-Stella reaction in endocervical glands.

Carlos Bacchi - Nice case. I was impressed by some degree of atypical but I didn't find any mitosis which inclined me to diagnose it as a benign endocervical polyp. Now I know why this funny appearance of the polyp (gestational-associated changes).

David Ben-Dor - Quite florid I must say. I remember a pathologist at one of the other hospitals in Israel telling me that in her interview for a job with the head of the department (a well known and formidable gynecological pathologist) she was given a slide of an endocervical lesion which she diagnosed as Arias Stella reaction. The diagnosis was correct and she got the job. (I don't recall if she was told that the patient was pregnant, but even still). I was very impressed by that and wondered what I would have done if I received a biopsy like that (especially without the history).

Michele Bisceglia - Benign endocervical polyp with exuberant gestational-associated changes**.** Agree. The lesion is benign and with gestational changes, which coupled with the diffuse microglandular hyperplastic proliferations account for some worry on the part of the observing pathologist. The clear cell changes seem focally approaching the Arias-Stella phenomenon.

Ira Bleiweiss - Kum-exuberant is an understatement. I find the cribriform area worrisome, but I guess as usual it's best to back off given all the inflammation.

Thomas Colby - Agree with diagnosis of exuberant microglandular hyperplasia. Missed the decidual reaction, but saw it in retrospect.

Kumarasen Cooper - My case. I subsequently did find a reference from none other than Dr. Scully himself who wrote about this entity (with Robin Young). Am J Surg Path 1989;13:50-6: Atypical forms of microglandular hyperplasia of the cervix simulating carcinoma.

Hugo Dominguez Malagon - Nice case of endocervical polyp with gestational changes, the squamous metaplastic epithelium is very prominent

Giovanni Falconieri - Nice case, Kum, challenging condition.

Franco Fedeli - I think there is a microglandular atypical hyperplasia that perhaps can be explained by the pregnancy of the woman. In the literature are described five case of atypical form of microglandular hyperplasia of the cervix simulating carcinoma. (Am J Surg Patho 13(1): 50-60, 1989). In this paper the histological aspects are very similar.

Cyril Fisher - Striking changes. Without the history (or even with it) a misdiagnosis of carcinoma could easily be made.

Christopher Fletcher - Very educational case, Kum – this polyp would certainty have worried me.

Jeronimo Forteza-Vila - Agree with diagnosis.

Masaharu Fukunaga - Thank you Kum. It is a good educational case.

Goran Elmberger - Very interesting case. Always good to know the clinical situation. Very exuberant microglandular hyperplasia with characteristic neutrophilic infiltration. Rather subtle clues to pregnancy with slight Arias-Stella-like changes in glandular epithelium and focal stromal deciduosis. These kinds of changes in biopsy or curettage might be a real pitfall and I often perform p16 and Ki67 IHC to try to sort out the various metaplastic, hyperplastic and neoplastic look-alikes. Pitfalls in staining pattern do exist.

Allen Gown - Very disconcerting lesion - without that history and even with it one could clearly entertain the diagnosis of clear cell carcinoma.

Thomas Krausz - Very nice example.

Janez Lamovec - A tricky lesion but definitively benign. Thank you, Kum.

Tom Mentzel - A nice example of an endocervical polyp with inflammation and prominent adenomatous hyperplasia.

Markku Miettinen - Cervicitis with polypoid and papillary elements with squamous metaplasia. Did not see pregnancy-specific changes but agree that this must be the case in the clinical context.

Liz Montgomery - Very scary at low power. Bland at high. Nice case!

Fredrik Petersson - Treacherous case indeed. I guess the clue to the diagnosis (apart from the clinical information), would be the striking architectural complexity in conjunction with the absence of significant nuclear atypia and the blending in with metaplastic squamous areas. Perhaps p16 immunohistochemistry (?and Ki-67) would help ?

Juan Rosai - Beautiful demonstration of microglandular hyperplasia of the cervix with associated gestational-like changes. It doesn't quite make it for Arias-Stella reaction because the nuclei tend to be regular and not particularly hyperchromatic. The lesion is associated with foci of squamous metaplasia, as is often the case. I'm sure that most of the society members are aware of the existence of a well differentiated adenocarcinoma that simulates microglandular hyperplasia, so theoretically one could have a well differentiated cervical adenocarcinoma that simulates cervical microglandular hyperplasia that simulates well differentiated cervical adenocarcinoma!

Brian Rubin - Very weird polyp. Thanks Kum.

Elvio Silva - I think I will agree with the diagnosis. The presence of a basal area of squamoid cells is important not only to recognize the lesion as benign but also because sometimes mitoses are seen in these polyps and I would be very concerned if the mitoses are in the glandular cells, but usually they are in the basal, squamoid cells. Sometimes we need Ki-67 and vimentin to differentiate this hyperplasia from endometrial microglandular carcinoma.

Dominic Spagnolo - This is a scary lesion at first (and longer) glance! But I agree it is a polyp with gestational change. The cribriforming and profusion of filiform micropapillae, the relative absence of smudgy nucleomegaly with hyperchromasia, little hobnailing and presence of a few mitoses all make for a minefield. Great case – thanks.

James Strauchen - Very impressive!

Saul Suster - Agree (although I'm no GYN pathologist!). BTW, I would like to congratulate Kum on his new appointment as Vice-Chair and Director of Anatomic Pathology at the University of Pennsylvania School of Medicine. I bet they're going to sorely miss you now in Vermont!

Bruce Wenig - My initial impression before seeing the decidualized stroma was some high-grade malignant neoplasm. Incredible degree of gestational changes.

Ady Yosepovich - Very nice case with a very important pitfall, thank you for sharing.

CASE NO. 6 – CONTRIBUTED BY: IVAN DAMJANOV, M.D.:

Abbas Agaimy - Nice case, quite challenging without a clinical history.

Phil Allen - Metastatic testicular nonseminomatous germ cell tumor differentiating as a pure parietal yolk sac tumour, post chemotherapy, retroperitoneal lymph node. I was not aware of the parietal yolk sac story. Many thanks for the contribution.

Carlos Bacchi - Thank you for teaching me about this curious and intriguing entity, which I didn't know.

David Ben-Dor - Of mice and men. I didn't know that there were parietal and visceral yolk sac tumor cells. Can an AFP negative yolk sac tumor composed only of parietal type cells arise spontaneously, or does this always result from prior treatment?

Michele Bisceglia - Yolk sac carcinoma, parietal yolk sac type, in a lymph node metastasis of a testicular NSGCT. Never heard of this tumor type. I assume that the hyaline globules in this metastatic and already treated YS tumor were AFP negative as well. Based on the evidence that both your personal cases of tumors you mentioned of this Pierce's variant were had both received chemotherapy.

Ira Bleiweiss - Impossible without the history.

Thomas Colby - Agree with diagnosis. I got as far as germ cell and then needed to be educated beyond that as to the specific subtype.

Kumarasen Cooper - Thank you Ivan. I have not encountered this variant before. Since the AFP is negative I wonder how GPC-3 performs? I also wondered about an intermediate trophoblastic tumor (p63, HPL).

Hugo Dominguez Malagon - The diagnosis of parietal variant of yolk sac tumor is a difficult one; in this case the hyaline material is very striking.

Giovanni Falconieri - Another phenomenal and impossible case. Thank you, Ivan, for this educative contribution.

Franco Fedeli - The paper that you have given us is really interesting and extremely comprehensive with regard to the historical-embryology of this type of tumor, and helps to understand how the terminology has been determined more by morphological features than by the tissue of derivation.

Cyril Fisher - Parietal yolk sac carcinoma, hard to diagnose unless familiar with this.

Christopher Fletcher - I find the range of morphologies accepted within the spectrum of yolk sac tumour to be quite bewildering and I often fail to think of this diagnosis, at least initially.

Jeronimo Forteza-Vila - It is emphasized the presence of hyaline material; this is clue to reach a yolk sac carcinoma diagnosis. Dr. Nogales citation is very interesting.

Masaharu Fukunaga - It is a very unusual tumor. It looks like myoepithelial carcinoma. I am not familiar with parietal yolk sac carcinoma, which is negative for AFP. What are diagnostic clues of parietal yolk sac carcinoma?

Goran Elmberger - Interesting case, comment and reference. These cases with an embryological aspect always fascinate me. Having a little problem in accepting such a rare diagnosis in metastatic site after chemotherapy with AFP negativity... Was primary testicular tumor resected and what was the diagnosis before chemo? Even so I believe diagnosis is probably correct and I don't have a better alternative to offer. Myself I would have performed more IHC than presented here before accepting the diagnosis. Pattern expected would be OCT3/4 (-), glypican 3 (+), CD30 (-), CK pan (+), CK7 (-), Sall4 (+), PLAP (+/-) and hPL (-). Hyaline globules are easily identified. So is fibrin deposition and vascular invasion. A differential diagnosis but rare would be placental site trophoblastic tumor (ITT) – hPL?

Allen Gown - Thank you Ivan, a lovely case highlighting the protean histologic appearance of yolk sac tumor!

Ondrej Hes - This is extremely interesting case. I haven´t seen such parietal variant of YST in pure form. Could have previous chemotherapy any influence to the morphology? Some parts reminded me so-called "postchemo" spindle cell tumor described by Dr. Ulbright et al. (Michael et al: The pluripotential nature of the mesenchyme-like component of yolk sac tumor. Arch Pathol Lab Med 1989;113: 1115-9; Ulbright TM, et al: Spindle cell tumors resected from male patients with germ cell tumors. A clinicopathologic study of 14 cases. Cancer 1990; 65: 148-56).

Thomas Krausz – Focally, I could recognize yolk-sac tumor. Whether this is the parietal subtype or secondary hyalinized changes in the tumor due to therapy, I am not sure.

Janez Lamovec - It would never occur to me that this was a variant of a yolk sac carcinoma; I thought of carcinoma metastasis, perhaps from liver. Thank you for teaching us.

Tom Mentzel - Many thanks for this interesting case!

Markku Miettinen - Agree with metastatic germ cell tumor but out of ignorance was thinking of trophoblastic differentiation. Ivan's case is better than Nogales' last review because this subentity was not (well) illustrated there.

Fredrik Petersson - Initially I thought of an epithelioid trophoblastic tumor (hyaline material and some "squamoid" features – trophoblastic tumors other than choriocarcinoma may rarely occur as a component of germ cell tumors in males, highlighted by a case I published together with Michal Michal and Ondrej Hes a few years ago (Testicular germ cell tumor composed of placental trophoblastic tumor and mature teratoma. Hum Pathol 41:1046-50, 2010). When I had a closer look, I thought I saw some "hepatocyte-like, trabecular areas" with hyaline bodies, ?? hepar IHC.

Juan Rosai - Beautiful example of yolk sac tumor as a component of a testicular NSGCT. It is remarkable how epithelioid this lesion can be. This case also brings to mind epithelioid hemangioendothelioma because of the prominent hyaline matrix. By the way, I liked very much the monograph written by Francisco Nogales on this subject, with a very erudite discussion in terms of whether this tumor should be called yolk sac carcinoma or endodermal sinus tumor.

Brian Rubin - Fantastic case.

Dominic Spagnolo - Stunning example of parietal yolk sac carcinoma. Have seen the basement membrane material post-chemotherapy before but never to this extent. Thanks.

James Strauchen - Was not aware of this variant of YST!

Saul Suster - Was not aware of the existence of a "parietal" type of YST – thank you for the education.

Bruce Wenig - Nice case and thank you for the heads-up on the Nogales et all review.

Ady Yosepovich - Never seen this peculiar variant before, thank you for sharing.

CASE NO. 7 – CONTRIBUTED BY OTTO DIETZ, M.D.:

Abbas Agaimy - Very rare example of tumor-to-tumor metastasis, never seen, I also do not believe that this has been reported before.

Phil Allen - Tumour in tumour metastasis of lobular breast carcinoma in a large (7 cm) adrenal myelolipoma in a patient also with disseminated spinal metastases. I have never seen this before. I think the suggested explanation based on the affinity of metastatic breast cancer for haemopoietic marrow is probably correct.

Carlos Bacchi - Nice collision tumor. I have never seen this association before. It may be that this lobular carcinoma metastasized to the adrenal, which happens to be hosting a myelolipoma.

David Ben-Dor - On low power scanning the deposits of tumor looks similar enough to those of the myelolipoma so unless you looked at the entire slide carefully you could miss them (a cognitive error called premature closure).

Michele Bisceglia - Breast carcinoma is (together with lung and prostate carcinoma) the most common donor tumor in phenomenon of tumor in tumor, while meningiomas and carcinomas of the kidney and thyroid are the main recipient tumors. The most exotic examples of tumor to tumor metastasis from breast cancer I was aware of (from the literature) are a case of metastasis to a solitary fibrous tumor in the lung (Gonullu G, et al. Indian J Cancer. 2010;47:76-78) and a case of metastasis to a liposarcoma of the thigh (Kabukcuoglu F, et al. Breast carcinoma metastasis in recurrent myxoid liposarcoma. Pathol Oncol Res. 2009; 15:467-71). The present case is in line with the latter examples.

Ira Bleiweiss - I've seen lots of metastatic lobular in all sorts of weird places but not this.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - The monotonous cells with intra-cytoplasmic mucin vacuoles are a great give-away. Thank you for sharing this excellent teaching case. No Otto, I have not encountered this combination before.

Hugo Dominguez Malagon - I also have not seen a case like this.

Giovanni Falconieri - Agree! Quite bizarre case. I have personally seen metastasis of breast into meningioma and renal carcinoma, but never in myelolipoma. Thank you for this contribution

Franco Fedeli I think the background myelolipoma plays an important role as "pabulum" for metastatic lesions (perhaps due to the presence of growth factors and stem elements?). In fact, even in pseudocystic adrenal lesion site of metastases was the presence of myelolipomatous metaplasia (Am J Clin Pathol. 1990 Dec;94(6):706-13).

Cyril Fisher - Lobular carcinoma of breast metastatic to myelolipoma, amazing occurrence. I have not seen this before.

Christopher Fletcher - Myelolipoma focally infiltrated by metastatic carcinoma. I have not previously seen metastasis into this tumour type – in my very biased world, the soft tissue tumour which most often seems to be a 'recipient' of metastasis is solitary fibrous tumour.

Jeronimo Forteza-Vila - Agree with angiomyolipoma diagnosis with lobular carcinoma metastasis of breast. Neoplasia appears in adrenal gland and metastatic cells have signet ring morphology.

Masaharu Fukunaga - It is very interesting and tricky.

Goran Elmberger - Beautiful case. No I have not seen anything like it. Interesting underlying biology.

Thomas Krausz - Impressive case. I haven't seen this combination before.

Janez Lamovec - We've seen discrete and grossly invisible metastases of ILC in several retroperitoneal sites/organs at autopsy but never in myelolipoma.

Tom Mentzel - What a wonderful example of a “tumour in tumour” phenomenon, many thanks!

Markku Miettinen - Fully agree on metastatic lobular carcinoma of the breast, colliding with myelolipoma of the adrenal.

Liz Montgomery - Amazing case. Have never seen a metastasis to a myelolipoma

Fredrik Petersson - Never seen metastatic lobular carcinoma in this setting before.

Juan Rosai - Very nice demonstration of metastatic lobular carcinoma of the breast in a myelolipoma. Interestingly, the adipose component has areas reminiscent of an atypical lipomatous tumor

Brian Rubin - Never saw this before but agree that it looks like carcinoma metastasizing to a myelolipoma.

Dominic Spagnolo - I have not personally seen metastasis of breast carcinoma to adrenal myelolipoma, and have not read about it either. Interesting case!

James Strauchen - Lobular carcinoma metastatic to myelolipoma, first one for me!

Saul Suster - Very cool – never seen this before.

Bruce Wenig - I have not seen this specific combination of morphologies reflecting a “tumor within tumor” but metastatic cancers to the thyroid gland typically have the “tumor within tumor” appearance showing contrasting morphologies. The primary thyroid lesion may be an adenomatoid nodule, follicular adenoma, follicular carcinoma or papillary carcinoma to which a distant metatsaiss (e.g., breast, kidney, melanoma, other) may metastasize.

Ady Yosepovich - Extraordinary example for lobular carcinoma metastasis that always take us by surprise with peculiar metastasis location., thank you sharing this case.

CASE NO. 8 – CONTRIBUTED BY VINCENZO EUSEBI, M.D.:

Abbas Agaimy - Very peculiar and misleading appearance! Looks superficially like metastatic carcinoma if one is not alert to the spindle component and the encapsulation. Thanks for sharing with us.

Phil Allen - Biphasic synovial sarcoma, right median nerve. I agree that this is an unequivocal case. I wonder how many malignant glandular schwannomas from the past were actually biphasic synovial sarcomas.

Carlos Bacchi - Very unusual case of synovial sarcoma. The presence of biphasic areas help to think about the diagnosis of SS. Thanks for sharing it.

David Ben-Dor - The glandular component reminded me of thyroid, especially with the presence of nuclear clearing in places.

Michele Biscegllia - Incredible case with a convincing diagnosis. Cyril contributed another case, mostly glandular synovial sarcoma microscopically resembling this one.

Ira Bleiweiss - Agree.

Thomas Colby - Agree with diagnosis of synovial sarcoma. Not sure I would have picked up the origin within a nerve. Is that is something that has been described in the setting of Von Recklinghausen disease?

Kumarasen Cooper - I remember reading about this entity in the Hum Path paper (that you quote) by the late Dr Scheithauer. Never thought I would now own a slide from such an unusual location. Thanks Vincenzo.

Hugo Dominguez Malagon - The case is predominantly glandular which makes it difficult to identify, but the spindle cell component can be recognized - thank you.

Giovanni Falconieri - Great case Vincenzo, it looks pretty monophasic glandular SS, remarkably comparable to a case submitted by Dr. Fisher years ago (AMR#33-9)

Franco Fedeli - This is a monophasic epithelial sarcoma, pure glandular type, from peripheral nerve! A generally easy diagnosis to make, except this one is in a very peculiar location.

Cyril Fisher - Beautiful example of intraneural synovial sarcoma, with prominent glandular component.

Christopher Fletcher - Biphasic synovial sarcoma (epithelial predominant !) – it is very difficult to recognise the pre-existing nerve – was the patient left with any neurologic deficit after the surgery?

Jeronimo Forteza-Vila - Immunohistochemistry and SS18 – SSX transcript are definite to diagnose as a synovial sarcoma. However, if we had only had a look at HE we would have thought it was a metastatic adenocarcinoma.

Masaharu Fukunaga - What a great case. I have never seen synovial sarcoma associated with nerve.

Goran Elmberger - Great case. I guess one clue is the biphasic nature of the tumor. PCR nails diagnosis even if my curiosity would prompt a FISH and IHC (TLE1) for confirmation. I don't trust the test tubes 100 % myself after running the molecular service at Karolinska last 15 years. Always strive at multiple support at protein, RNA and DNA level. PS typo in Turkish manuscript median/radial nerve used in title/abstract… Seems to be a relevant journal as you indicated.

Allen Gown - Would be interesting to see which fractions of the tumor cells are positive for expression of TLE1 – particularly the glands v. spindle cell components.

Thomas Krausz - Nice case. I haven't seen one arising in nerve before.

Janez Lamovec - Very instructive case. The most spectacular case of glandular synovial sarcoma with very scant spindle cell component was submitted to AMR seminars by Cyril Fisher (Seminar 33, Case 9).

Tom Mentzel - Given the prominent epithelial component it's a difficult case on H&E – wonderful case.

Markku Miettinen - Agree on biphasic synovial sarcoma, especially considering documented SS18-SSX1 fusion. Certainly metastatic carcinoma (such as endometrial or ovarian) comes to mind for differential diagnoses. Cannot remember seeing truly convincing "malignant glandular schwannomas", another potential differential diagnosis.

Liz Montgomery - I thought this was metastatic adenocarcinoma when I first looked at the slide! I guess there is no doubt of the dx with your thorough evaluation.

Fredrik Petersson - Deceptively bland appearance, both cytologically and architecturally. Looked (in vain) for apocrine secretion in the glandular component, as was recently published by Michal & Kazakov. (Superficial Soft Tissue Biphasic Synovial Sarcoma With Apocrine Differentiation in the Glandular Component: A Report of Two Cases. Am J Dermatopathol. 2013 Apr 4. [Epub ahead of print]).

Juan Rosai - This is the most glandular synovial sarcoma I have ever seen. I take it back: It is the second such case, the other was presented at a seminar many years ago, and several pathologists made the diagnosis of metastatic adenocarcinoma. To me, the histogenesis of this tumor remains a mystery. It probably has nothing to do with the synovial membrane. I think there is something neural about it, and the fact that this tumor happens to be within a nerve may point in that direction.

Brian Rubin - Nice case of a predominantly epithelioid synovial sarcoma. Synovial sarcomas do occasionally arise within nerves but it is rare. The other cases I've seen were monophasic spindle cell lesions that were difficult to differentiate from MPNST.

Dominic Spagnolo - What a spectacular case of synovial sarcoma arising in nerve. I have not encountered this before.

James Strauchen - Synovial sarcoma arising from median nerve. Very nice case!

Bruce Wenig - Fantastic case. Nothing to add in English or in Turkish.

Ady Yosepovich - A very peculiar and challenging lesion, thank you for sharing this case.

CASE NO. 9 – CONTRIBUTED BY: CYRIL FISHER, M.D.:

Abbas Agaimy - Pretty case, the clinical history is quite interesting; the presence of a histologically malignant component still retaining some SFT/HPC architecture is interesting. I wonder whether this is a prerequisite for dedifferentiation or is it possible for bland looking (benign!) SFT to immediately undergo dediff? Thanks for this case.

Phil Allen - It is rather comical how the concept of dedifferentiation, which used to be heretical about 25 years ago particularly amongst experimental pathologists, has now become well-established, mainstream doctrine.

Carlos Bacchi - Great example of dedifferentiated solitary fibrous tumor!

David Ben-Dor - Whereas the osteoid is obvious, the diagnosis of the rhabdomyosarcoma element is purely immunohistochemical?

Michele Biscegllia - Dedifferentiated solitary fibrous tumor with divergent osteosarcomatous and rhabdomyosarcomatous differentiation. Very unusual and interesting case. Thank you, Cyril for sharing this with us. Incidentally the first dedifferentiated case of SFT (I think) was reported in the kidney by Magro G. et al. (Solitary fibrous tumour of the kidney with sarcomatous overgrowth. Case report and review of the literature. APMIS. 2008;116:1020-5).

Ira Bleiweiss - Agree. Wow.

Thomas Colby - Agree with diagnosis. Lovely example. I buy the immunos but was unable to find any cross striations. Us old guys still like to look for cross striations.

Kumarasen Cooper - Thank you, Cyril for this exciting example of Dediff SFT. I don't think I would have picked up on the rhabdo component.

Hugo Dominguez Malagon - Nice case of dedifferentiated SFT, divergent differentiation is exceptional. Well illustrated.

Goran Elmberger - Interesting case illustrating the ubiquitous (?) HGT seen in most tumors - mesenchymal, epithelial and hematolymphoid alike. New molecular handle always handy, especially for HGT cases...) I believe the terminology of dedifferentiation is not optimal since in most studied cases the high-grade component seems to harbour additional genetic abnormalities most probably responsible for tumor progression. High-grade transformation seems more descriptively correct.

Giovanni Falconieri - Thank you Dr. Fisher for this extraordinary contribution. A great collector's case.

Franco Fedeli - A beautiful example of a dedifferentiated tumor, which indeed seems having read books (high grade sarcomatous areas juxtaposed to a morphologically low grade ones). Solitary fibrous tumor is the most recent example of a mesenchymal tumor capable of dedifferentiation after chondrosarcoma, liposarcoma, low grade parosteal osteosarcoma, chordoma.

Christopher Fletcher - Stunning example of dedifferentiated SFT with two heterologous components in the dedifferentiated component – many thanks, Cyril !

Jeronimo Forteza-Vila - Agreement with diagnosis.

Masaharu Fukunaga - A very nice case of dedifferentiated SFT, thank you Cyril.

Allen Gown - Wow, interesting case, highlighting the plasticity of many high grade sarcomas.

Thomas Krausz - Great case. I have seen a couple of dedifferentiated SFTs before but neither of them showed heterologous differentiation. I agree, exclusion of a dedifferentiated liposarcoma was important in this case.

Janez Lamovec - Dedifferentiated SFT, I have never seen one. While osteosarcomatous component of malignant part is well evident, I had problems to spot clear-cut rhabdomyosarcomatous one on H&E.

Tom Mentzel - This beautiful case nicely emphasizes the concept of rare malignant transformation in mesenchymal neoplasms, many thanks for sharing this exceptional case

Markku Miettinen -Agree on solitary fibrous tumor with a malignant/dedifferentiated component. High-grade malignant features with osteosarcomatous component are evident on the slide but cannot see rhabdomyosarcomatous component (by HE-stain).

Liz Montgomery - This is an amazing case. Thanks for sharing it, Cyril.

Fredrik Petersson - Interesting case. Nice to see our publication in the reference list. Our case was located to the nasal cavity and displayed the presence of a TP53 mutation, selectively in the dedifferentiated component. Also worth noting is a Japanese case published by Moritani S et al. in Pathol Int. 2011 Mar;61(3):143-9: Dedifferentiation and progression of an intracranial solitary fibrous tumor: autopsy case of a Japanese woman with a history of radiation therapy of the head during infancy. Our case has shown no evidence of recurrence or metastasis at 1 year FU (including MRI-studies).

Juan Rosai - Very nice case of solitary fibrous tumor, with the high grade component containing bone and skeletal muscle. I am pretty sure that in the past this tumor would have been called hemangiopericytoma with an anaplastic component. I also believe that sooner or later a dedifferentiated variant of most if not all soft tissue sarcomas will be described. As Dr. Ackerman used to say, “Anything can happen, anywhere, sometimes.”

Brian Rubin - Nice case. Not sure I've totally bought into the distinction between malignant and dedifferentiated SFT yet but there is a convincing SFT 'precursor' in this case.

Dominic Spagnolo - You got the trifecta with this one, Cyril. Such a nice example of a dedifferentiated SFT with divergent osteosarcomatous and rahbdomyosarcomatous elements.

James Strauchen - Dedifferentiated SFT. Didn't know they could do that!

Saul Suster - Nice case Cyril, thank you for sharing it. We’ve seen several examples similar to this in the mediastinum and pleura. Not sure I entirely buy the concept of “de-differentiation” here. It seems like this term has turned into a very convenient and popular rubric for any tumor that shows a higher grade component that is different from the better-differentiated (original/underlying) component. Dr. Rywlin wrote about this many years ago (Rywlin AM. Hum Pathol 13:963-4, 1982). As he pointed out, in the classical examples of “dedifferentiated” tumors, the probability that a mature neoplastic cell would revert spontaneously to a more primitive phenotype and then re-differentiate itself along a totally different cell line seems rather difficult to conceptualize. Dr. Rywlin proposed that what we were observing in such cases might be better described as a phenomenon of “progression of malignancy” in which subsequent generations of tumor cells *lost* their capacity for differentiation and reverted to a more primitive phenotype. In the current case, this would have been regarded by Dr. Rywlin as an example of the phenomenon of “multiple differentiation”, in which a genetically unstable tumor cell population acted as the substrate for the generation of different clones of tumor cells that followed divergent lines of differentiation. He felt the term “de-differentiation” was biologically not a sound term and actively discouraged its use. The widespread use of this term in the current literature may, thus, be an example of what Rywlin used to designate as the practice of “elephantine” medicine (i.e., “follow the leader” attitude).

Bruce Wenig - Fantastic case. Thank you, Cyril.

Ady Yosepovich - Thank you for sharing this illustrative case , apparently de-differentiation is quite an issue in soft tissue pathology that can have effect in drug selection (as is the case in dedifferentiated GIST), and we should look and pay attention for this in every case.

CASE NO. 10 – CONTRIBUTED BY: CHRISTOPHER FLETCHER, M.D.:

Abbas Agaimy - Impressive case! The multinodular "plexiform" invasive growth pattern is intriguing and superficially mimics that of SDHB-negative GIST, but histology is completely different. Thanks for this nice case.

Phil Allen - This diagnosis is bound to be controversial. The tumour does not really look much like glomus tumor to me. It's a pity we can't ask Stout if it is a haemangiopericytoma.

Carlos Bacchi - Does malignant glomus tumor originate de novo or can it arise from a benign glomus tumor? I am asking this because in the H&E slide that I received there is a small focus (5%) of benign-looking glomus tumor.

David Ben-Dor - This doesn't look like the usual run of the mill glomus tumor. I had a case of gastric glomus tumor that looked very typical for that entity and which I showed at the meeting organized by Michal in Srni. I think one of the earliest papers on this was written by Henry Appelman, who said that they are "rarer than hen's teeth" (try translating that into Czech!!) Is the implication here that despite the malignant histological features the patient will do well?

Michele Biscegllia - Malignant glomus tumor of stomach. Indeed a rare case. In 2010, at the national congress of anatomic pathologists, we presented in abstract form a series of 7 cases of gomus tumors (GT). Among the authors also 2 members of the AMR group, Ira Bleiweiss and Marku Miettinene. From that abstract I copy the following paragraph <<<To date 104 GT [exclusive of the cases herein presented] have been recorded in the English Literature since 1951. Only 4 papers included more than 1 case [1,2,3,4]. The two largest series were compiled in 1969 by Appelman and Helwig[3] and in 2002 by Miettinen et al[4], both from the Armed Forces Institutes of Pathology (Washington, D.C.), who reported 12 and 31 cases, respectively. In most cases the tumor was solitary, but in 4 cases multiple tumors were described. Most GT are histologically benign, but 3 malignant cases cases have been published. Refs. ***1.*** Kay S, et al.. Glomus tumors of the stomach. Cancer 1951; 4:726-736. ***2.*** Allen RA, Dahlin DC. Glomus tumor of the stomach: report of 2 cases. Proc Staff Meet Mayo Clin. 1954;29:429-36. ***3.*** Appelman HD, Helwig EB. Glomus tumors of the stomach. Cancer 1969; 23:203-213. ***4.*** Miettinen M, et al. Gastrointestinal glomus tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 32 cases. Am J Surg Pathol. 2002;26:301-311.

Ira Bleiweiss - As you say, frankly malignant. I would not have pegged this as glomus tumor (and I thought I knew a thing or 2 about this entity, since, as the older members may remember, I submitted a case to the club long ago-the patient was my now late father-in-law - He died of unrelated causes by the way).

Thomas Colby - Agree with diagnosis. Architecturally this appears to be an aggressive lesion and it does have appreciable atypia/mitotic activity.

Kumarasen Cooper - GIST, WT-GIST, CCS and epithelioid LMS were in my DD. Glomus tumor did not cross my mind. Great case. Thanks you Chris.

Hugo Dominguez Malagon - I completely agree with the diagnosis of malignant glomus tumor, in my slide there is a nodule recognizable as a regular glomus.

Goran Elmberger - Very interesting and rare case. Since cytology is not very characteristic for glomus tumor I will try to remember in differential diagnosis and include markers in IHC panel work up.

Giovanni Falconieri - No clue whatsoever, impossible case, Chris.

Franco Fedeli - A rare tumor, even rare in the skin and soft tissue. I think the most striking thing in this variant of glomus tumor is the presence of spindle cells areas suggest that it is a malignant form, in agreement with the "criteria" suggested by Miettinen.

Cyril Fisher - Glomus tumor with malignant histological features, unusual case. Immunohistochemistry is key to diagnosis and exclusion of GIST etc.

Jeronimo Forteza-Vila - Agreement with diagnosis. Rare location but diagnostic morphology.

Masaharu Fukunaga - The malignant glomus tumor of the stomach. It is extremely difficult to make a diagnosis of the malignancy.

Allen Gown - Thanks, Chris. Am I correct in assuming that desmin was not expressed by these cells?

Thomas Krausz - The diagnosis of malignant glomus tumor is problematic for me also.

Tom Mentzel - Many thanks for this rare case. In the slide I received there is a small area composed of smaller and more uniform looking glomus cells – another example of a malignant transformation?

Markku Miettinen - Agree on glomus tumor – although I thought Chris might call it myopericytoma. Definitely atypical but not sure if truly malignant. As Chris mentioned, intravascular component is often seen in even benign gastric glomus tumors and is not a reliable sign of malignancy.

Liz Montgomery - Glorious case. We just had a similar one – maybe it got sent to both places!

Fredrik Petersson - On my slide, there was clearly invasive growth pattern, but with no high-grade cytological atypia, no definitive LVI and only very rare mitotic figures.

Juan Rosai - Very nice case of malignant glomus tumor of the stomach. It reminds me of a case I saw at Yale many years ago, which was later reported by Haque S et al (Am J Surg Pathol 16: 291-299, 1992). I suppose one could call the present tumor a glomangiopericytoma because some of the cells are oval or spindle rather than round, and there are some staghorn vessels, but the distinction is probably probably of not great significance.

Brian Rubin - Neat case. Never seen a malignant glomus tumor of the stomach. Benign glomus tumors are already quite unusual in the stomach.

Dominic Spagnolo - Agree that this is a cytologically malignant glomus tumour. Thanks for the case.

James Strauchen - Malignant glomus tumor of the stomach. Fabulous case!

Saul Suster - Chris, I agree with your diagnosis. The unusual feature in this case is the plexiform growth pattern separated by bands of connective tissue that give it an infiltrative appearance. I think calling it low-grade malignant is the safest approach, although I suspect this may behave in a benign fashion. Long-term follow-up would be helpful in this case.

Bruce Wenig - Malignant glomus tumor including LVI in my slide. Thanks, Chris.

CASE NO. 11 – CONTRIBUTED BY ANDREW FOLPE, M.D.:

Abbas Agaimy - Thanks Dr. Folpe for sharing this interesting case. I never heard of this entity.

Phil Allen - Polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy. This slide is missing from my set, which is a pity. Like Andrew, I had never heard of it before. Even without the slide, there is enough information provided for those with a good memory to diagnose the next case they see.

Carlos Bacchi - What a spetacular case! The histology with this distinctive membranous material within the fat is really impressive.

David Ben-Dor - What term or terms did you insert in the search query? Funny looking laminated membranes in fat tissue? Hats off for the diagnosis.

Michele Biscegllia - Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL). This is very new for me. The adipose tissue changes in this case are evocative of the "lipomembranous (or membranocystic) changes in chronic panniculitis" of subcutis (Alegre VA et al. J AM Acad Dermatol 1988;19:39-46), where the small cystic cavities are covered by crenulated membranes (also PAS positive in that condition). This must represent a peculiar form of teatonecrosis, which has also been seen in association with scleroderma and with LES. Saul Suster circulated the quiz case n. 1 in Sem. 34 of a case of "membranous fat necrosis" (as described by AM Rywlin in AJSP 1986; 10:62-69) from male breast parenchyma following trauma. Nothing to do with the case you presented but showing some morphological overlapping with the membranes seen in your case.

Ira Bleiweiss - I said exactly the same thing to myself - This looks funny. Its foreign material looks like elastic material.

Thomas Colby - Andrew gets the gold star for this case. I am not sure I would have figured out what this was but it all seems to hang together very well. A quick PubMed search shows 64 papers! I'll probably never see this again, but if I do it will be familiar.

Kumarasen Cooper - PLOSL. Only from the Mayo, Andrew! Did they have a diagnosis preoperatively? Fascinating! Thank you for sharing. All I could think of was fetal squames (pulmonary amniotic fluid embolism) from my days as a resident in Africa.

Hugo Dominguez Malagon - PLSOL???? Never heard of it!!!! Great case.

Giovanni Falconieri - I have a hard time even catching the name. Thank you for submitting this impossible case.

Franco Fedeli - It is definitely impossible to say anything about this case! I had thought it was a storage disease. Never heard of this disease before.

Cyril Fisher - What a striking appearance! I have heard of this but not seen an example. Many thanks Andrew.

Christopher Fletcher - Astonishing diagnosis – I had never heard of this syndrome previously.

Jeronimo Forteza-Vila - I must admit as Dr. Folpe stated that "I had never heard of this syndrome until I got this case". My initial reaction on viewing the biopsy was something along the lines of ''this fat looks funny'', and it took me a little while to realize it was some type of membranous foreign material. Then I just hit PubMed until the right thing came up".

Masaharu Fukunaga - Thank you very much for the rare lesion. I have never seen any case of PLOSL.

Goran Elmberger - New to me as well. Hats off as we say in Sweden! Great diagnosis.

Allen Gown - That's a new one on me, too, Andrew. Thanks for the write up!

Janez Lamovec - We see similar membranous material in membranous fat necrosis in the breast. Never heard of this particular affliction.

Tom Mentzel - What a case and what a story, many thanks for teaching us this rare disorder.

Markku Miettinen - Thanks Andrew, nice case, would easily go as a good intraosseous lipoma with some peculiar artifact. Also called Nasu-Hakola disease. The latter author is a Finnish psychiatrist who reported this in Finnish 1974 with Dr. Jarvi (author of elastofibroma) as "Polycystic osteodysplasia associated with progressive dementia-a new hereditary disease". I heard about this a lot in Finland but never saw a case.

Liz Montgomery - Polycystic lipomembranous osteodysplasia with sclerosing leukoencelopathy. I have a large stack of these on my desk. Yeah, right. I never hear of it til this moment.

Fredrik Petersson - Never heard about this condition. Did the patient have any radiologically detectable cerebral lesions?

Juan Rosai - This case reminds me very much of the condition designated as membranous fat necrosis by none other than the man: Arkadi Rywlin, the man honored by this society (Am J Surg Pathol 10:62-69,1986).

Brian Rubin - Amazing case - never heard of it before but I'll be on the lookout for more cases.

Dominic Spagnolo - I got as far as florid lipomembranous dystrophy/lipomembranous necrosis, the best I've ever seen, but have never heard of PLOSL!! And no doubt, sadly destined to forget it in a week or two. Thanks for the education.

James Strauchen - PLOSL! Wow!

Saul Suster: This is a spectacular case – thank you Andrew for sharing it! Never heard of this before and never seen anything quite like this before. Rywlin's "membranous fat necrosis" is as close as it gets, but quite different in its distribution.

Bruce Wenig - "This fat looks funny." If you say PLOSL then so be it. Never heard of it but thanks for educating me, Andrew.

CASE NO. 12 – CONTRIBUTED BY: JANEZ LAMOVEC, M.D.:

Abbas Agaimy - Agree with this, true pitfall for the non-wary, irradiation or mechanical irritation might be possible contributory causes. Thanks

Phil Allen - Radiation associated pseudosarcomatous fibroepithelial stromal polyp of the perivulvar skin. I think it likely that this has been radiation induced. It could be regarded as analogous to atypical fibroxanthoma of the sun exposed skin of the elderly.

Carlos Bacchi - I have seen a somewhat similar case in the tongue (pseudosarcomatous polypoid lesion) which I shared with Chris Fletcher. Unfortunately in my particular case a detailed clinical history (like previous surgical procedure) was not possible to obtain.

David Ben-Dor - Rightfully or wrongfully the thought of PHAT entered my mind.

Michele Biscegllia - Thank you very much, Janez, for sharing this case with us. Agree on the fact that the tumor is benign: however this tumor should induce us to briefly discuss whether bizarre cells can or cannot give rise to "physiological" atypical mitoses (something which as far as healthy tissue is concerned we see only in bone marrow megakaryocytes). The (?rethorical) question is: if we see so many atypical mitoses in what is otherwise a typical pleomorphic lipoma, what diagnosis should we make?

Ira Bleiweiss - A new diagnosis for me.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Great call Janez. Thank you for sharing this educational experience. I have seen only one other case in the vulva of a young woman in 2008.

Hugo Dominguez Malagon - In my slide I see ulceration and many atypical mitoses. I would regard this lesion as a malignant tumor, it could be a sarcoma or a sarcomatoid carcinoma.

Giovanni Falconieri - Nice case Janez, I agree with your assessment although I must admit that I would have hard time in coming up to the correct interpretation.

Franco Fedeli - Interesting Case. The activated fibrovascular stroma you see in this preparation reminds me of what I usually see in surgical specimens from previous resection after neo-adjuvant chemotherapy and radiotherapy. I understand that there has been a very long latency time and so do not know if this is possible. But the morphological alterations are really similar.

Cyril Fisher - Fibroepithelial polyp with pseudosarcomatous changes. As you say, it is interesting to speculate about the role of prior irradiation if this has arisen in the therapeutic field.

Christopher Fletcher - Agree entirely – this lesion has appearances which fit very well with a pseudosarcomatous fibroepithelial stromal polyp – the absence of any discernible margin is often a useful diagnostic clue, although less so in this case which is so extensively ulcerated.

Jeronimo Forteza-Vila - Agreement with diagnosis. It is important to take into account that despite the pseudosarcomatous transformation, neoplasia is benign.

Masaharu Fukunaga - Thank you Janez, it is very impressive. It shares feature of pyogenic granuloma and reactive angioendotheliomatosis.

Goran Elmbergher - Difficult case and important entity you bring up. Maybe you are right but age, location, previous squamous cell carcinoma and this degree of atypia, mitotic activity and atypical mitoses... Furthermore, I suspect the squamous epithelium covering one side of the polyp reveals true dysplastic features. I would perform extensive IHC panel

focusing on epithelial phenotype (including p63/p40) and also include p16 (HPV?) and p53/p21 on the suspicion we are dealing with a squamous cell carcinoma spindle cell type. If nothing else follow-up!

Thomas Krausz - I am a bit worried about this case. There is focal atypia in the epidermis with some downward proliferation. I assume immunostains excluded sarcomatoid carcinoma?

Tom Mentzel - If you come too close it's a difficult case given the cytological atypia associated with many cells, even atypical mitoses.

Markku Miettinen - Excellent case for discussion, atypical mesenchymal (?) proliferation. It is very superficial so when completely excised by this generous excision is probably cured. The diagnosis of pseudosarcomatous stromal polyp would probably help to appropriately spare the old patient from additional quite complicated treatments. Could also think of a possible early post-radiation neoplasia (atypical fibroxanthoma-like, with some superficial resemblance to hyaline angiectatic tumor). Sarcomatoid squamous carcinoma is also a consideration as the overlying epithelium has atypia but seems less likely than a mesencymal process.

Liz Montgomery - Cute case of fake sarcoma. Looks like what you see in polyps in the GI tract as well.

Fredrik Petersson - The degree of nuclear atypia/pleomorphism is striking. I could see a few odd-looking mitotic figures on my slide. ?Any Ki-67 activity in the atypical cells. Given the history of radiation (was the excised lesion from an area that was included in the radiation field?) – Reason for a guarded diagnosis?

Juan Rosai - This vulvar polyp looks very reactive, with features similar to those shown in the paper by Nucci, Young and Fletcher (Am J Surg Pathol 24:231-240,2000). The differential diagnosis includes pleomorphic hyalinizing tumor of solid parts (Am J Surg Pathol 20:21-29,1996) because of the numerous vessels, the extensive thrombosis, and the disposition of some of the atypical cells around the vessels was the location is wrong and the atypia too pronounced.

Brian Rubin - Great case. I love these pseudosarcomatous stromal polyps. This is one of the best I've seen.

Dominic Spagnolo - A very striking example of a pseudosarcomatous stromal polyp in an atypical location. I do wonder if the DXT has had anything to do with it.

James Strauchen - Fibroepithelial polyp with striking stromal atypia. Very informative case!

Bruce Wenig - This case reminded me of sinonasal antrochoanal polyps with atypical stromal cells, which have been shown to represent myofibroblasts. There is surface ulceration, a reactive vascular proliferation, vascular thrombosis and a tendency of the atypical stromal cells to cluster near/around thrombosed vessels. I must say the presence of atypical mitoses really gave me pause and made me concerned for a diagnosis of malignancy. Nice case. Thank you.

Ady Yosepovich - A very nice and illustrative case for a major pitfall in pathology, some of us were taught that atypical mitotic figures are diagnostic of malignancy, apparently this is not the case. Thank you for bringing this case to the club.

CASE NO. 13 – CONTRIBUTED BY: MICHAL MICHAL, M.D.:

Abbas Agaimy - Thanks Michal for this very rare and unusual and misleading phenomenon in endometrioid carcinoma, impressive case.

Phil Allen - I think I would have called it a high-grade malignant tumour with sarcomatous features just like the referring pathologists. Thanks for the contribution Michal.

Carlos Bacchi - I thought this was a carcinosarcoma with very unusual hyalinization!

David Ben-Dor - I agree that a MMMT would have much greater pleomorphism though the amorphous material reminded me of osteoid. Sounds like you've seen this before and not uncommonly- I don't recall having seen this myself.

Michele Biscegllia - Hyalinized endometrioid adenocarcinoma. Do not recall having seen any case of this variant of endometrioid carcinoma. Indeed a diagnostic pitfall at risk to be called mullerian carcinosarcoma!

Ira Bleiweiss - Very interesting. Great case.

Thomas Colby - Agree with diagnosis – I fell in the pitfall of MMMT but must admit I thought there were some peculiarities to the case as a MMMT. Thanks for the education Michal.

Kumarasen Cooper - Thank you Michal for sharing this case. I remember reading the paper; but did not realize that the hyalinization could be so extensive.

Hugo Dominguez Malagon - The stroma is hyalinized but in my slide the epithelial component does not look malignant to my eyes.

Goran Elmberger - New to me and important. Not emphasized in standard textbooks or WHO. According to WHO, one might be tempted to classify as carcinosarcoma or carcinofibroma but I guess original publication nomenclature is far better. Absence of the epithelial high-grade component is the tip off.

Giovanni Falconieri - Great case Michal. Agree, this could be misleading.

Franco Fedeli - I believe that you have emphasized the problem: I too was considering the hyaline stroma as sarcomatous. The article that you have recommended is enlightening about the new category of endometrioid tumors called CHEC (corded and hyalinized EC); in my opinion two features of CHEC are very interesting: they include a younger age (mean, 52 years) at presentation relative to typical EC (mean age, 60 years) and the higher than usual frequency (70%) of squamous differentiation.

Cyril Fisher - Endometrioid endometrial carcinoma with hyalinization, very good slide and a pitfall to be aware of.

Christopher Fletcher - Thanks – I have no prior personal experience with hyalinized endometrioid adenocarcinoma and this case was very educational.

Jeronimo Forteza-Vila - It strikes to me atypia in hyalinized areas that may be confused with carcinosarcoma.

Masaharu Fukunaga - It looks like adenosarcoma with sarcomatous overgrowth. As far as in the slide, there are no convincing parts of endometrioid adenocarcinoma although atypia is seen. It is very a nice case, thank you Michal.

Allen Gown - I assume that all the tumor cells were keratin positive (and perhaps PAX8), which would help in their identification as adenocarcinoma.

Thomas Krausz - Superb case. I agree that in most areas the “pink” material is hyalinized collagen, but in a few microscopic foci I feel there is also osteoid. Focal osteoid formation can be present in hyalinizing endometrial carcinoma and it is mentioned in the reference cited.

Janez Lamovec - I must admit that I have fallen in the same trap as your referring pathologists although the ''osteosarcomatous'' component appears too low grade. Thank you for this instructive case.

Tom Mentzel - To be honest I made the same mistake, because atypical plump spindled tumour cells are seen in or around the hyalinized areas.

Markku Miettinen -Agree on endometrioid adenocarcinoma. Tumor has also osteoid formation so could be called metaplastic carcinoma.

Liz Montgomery - Thanks for this. A beautiful pitfall.

Fredrik Petersson - What a pitfall! I was not aware of the entity – phenomenon. Initially I thought this could be a metastatic breast cancer (pleomorphic lobular or matrix producing) to an endometrial lesion. However, when I had a closer look at the cells in the hyalinized areas, they seem to focally merge with (?) endometrial stroma surrounding some of the glands. Were the cells in the hyalinized areas CK-positive? I guess a clue to the diagnosis is that normally the glandular component in a MMMT is not uniformly grade 1, but rather pleomorphic/variable both in type and grade.

Juan Rosai - Very peculiar case. The extracellular material sure looks like osteoid to me. Maybe it is just an endometrioid adenocarcinoma with osseous and chondroid metaplasia, but I would also consider a low grade mixed Mullerian tumor.

Brian Rubin - Never heard of this or seen it before. Thanks.

Elvio Silva - Michal, probably you have more slides with obvious endometrioid carcinoma. I am not convinced about endometrioid carcinoma in my slide. I have seen hyalinization of the stroma not only in endometrioid carcinomas but also in some endometrial hyperplasias and serous tumors. My comment is that in an epithelial proliferation in the GYN we should not diagnose endometrioid carcinoma based on the presence of hyalinized stroma. I have not published this because I do not have an explanation for the hyalinization.

Dominic Spagnolo - Simply stunning corded and hyalinized endometrioid adenocarcinoma. Thanks Michal.

James Strauchen - Hyalinized endometrial adenocarcinoma. I have never seen one before. Thank you!

Saul Suster - I would have called it MMMT – thanks for the education! Was not aware of this phenomenon.

Bruce Wenig - I certainly can understand the consideration of concomitant matrix formation. The hyalinization looks like osteoid. Great case.

Ady Yosepovich - Thank you for sharing this very unusual variant.

CASE NO. 14 – CONTRIBUTED BY: MARKKU MIETTINEN, M.D.:

Abbas Agaimy - Very interesting case, looks deceptively chondroid, thanks Markuu.

Phil Allen - Adult myofibroma, subcutis, thigh. I had no trouble with this one. Funnily enough, only this morning I received in consultation a very cellular myofibroma from the eyebrow of a 23-year-old woman. At my age, a 23-year-old counts as a child. As I'm not too keen on raising any more haemangiopericytomas from the dead, I called it a cellular myofibroma of the young.

Carlos Bacchi - Nice case.

David Ben-Dor - Nothing to add. Thanks for the reminder of the existence of this lesion and especially the possible occurrence in adults. I remember seeing it in Dr Fletcher's soft tissue course but have never since come across this.

Michele Biscegllia - Adult myofibroma. A very peculiar variant of (solitary) adult myofibroma.
Ira Bleiweiss - Another new diagnosis for me.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Thank you Markku. The zoning phenomenon is well illustrated. My “fibroma” component had a basophilic hue to the stain.

Hugo Dominguez Malagon - Very interesting and illustrative case.

Goran Elmberger - Very characteristic low-power features. Slight chondroid quality. A vascular tumor as suggested by Requena?

Giovanni Falconieri - Never seen before, thank you Markku for this contribution.

Franco Fedeli - Agree. Nice case

Cyril Fisher - Adult myofibroma. The relationship to blood vessels is well shown.

Christopher Fletcher - Perfect example of adult myofibroma/myopericytoma with characteristic blueish pseudochondroid hyalinisation.

Jeronimo Forteza-Vila - I had not seen before this entity.

Masaharu Fukunaga - My impression is myopericytoma with cartilaginous differentiation.

Allen Gown - Thanks, Markku.

Thomas Krausz - Agree with diagnosis.

Janez Lamovec - Adult myofibroma. Quite a typical case.

Tom Mentzel - A beautiful example of solitary myofibroma with nice myxohyaline stromal changes.

Liz Montgomery - Lovely myofibroma.

Fredrik Petersson - The myxoid areas (on my section) led me into initial difficulties in the interpretation.

Juan Rosai - So, that is how myofibromas look like! But what about all the vessels? I would have considered a vascular neoplasm in the hemangiopericytoma family with cartilaginous metaplasia.

Brian Rubin - Nice case.

Dominic Spagnolo - The overlap with myopericytoma is seen nicely in this striking example of adult myofibroma.

James Strauchen - Adult myofibroma. Very striking!

Saul Suster: Agree – classical case.

Bruce Wenig - Myofibroma; beautiful example. Thank you, Markku.

Ady Yosepovich - Very peculiar case, thank you for sharing.

CASE NO. 15 – CONTRIBUTED BY: MANUEL SOBINHO SIMOES, M.D., Ph.D:

Abbas Agaimy - Very unusual case! Why not a poorly differentiated neuroendocrine carcinoma? TTF1? EWS FISH? Adamantinoma-like Ewing is one possibility if neuroendocrine is excluded.

Phil Allen - Poorly differentiated neuroendocrine carcinoma, left pulmonary hilum with multiple pulmonary metastases in the left lower lobe, female aged 20. I haven't checked out the latest fashions for classifying pulmonary tumours with neuroendocrine differentiation.

David Ben-Dor - All in the hands of the gods of immunohistochemistry. In my own hands, given the lung location I would have looked for positivity for neuroendocrine markers and called it small cell carcinoma on that basis without necessarily going further. Maybe a lack of smoking history and the young age of the patient would go against that and lead to further reflection and hopefully investigation and consultation.

Michele Biscegllia - Neuroendocrine carcinoma versus PNET of lung. Would favor the diagnosis of neuroendocrine carcinoma but would include in the differential diagnosis even the (extrabdominal) intrabdominal round cell tumor, pending consistent results from additional immunos (TTF1, Fli-1, WT1) and/or molecular FISH studies...

Ira Bleiweiss - Neuroendocrine carcinoma.

Thomas Colby - Obvious issue of classification. Considered NUT midline carcinoma (could do further studies for that), desmoplastic small round cell tumor, and a new entity I just thought up called a thymoblastic carcinoma.

Kumarasen Cooper – Ewing sarcoma vs. poorly-differentiated synovial sarcoma (PDSS). FLI-1, TLE-1, FISH for EWSR1 and SYT gene rearrangements. I saw a similar case in a young woman who had past history of mediastinal Hodgkin's lymphoma that was irradiated. Turned out to be a PDSS.

Hugo Dominguez Malagon - Another possibility is DSRCT.

Goran Elmberger - Case needs full scale work-up for small blue round cell tumors including translocation markers including those for Ewing/PNET. Your tentative diagnosis is quite reasonable but I would prefer broader panel and also consider metastasis in this young female. To me not in itself convincing for typical primary pulmonary tumor. Whole body CT/PET? Gyn?

Giovanni Falconieri - Sorry Manuel, I am clueless; PNET is my guess here. An amazing case though! Thank you for this contribution.

Franco Fedeli - I would propose the enigmatic definition of "small round cell tumor with stromal desmoplasia" for this tumor which I assume at the end will came up with some surprise.

Cyril Fisher - Genetic investigation will be of interest for PNET.

Christopher Fletcher - Round cell malignant neoplasm. The aggregates of tumour cells, at least in areas, appear somewhat more cohesive than usually seen in Ewing sarcoma, so it would be of interest to know the results of any *EWSR1* gene rearrangement. I would be concerned that this might represent some type of neuroendocrine carcinoma.

Jeronimo Forteza-Vila - According to location and morphology, the first impression is a neuroendocrine carcinoma of intermediate-sized cell. Seeing this, it is more difficult to know for sure and PNET is a better possibility, but considering it can be objective via FISH.

Masaharu Fukunaga - Very difficult case. It looks like desmoplastic round cell tumor or PNET.

Allen Gown - I would seriously consider the diagnosis of PNET/ES, given the histology, patient demographics, and immunophenotype. IHC for markers such as NKX2.2 or FISH studies looking for the presence of a translocation involving the EWSR gene might be most helpful.

Thomas Krausz - I would consider poorly differentiated synovial sarcoma (round cell type) also in the differential diagnosis.

Janez Lamovec - Poorly differentiated small round cell tumor; in places it is somewhat similar to DSRCT although the immuno is not right.

Tom Mentzel - Despite the immunohistochemical results the H&E is similar to what is seen in desmoplastic small round cell tumour.

Markku Miettinen -Desmoplastic small round cell tumor seems a good possibility given the histology and co-expression of keratins and desmin. Genetics for the fusion or nuclear WT1 testing would be decisive, certainly this very aggressive tumor is clinically fairly equal to Ewing family tumor/PNET.

Liz Montgomery - Beats me. DSRCT sans desmin? Myoepithelial lesion (was an S100 done). Strange Ewing's sarcoma. Not sure.

Fredrik Petersson - Were molecular genetic studies (EWS) done?

Juan Rosai - Generically speaking, I would place this tumor into the category of small round blue cell tumor. It could be a PNET, and I am surprised that the translocation was not looked for. Another consideration would be a neuroendocrine carcinoma, perhaps in the family of carcinoid tumor. Again, I am surprised that a chromogranin stain was not preformed.

Brian Rubin - I'd want to do genetic analysis to exclude unusual Ewing/PNET or DSCRT. Otherwise, I think I'd opt for myoepithelial carcinoma.

Dominic Spagnolo - PNET seems reasonable. Desmoplastic round cell tumour is another consideration though the site would be odd (unless it was pleural based). A more extensive IPX work-up would seem indicated for me.

James Strauchen - PNET seems plausible. ? EWS translocation.

Bruce Wenig - Looks like a high-grade neuroendocrine or neuroectodermal-type malignancy. Was there evidence of EWSR1 translocation?

Ady Yosepovich - Could this be mesenchymal chondrosarcoma?

CASE NO. 16 – CONTRIBUTED BY: ELVIO SILVA, M.D.:

Abbas Agaimy - Nice case. Never seen before in the placenta. Thanks.

Phil Allen - Small (2 cm), apparently incidental, intraplacental gestational choriocarcinoma in an otherwise normal term placenta. This is the first case I have seen. Thanks very much for the contribution.

Carlos Bacchi - I thought about choriocarcinoma but I didn't know one could be found intraplacentally as a nodule like this. Thanks for the case.

David Ben-Dor - Pretty amazing for me. I'll have to start looking more carefully at the infarcted areas in the placentas I see! I learned from a recent case of gestational trophoblastic disease that not all gynecological pathologists even when very renowned are comfortable or happy to deal with this particular area of trophoblastic disease.

Michele Biscegllia - Intraplacental gestational choriocarcinoma. Never seen a case. Thank you, Elvio.

Ira Bleiweiss - Agree. Cool.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Elvio, for a first time diagnosis this is always going to be difficult for me. I was aware of your paper and thought about the diagnosis but considered an infective etiology with intranuclear inclusions!!! Upon review I see the subtle islands of syncytial trophoblasts. Thank you for sharing this case.

Hugo Dominguez Malagon - Very interesting case, the trophoblastic atypia is striking.

Goran Elmberger - Thanks for rare case obviously of great importance due to possible metastatic spread to mother and baby.

Giovanni Falconieri - Never seen before, thank you, Elvio for this great contribution.

Franco Fedeli - Very nice case. We can see both a focus of ischemic necrosis that is usually seen in the parenchyma of the term placenta next to a focus of tumoral necrosis. The diagnosis in this way is easier, and of course, I agree with your comment about the differential diagnosis.

Christopher Fletcher - Truly a remarkable case in this clinical context.

Jeronimo Forteza-Vila - Very interesting case.

Masaharu Fukunaga - Thank you, Elvio. It is very beautiful and relatively large lesion.

Thomas Krausz - Agree with diagnosis.

Janez Lamovec - What a fascinating case! Thank you.

Tom Mentzel - Many thanks for sharing this rare neoplasm showing extensive necrosis.

Markku Miettinen -Looks cytologically very bad and has necrosis, so one has to believe it is malignant. Could be very challenging if ever seen in a biopsy.

Liz Montgomery - Thanks for the education.

Fredrik Petersson - Nice case. Did the patient have elevated serum level of beta-HCG?

Juan Rosai - Great case of choriocarcinoma developing in a mature placenta. I was taught that if you see villi in a trophoblastic tissue, it cannot be a choriocarcinoma. I guess Dr. Ackerman was right when saying that “anything can happen, anywhere, sometimes.”

Brian Rubin - Very interesting case.

Dominic Spagnolo - Have never seen an intraplacental gestational choriocarcinoma Elvio. Thanks for the case.

James Strauchen - Intraplacental choriocarcinoma.

Bruce Wenig - Agree with choriocarcinoma. Very unusual case and one that I never get to see. Thanks, Elvio.

CASE NO. 17 – CONTRIBUTED BY: JAMES STRAUCHEN, M.D.:

Abbas Agaimy - Very nice and really challenging case, peculiar coincidence with my case 1 in this seminar. Looks somewhat similar to my case but lacked isolated fat vacuoles/cells and seems to contain widely distributed residual liver cells and lack myoid and giant cells. Just as a matter of interest, I would suggest to stain for HMB45, cathepsin K and IgG4.

Phil Allen - EBV positive inflammatory pseudotumour of the liver with oligoclonal T-cell expansion secondary to EBV infection vs. peripheral T-cell lymphoma. I haven't had enough lymphoma experience to know which of the two suggestions is more likely but it certainly bears no resemblance to an inflammatory myofibroblastic tumour.

Carlos Bacchi - Very difficult case to decide if there is a lymphoma associated with IMT or not.

David Ben-Dor - Can the islands of residual hepatocytes be considered a homologue of lymphoepithelial lesions seen in B cell proliferations?

Michele Biscegllia - This case is in line with the differential diagnostic problems seen in case n. 1 of this same seminar. Very interesting as well as difficult to assess in every facet.

Thomas Colby - Confession of ignorance; morphologically I considered a low-grade lymphoma.

Kum Cooper - A very neat case with an excellent work-up (and consultations). Thank you for sharing.

Hugo Dominguez Malagon - Nice case and discussion.

Goran Elmberger - Interesting case where I would prefer interpretation as IPT rather than peripheral T-cell lymphoma based on EBER positivity within spindle cells. Just presented case of pulmonary IMT in Tel Aviv AMR slide seminar and in my presentation I stressed the fact that unqualified diagnosis of IPT is probably no longer advisable. Based on IHC maybe this should be viewed as EBV associated smooth muscle tumor or myofibroblast tumor (depending on outcome of extended IHC) with IPT-like presentation.

Giovanni Falconieri - Challenging slide, thank you. Unfortunately I cannot offer any valuable comment.

Franco Fedeli - I favor peripheral T-cell Lymphoma. I know that malignant lymphoma confined to the liver is a very rare occurrence and also that some of the primary hepatic lymphomas have occurred in association with HCV infection. But here is a continuous spectrum of small, medium-sized, and large lymphoid cells with nuclear irregularities and a rich component of inflammatory cells (such as histiocytes and eosinophils). The spindle cells could be reactive to neoplastic lymphoid cells.

Cyril Fisher - What a difficult case. On morphology I would have gone for inflammatory pseudotumour like variant of FDCS (also EBV positive) but the markers exclude it.

Jeronimo Forteza-Vila - This a pseudoinflammatory tumour related to EBV. It would be arguable whether an ogligoclonal T-cell expansion is equivalent to a peripheral T-cell lymphoma.

Masaharu Fukunaga - It is very difficult for me. How about IgG4?

Allen Gown - The distinction of an oligoclonal T cell expansion driven by EBV from an EBV driven lymphoma can be exceedingly difficult, and the clinical follow up of this case would be most critical in retrospectively assigning the correct diagnosis!

Thomas Krausz - Very interesting case.

Janez Lamovec - Without immuno and apparently even with immuno and cytogenetic studies this is a very difficult lesion to classify. I cannot offer any useful suggestion.

Tom Mentzel - An interesting case that looks like an EBV-associated pseudolymphoma.

Markku Miettinen -Could not histologically tell low-grade lymphoma vs. atypical lymphoid hyperplasia. Glad to know that even hematopathologists had problems. Clinical follow-up would also be informative.

Liz Montgomery - Looks like an EBV-driven pseudotumor to me but I have no expertise.

Fredrik Petersson - Interesting, educational. No comment, leave this for the hematopathologists.

Juan Rosai - I would be glad to leave this case to the hematopathologists.

Brian Rubin - Great case and very educational for me. Thanks.

Dominic Spagnolo - With due deference to all 3 experts who have seen the case, because of the EBER positivity I would still be favoring an IPT-like FDC sarcoma in this case. The commonly used FDC markers may rarely be negative, or there may only be focal staining seen in some sections and not others. If possible, a wider panel of FDC markers might be used in these circumstances. Ultrastructure still has a role in such difficult cases.

Bruce Wenig - One needs to know one's limitations. Looked like an inflammatory rather than neoplastic lesion to me but if this was my case I would have sent it to a hemepath expert in consultation.

CASE NO. 18 – CONTRIBUTED BY: SAUL SUSTER, M.D.:

Abbas Agaimy - Very interesting antral lesion with plexiform pattern. In light of the localization, H&E and the expression of SMA alone I would consider this case a “plexiform angiomyxoid myofibroblastic tumor” which has been recently renamed “plexiform fibromyxoma” by Markuu Miettinen. This case is somewhat more cellular. All behaved benign till now. Thanks Saul for this nice case.

Phil Allen - Undiagnosed, 3.5 cm, histologically bland, spindle to round clear cell tumour, gastric antrum. The only suggestion I can make would be to try some neuroendocrine stains.

David Ben-Dor - Maybe we don't yet have the tools to give a "name" to everything. It looks plexiform to me which would lead me to think of some sort of nerve sheath tumor but the negativity for S100 would go against that. How is the patient doing?

Michele Biscegllia - Low-grade stromal tumor of the gastric wall – type undetermined??? Agree with the definition given. No suggestion on my part.

Ira Bleiweiss - Saul- if you don't know what this is, no one else does either.

Thomas Colby - I too favored a peculiar GIST but the immunos don’t really support that and the morphology is indeed peculiar. Hopefully one of our soft tissue or GI members will have some bright ideas.

Kumarasen Cooper - Sorry Saul. I have no better suggestions.

Hugo Dominguez Malagon - I do not know how to call this interesting lesion, it has a peculiar hyaline material. Perhaps it has a myoepithelial phenotype??

Goran Elmberger - Unusual variant of plexiform fibromyxoma?? Markku?

Giovanni Falconieri - Sorry Saul, do not have better alternatives.

Franco Fedeli - I'm so sorry Saul, but I too thought to be a low-grade GIST!

Christopher Fletcher - Very unusual morphology – possible options could include an unusual plexiform smooth muscle neoplasm or perhaps an SDH-deficient GIST, given the multinodular growth pattern. Was staining for SDHB performed?

Jeronimo Forteza-Vila - Morphology would be compatible with GIST. Immunohistochemistry seems to invalid that diagnosis. I don’t know whether studying mutations could help.

Masaharu Fukunaga - It is very challenging. My impression is retiform perineurioma.

Allen Gown - Is this a PEComa?

Thomas Krausz - First I was considering reticulated microcystic schwannoma, but immunoprofile is against it. My differential also includes plexiform myxofibroma as described by Marku.

Janez Lamovec - Myxoid spindle cell tumor, ?myofibroblastic. EM might be helpful.

Tom Mentzel - Given the presence of thin and elongated cell processes I was thinking on a case of perineurioma (have you done EMA stainings ?), but the reported staining for actin does not fit with this. Since the lesion is lobular or plexiform and shows myxoid stromal changes I was thinking also on plexiform angiomyxoid myofibroblastic tumour of the stomach, but the cytomorphology of the neoplastic cells is different.

Markku Miettinen - Mesenchymal neoplasm, probably indolent, possibly plexiform fibromyxoma. Location and growth pattern would also be good for this possibility. Judging from focal epithelioid morphology could even have some glomus

tumor-like differentiation although h-caldesmon negativity does not fully support this. Cannot identify here any form of GIST or gastroblastoma (keratin immunohistochemistry would be useful to rule out epithelial components).

Liz Montgomery - Maybe try a keratin for weird myoepithelial lesion and EMA et al for a perineurial/meningothelial one. The plexiform look is like Markku's plexiform fibromyxoma but the cells look different!

Juan Rosai - I would ignore the immunohistochemistry and favor a peculiar morphologic variant of GIST.

Brian Rubin - I think desmin negativity excludes smooth muscle tumor. Could it be a really weird glomus tumor? I've never seen anything exactly like it.

Dominic Spagnolo - Not sure either Saul, but wondered if it might be a reticular and plexiform perineurioma. Looks very bland and is amitotic as far as I can tell (thought there is not much of the lesion in my slide). I did also consider a plexiform angiomyxoid myofibroblastic tumour but seems too cellular and the vascularity not right either.

James Strauchen - No idea!

Bruce Wenig - It has a myoid look to me, too, but I have not seen a leiomyoma/leiomyosarcoma with this morphology. Not sure what it is either.

CASE NO. 19 – CONTRIBUTED BY: SAUL SUSTER, M.D.:

Abbas Agaimy - An interesting and challenging case! I agree Saul; one has great difficulty calling this lesion malignant. I have the impression that it is a chronic pericarditis related to chronic effusion with exuberant vascularized granulation tissue. Vessels and vacuoles have some perpendicular orientation to the surface. The vacuoles are very peculiar. They reminded me of a phenomenon I have seen a few years ago in diverse specimens (extensive irregular adenomatoid-like changes in uteri and colon resections). Our enquiries revealed that tissue was refrigerated overnight and then put into formalin. I am not sure if this is something similar but I strongly feel that there is here some type of fixation or other tissue artifact.

Phil Allen - Organizing non-specific pericarditis with vacuolar change in spindle cells. I suspect that the vacuoles are artefactual due to handling and fixation of the tissues prior to processing. I don't think it is malignant.

David Ben-Dor - My own instinctive gut reaction was some sort of strange organization process related to the fibrinous material adjacent to it. The negativity for CD31 wouldn't support that but then again the immunos don't seem to support much of anything else. Would it help to try other vascular markers- CD34, factor VIII?

Michele Biscegllia - Unknown. I do not know what it is either. Maybe no tumor at all is there.

Ira Bleiweiss - I think this is reactive and not neoplastic. Don't know why.

Thomas Colby - I would probably have to study a bunch of immunos in this case to convince myself but I wonder if the vacuolated spaces aren't some peculiar artifact since they seem to be somewhat zonal in the tissue. Otherwise this looks like a fibrinous and fibrous pericarditis to me.

Kum Cooper - Again Saul, my thoughts were similar to yours; mesothelial (adenomatoid tumor??site unusual); vascular (D2-40 ?lymphatic; ERG for endothelial).

Hugo Dominguez Malagon - My first impression was of an adenomatoid tumor which is denied because of the immunos. I do not have a diagnosis, perhaps an inflammatory condition with a peculiar degenerative change.

Goran Elmberger - Considering negative markers I might have included vascular markers, CT4 but I believe this may be an artefact due to tissue processing much alike the "fake fat" phenomenon recently emphasized in pleural-mesothelioma pathology.

Giovanni Falconieri - Very frustrating Saul, this is also impossible although I share your pain.

Franco Fedeli - Adenomatoid tumor was excluded by immunostains performed. I don't know.

Christopher Fletcher - It seems to me that there are changes very suggestive of some type of infective pericarditis and I wonder if these vacuolated cells are some type of artefact or degenerative alteration.

Jeronimo Forteza-Vila - It is not clear for me we are facing a tumour, and even more a malignant one. I think it is pseudotumoral process of immune nature. I would perform an IgG4 in order to rule out diseases related to IgG4, since perycarditis has an autoimmune mechanism in many cases.

Masaharu Fukunaga - Another challenging case. It looks like adenomatoid tumor.

Allen Gown - Thanks, Saul. I'm with you, and I am not convinced this is an infiltrating malignancy, based both on the histology as well as the results of your immunostains. But how do the cells lining the vacuoles mark?

Thomas Krausz - Very "strange" features. I am not sure either. Perhaps continue with immuno-studies to make further attempt to establish the lineage of the vacuolated cells (CD68 for histiocytes, collagen IV, laminin to outline fat cells because sometimes damaged fat cells are S100 negative). A degree of vacuolation has been described also cases of monocyte/mesothelial hyperplasias (MICE). I think this is and organizing pericarditis and not a neoplastic process.

Janez Lamovec - This lesion seems reactive to me. I wonder whether the spaces represent some dissolved stuff but no foreign body giant cells are present.

Tom Mentzel -??? There is a prominent mixed inflammatory infiltrate – could these vacuolated changes simply degenerative in nature?

Markku Miettinen -Cannot think anything better than just a bad fibrinous (? infectious) pericarditis, with luminal side granulation tissue formation and evolving fibrosis. Vacuolization could sometimes be caused by a freezing artifact.

Liz Montgomery – Clueless

Fredrik Petersson - Never seen before. I also thought this was an adenomatoid tumor (actually I was quite convinced I could see the "thread-like bridging strands" as described by Michal). Could it be secondary to the procedure, e.g. a pseudolipomatosis type lesion???

Juan Rosai - I have the feeling that we are dealing with some kind of bizarre artifact involving fibroadipose tissue. In some areas it looks like an adenomatoid tumor, but this is ruled out by the immunostains.

Brian Rubin - Yikes. You covered the most obvious differential diagnosis pretty well. I don't have any additional ideas.

Dominic Spagnolo - No idea Saul. I came back to thinking the spaces are probably fat after all (epicardial), maybe with interspersed lymphatics. It has a zoned organizing fibrinous pericarditis look about it, and the intervening spindle cells between the spaces look like fibromatosis. Could it just be a weird organizing pericarditis of whatever cause??

James Strauchen - I think's it's all reactive, organizing effusion, etc.

CASE NO. 20 – CONTRIBUTED BY: LAWRENCE WEISS, M.D.:

Abbas Agaimy - A pretty metanephric adenoma, thanks.

Phil Allen - Thanks for this, Larry. I have never previously made that diagnosis. I dare not think of the possibility of having missed one.

Carlos Bacchi - Thank you Larry for this nice example of renal metanephric adenoma. It is really photogenic one.

David Ben-Dor - Nice case. I think that WT-1 is also discriminatory in the differential with say papillary adenoma of the kidney- it would be positive in metanephric adenoma and negative in papillary adenoma.

Michele Biscegllia - Renal metanephric adenoma. Agree. The term "metanephric adenoma" was coined for the first time at "G. Gaslini" Pediatric Institute (Genoa, Italy) by M. Brisigotti in 1992 in a case report concerning a young girl of 7 years of age, which was being investigated due to (paraneoplastic) polycytemia.

Ira Bleiweiss - Wow. Rare and photogenic indeed.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Thanks Larry for this lovely example. CK 7 and AMACR negativity rules out papillary renal carcinoma. Also metanephric adenomas are WT-1 positive and EMA negative.

Hugo Dominguez Malagon - I agree with the diagnosis of metanephric adenoma, thank you.

Goran Elmberger - Pretty case.

Giovanni Falconieri - Nice teaching case. Thank you for this submission.

Franco Fedeli - I saw a renal metanephric adenoma for the first time about 15 years ago and sent the case to Dr Rosai who showed it to Dr Reuter because at that time I did not see a tumor like this.

Cyril Fisher - Metanephric adenoma, very pretty example.

Christopher Fletcher - Perfect example of metanephric adenoma – many thanks.

Jeronimo Forteza-Vila - Agreement with diagnosis.

Masaharu Fukunaga - Thank you for the case of renal metanephric adenoma. Its histology is very similar to mesonephric adenocarcinoma of the uterine cervix.

Allen Gown - Nice case, thanks Larry.

Ondrej Hes - Very nice case, thank you. Sometimes it is not easy to make diagnosis in cases, where "solid", "blatomatoid" component is present or where such structures are predominant. I believe, there is "gray zone" among very well differentiated adult Wilms tumor, solid variant of papillary renal cell carcinoma and metanephric adenoma. Immunohistochemistry helps to exclude solid variant of PRCC (sometimes also FISH detection of polysomy of chromosomes 7 and 17 is very useful), but differentiation between well differentiated Wilms tumor and metanephric adenoma could be painful. This phenomenon was nicely described by Dr Arroyo et al (Arroyo MR, Green DM, Perlman EJ, Beckwith JB, Argani P.: The spectrum of metanephric adenofibroma and related lesions: clinicopathologic study of 25 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol. 25(4):433-44, 2001).

Thomas Krausz - Nice example of metanephric adenoma.

Janez Lamovec - Very characteristic case of this benign kidney tumor.

Tom Mentzel - Many thanks for sharing this wonderful example of metanephric adenoma.

Markku Miettinen -Agree on metanephric adenoma. Nice case.

Liz Montgomery - Lovely case.

Fredrik Petersson - Several glomeruloid structures on my section. On core biopsy pitfall for epithelial predominant WT. CD57 helpful.

Juan Rosai - Very pretty case of metanephric adenoma of kidney.

Brian Rubin - Pretty example.

Dominic Spagnolo - Very nice metanephric adenoma Larry. Don't see these often.

James Strauchen - Metanephric adenoma. Very nice example!

Bruce Wenig - Yes it is a pretty case and a textbook example. Thank you.

CASE NO. 21 – CONTRIBUTED BY: BRUCE WENIG, M.D.:

Abbas Agaimy - Very unusual case! Looks in some areas like epithelioid angiosarcoma. Because of the complete encapsulation. I would also think of Tumor-to-Tumor metastasis. Thanks for sharing this nice case.

Phil Allen - Intrathyroidal anaplastic carcinoma arising in a better differentiated follicular lesion, right lobe, in a multinodular goiter. I agree. All the anaplastic thyroid carcinomas I have seen have been widely invasive.

Carlos Bacchi - Thanks Bruce for this great case and discussion about anaplastic carcinoma, in this context (intrathyroidal location).

David Ben-Dor - This reminds me of a situation which arose some years ago in my department. A woman comes off the street and told me that a few years (say 5-6 or maybe more) previously (which was before I had started working here) she had a thyroid lesion removed in my hospital which was reviewed in a different hospital by a very prominent pathologist who called it anaplastic carcinoma. She then received brutally intensive chemotherapy in a third institution. She had wanted the case to be reviewed. Unfortunately I couldn't locate any of the pertinent materials or at least the blocks but I said that given the fact that she appeared intact though slightly the worse for wear meant that she probably didn't have anaplastic thyroid carcinoma. I was intrigued by the fact that the nodule was described as being grossly circumscribed (I don't remember if in the path report which did locate or in the surgeon's description) which would be not typical for anaplastic carcinoma. I found descriptions of medullary carcinomas showing marked pleomorphism; in fact I think that in the past medullary and anaplastic carcinomas were confounded and not separated until later on. I apologized to the lady for not having her materials available to prove my hypothesis but suggested that she be evaluated for any of the syndromes in which medullary carcinoma can present. I didn't see any reference in the write-up as to whether stains for amyloid or calcitonin were performed; if they weren't performed does it pay to try?

Michele Biscegllia - Intrathyroidal anaplastic carcinoma with angiomatoid component and a differentiated follicular epithelial cell lesion. Never seen a case of circumscribed anaplastic (intrathyroidal) carcinoma. The angiomatoid component in this case is in agreement with a phenomenon of transmesenchymal differentiation.

Ira Bleiweiss - Agree.

Thomas Colby - Agree with diagnosis. I guess I could not write off the atypia here as “endocrine anaplasia.” This is endocrine.

Kumarasen Cooper - Thank you, Bruce for sharing this undifferentiated (anaplastic) encapsulated thyroid carcinoma. I saw an example last week that arose in a poorly differentiated thyroid carcinoma (which is described in the Turin Classification paper by Dr Rosai et al). Needless to say my case was Stage IV.

Hugo Dominguez Malagon - Anaplastic encapsulated carcinoma, in my slide there is no angiomatoid component but there are some lumina containing erythrocytes among the cells.

Goran Elmberger - Interesting case. Wonder how the situation will evolve. If indeed these encapsulated variants behave better than other undifferentiated thyroid carcinomas it seems too aggressive to stage them T4a. Analogous to CEPA intracapsular?

Giovanni Falconieri - What a case, Bruce. Agree of course with your assessment. All cases of anaplastic carcinoma I have seen were wildly invasive at time of diagnosis, first time I see an encapsulated variant.

Franco Fedeli - This is a very nice case. Maybe the tumor circumscription and the absence of extrathyroidal extension are the expression of early development. I have never seen this.

Cyril Fisher - Very interesting case and discussion.

Christopher Fletcher - Given your immunophenotypic findings, the diagnosis seems to be proven but I suspect that I would have missed this and simply labelled this as an epithelioid angiosarcoma – thank you for the helpful write up.

Jeronimo Forteza-Vila - Agreement with diagnosis.

Masaharu Fukunaga - Thank you for the unusual thyroid tumor and detail discussion. Bruce. I have never seen it before.

Allen Gown - Strange case, Bruce! One wishes it were possible to perform molecular studies on the angiomatoid component, to see its relationship to the rest of the tumor.

Thomas Krausz - Highly educational case. Thank you very much for the excellent discussion.

Janez Lamovec - We've seen a few cases of epithelioid angiosarcoma of the thyroid without any admixture of carcinomatous component. Here we are in Alpine region and most described cases were also seen in this area. Immunohistochemistry and EM examination confirmed the endothelial nature of these tumors. So, we believe that such tumors in the thyroid exist despite some claims to the contrary.

Tom Mentzel - These encapsulated non-invasive but anaplastic carcinomas of the thyroid are indeed an unusual entity, many thanks.

Markku Miettinen -Agree, anaplastic carcinoma - arising from a follicular carcinoma?, or can anaplastic carcinoma arise from a follicular adenoma or goiter? A differential diagnosis is metastasis to the thyroid from another anaplastic tumor, such as lung cancer. Clinical correlation is useful.

Liz Montgomery - This is stunning.

Fredrik Petersson - Working in a country where "NPC" is endemic can't help to wonder if there was EBV in the tumor.

Juan Rosai - Anaplastic carcinoma of the thyroid. The tumor, as usual, is arising in a well differentiated follicular lesion. The massive leukocytic infiltrate is pretty characteristic of the squamoid type of this tumor.

Brian Rubin - Very interesting case. It makes sense that it could happen when you think about it but I've never seen a case of encapsulated anaplastic thyroid carcinoma. Lucky patient!

Saul Suster - Great case of a tumor "caught in the act" of transforming from a well-differentiated follicular lesion into anaplastic carcinoma. I have seen this once before as a focalized phenomenon in a tumor that was arising in a papillary carcinoma.

Dominic Spagnolo - Instructive case of an unusually encapsulated anaplastic thyroid carcinoma. One might have imagined that there would have been a recent history of more rapid growth. Thanks for the case and nice discussion.

James Strauchen - Anaplastic thyroid carcinoma arising in follicular lesion. The anaplastic carcinoma cells show emperipolesis!

CASE NO. 22 – CONTRIBUTED BY: ADY YOSEPOVICH, M.D.:

Abbas Agaimy - Very nice example of secretary carcinoma, thanks.

Phil Allen - Secretory carcinoma, left breast in a 58-year-old female. Thanks for the discussion on this very well worked up case.

Carlos Bacchi - Nice case!

David Ben-Dor - Nice case - I wonder in what way I would have mangled the diagnosis. Good that the oncologist smelled a rat and asked for histological review. I learned that to dispute any of Adi's diagnoses is at my own peril. Interesting as to why the receptors are negative- one would think that given the differentiated architecture and low cytological grade they would be positive.

Michele Biscegllia - Nice case of secretory carcinoma of the breast in adult, with beautiful illustrations. Thank you, Ady.

Ira Bleiweiss - Agree. Beautiful case.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Thank you for the exciting example. This looks remarkably similar to the MASC of the salivary gland that Goran presented in South Africa. The t(12;15) is very useful.

Hugo Dominguez Malagon - I agree with the diagnosis of secretory breast carcinoma nice example.

Goran Elmberger - Got this one from my H&N perspective. Found 8 cases so far prospectively in our routine salivary gland service since Alena Skalova and Michal described this entity MASC recently. Interestingly, this salivary gland tumor named mammary analogue seems to occur much more frequently in salivary gland than in breast.

Giovanni Falconieri - Great case to start with! No single word to add to the perfect description.

Franco Fedeli - Educational case. And we now know also that there's a salivary gland analogue with the same specific translocation at the same chromosal breakpoint (Skalova A. eta al. AJSP 2010;34:599).

Cyril Fisher - Nice example of secretory carcinoma of breast with genetic confirmation.

Christopher Fletcher - Very convincing example of secretory carcinoma.

Jeronimo Forteza-Vila - Agreement with diagnosis.

Masaharu Fukunaga - Welcome, Ady. It is a very beautiful case of secretory carcinoma of the breast with a detail description. Thank you very much.

Allen Gown - Lovely case, thank you.

Thomas Krausz - Very nice example. I haven't seen one for many years but I was fortunate enough to study a small series with John Azzopardi a few decades ago.

Janez Lamovec - Typical morphology of secretory carcinoma of the breast.

Tom Mentzel - A nice example of a very rare breast neoplasm that I haven´t seen before.

Markku Miettinen - Great case – secretory carcinoma definitely agreeable and well-documented, have not seen any at least lately to build an impression.

Liz Montgomery - This is a beautiful case.

Fredrik Petersson - Looks exactly as its salivary gland counterpart!

Juan Rosai - Great case of secretory carcinoma of the breast, supported by the molecular findings.

Brian Rubin - Beautiful case – thanks.

Saul Suster - Very classical example of secretory carcinoma of breast – hadn't seen one in a while!

Dominic Spagnolo - Great case of secretory carcinoma of the breast. Is it the salivary tumour that is the analogue, or the breast cancer that is the analogue? We have recently had a salivary case diagnosed on FNA by one of our cytopathologists.

James Strauchen - Secretory carcinoma of the breast. Thank you for this rare lesion!

Bruce Wenig - Agree with secretory carcinoma; thank you. In the past few years I have seen many more examples of salivary gland mammary analogue secretory carcinoma than breast secretory carcinoma. These organ specific neoplasms are histologically identical with the same translocation.

QUIZ CASE #1 – CONTRIBUTED BY: SAUL SUSTER, M.D.:

Abbas Agaimy - Lymphadenopathy with focal Castleman-like features and plasma cells, capsular Kaposi-like foci, I strongly suggest an HIV setting in this patient.

Phil Allen - Kaposi's sarcoma vs. epithelioid haemangioma with some spindle cell features, inguinal lymph node. I think Kaposi's is more likely.

David Ben-Dor - Lymphoplasmacytic lymphoma?

Michele Biscegllia - Likely unicentric Castleman disease, plasma cell variant, with subcapsular focus of Kaposi's sarcoma (maybe this is the HHV8 subset of CD).

Thomas Colby - Kaposi's sarcoma with background lymph node changes that could be compatible with something like systemic Castleman's disease.

Kumarasen Cooper - Castleman's (plasma cell variant/multicentric type) with Kaposi's sarcoma (involving capsule and extending into parenchyma). HIV status please?

Hugo Dominguez Malagon - Kaposi sarcoma vs. angiomatous transformation of sinuses.

Goran Elmberger - Capsular spindle-epitheloid proliferation with some hemosiderin. Kaposi sarcoma? HIV related lymphoproliferative disease????

Giovanni Falconieri - Atypical Kaposi-like proliferation in lymph node capsule.

Franco Fedeli – Castleman's disease associated with sarcoma of Kaposi.

Christopher Fletcher - This lymph node appears to show subtle subcapsular involvement by Kaposi sarcoma. Does the patient have any risk factors?

Masaharu Fukunaga - Kaposi sarcoma is considered.

Janez Lamovec - Kaposi sarcoma +? Castleman's disease

Markku Miettinen - Kaposi sarcoma involving lymph node.

Fredrik Petersson - HIV-positive patient? Kaposi + B-cell lymphoma arising in HHV+ Mb Castleman ?? Plasma cell proliferation – monoclonal???

Brian Rubin - I'm terrible at heme and the lymph node looks more or less normal with the exception of a nodule of spindle cells within the subcapsular area. Could it be Kaposi sarcoma? Not sure but I'd want to exclude it. Looks like a vascular proliferation to me.

Dominic Spagnolo - Kaposi sarcoma in association with Castleman disease-like (plasma cell/plasmablastic type) changes in the node. Is there a history of HIV infection? Is this HHV-8-associated? If yes to the latter, would be pretty unusual to be strictly localized disease and asymptomatic.

James Strauchen - Castleman disease and capsular Kaposi sarcoma.

Saul Suster - My case. This is a great example of lymphadenopathic Kaposi's sarcoma with Castleman-like changes, first described by Dr. Rywlin in Arch Pathol Lab Med 92:338-341, 1971. This particular patient was HIV+ with a solitary enlarged lymph node. The spindle cell nuclei stained very nicely with HHV8. An interesting feature in the original slides was the presence of areas where the cells were round to polygonal and contained abundant cytoplasm closely resembling epithelioid hemangioendothelioma.

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

Abbas Agaimy - Malignant epithelioid and sarcomatoid neoplasm with rhabdoid features/phenotype, favor metastatic carcinoma (e.g. kidney), DD angiosarcoma, etc.

Phil Allen - High-grade sarcoma with rhabdoid features and necrosis, lumbar region. The pink cells look like rhabdomyoblasts but in patients of this age (68), they usually do not exhibit genuine rhabdomyoblastic differentiation.

David Ben-Dor - Plasmacytoma?

Michele Biscegllia - Malignant mesenchymal tumor (my first choice is anaplastic large cell lymphoma, but it can be other tumors). Immuno needed.

Thomas Colby - ? rhabdomyosarcoma.

Kumarasen Cooper - Anaplastic plasmacytoma with pseudoangiomatous architecture.

Hugo Dominguez Malagon - Epithelioid sarcoma, proximal type vs. plasmacytoma.

Goran Elmberger - Malignant epithelioid tumor. Sorry don't get that one without IHC. Would include epitheloid angiosarcoma in my work-up. The peculiar relationship to vessels might also actualize GCT with placental differentiation in ddx. Lumbar??? GCT??? Ependymal???

Giovanni Falconieri - Pleomorphic sarcoma.

Franco Fedeli - High grade sarcoma nos. poorly differentiated epithelioid angiosarcoma?

Christopher Fletcher - Pleomorphic epithelioid and spindle cell malignant neoplasm with foci which appear to show rhabdomyoblastic differentiation – could this be pleomorphic rhabdomyosarcoma or some other tumour type with heterologous rhabdomyoblastic differentiation?

Masaharu Fukunaga - Proximal synovial sarcoma.

Janez Lamovec - Pleomorphic sarcoma with epithelioid morphology - ? epithelioid myxofibrosarcoma.

Markku Miettinen - Malignant mesothelioma strongly favored, I thought there were microvilli, as well as some cohesive epithelioid cytology. Alternatively considered rhabdomyosarcomatous process but felt it less likely.

Fredrik Petersson - Pleomorphic RMS? Malignant PEComa???

Brian Rubin - Pretty broad differential (epithelioid malignant neoplasm). The two most likely diagnoses to me are poorly differentiated squamous cell carcinoma with a pseudoangiosarcomatous growth pattern and angiosarcoma.

Dominic Spagnolo - I would first want to exclude an anaplastic myeloma. Then consider a zillion other things!

James Strauchen - Malignant? Melanoma, sarcoma, carcinoma?

Saul Suster - My case. This is a pleomorphic rhabdomyosarcoma in an adult patient. When I first saw it my initial diagnosis was "pleomorphic high-grade sarcoma" (MFH). Review of the initial panel of immunostains showed strong positivity in many of the tumor cells for desmin, subsequently followed by myogenin and focal Myo-D1 nuclear positivity. Stains for keratins, CD30, CD31, CD34, INI, S100, EMA, CEA, HMB45, MDM2, etc, were all negative.

QUIZ CASE #3 – CONTRIBUTED BY: SAUL SUSTER, M.D.:

Abbas Agaimy - Extensive lymphovascular invasion by a malignant rhabdoid neoplasm, a few cytoplasmic vacuoles evident. Without immunos not possible to reliably classify. For me the list includes hyaline signet ring carcinoma, rhabdoid melanoma, angiosarcoma, other carcinomas with rhabdoid dedifferentiation etc.

Phil Allen - ? Extensively invasive malignant mesothelioma, ?Metastatic malignancy, left lung and pleura. If it's not mesothelioma, try melanoma before proceeding to other possibilities.

David Ben-Dor - Again plasmacytoid cells. A trap?

Michele Biscegllia - Pulmonary tumor embolism (maybe large cell carcinoma of the lung itself).

Thomas Colby - Epithelioid angiosarcoma/high-grade epithelioid hemangioendothelioma.

Kumarasen Cooper - Metastatic malignant rhabdoid tumor. Primary? renal, soft tissue or brain (atypical teratoid tumor)

Hugo Dominguez Malagon - Lymphangitis carcinomatosa with signet ring cells.

Goran Elmberger - Lymphangitis carcinomatosa. Signet-ring-cell carcinoma.? Gastric?? IHC!

Giovanni Falconieri - Adenocarcinoma with acinic features.

Franco Fedeli - Lymphangitic carcinomatosa. A peculiar intravascular epithelioid hemangioendothelioma?

Christopher Fletcher - Epithelioid haemangioendothelioma versus epithelioid sarcoma – I would need IHC to make this distinction with certainty.

Masaharu Fukunaga - Epithelioid hemangioendothelioma or epithelial mesothelioma. It is very interesting. Thank you for the challenging quiz cases, Saul.

Janez Lamovec- ?malignant epithelioid hemangioendothelioma/angiosarcoma.

Markku Miettinen - Epithelioid hemangioendothelioma involving pleura and metastatic to the lung. Immunohistochemistry (CD31, ERG) and WWTR1-CAMTA1 fusion test are expected to be positive.

Fredrik Petersson - Epithelioid hemangioendothelioma with rhabdoid features?

Brian Rubin - Horrible lymphatic spread of a likely carcinoma with eccentric nuclei and occasional signet ring cells. I doubt it's epithelioid sarcoma. I'd favor gastric origin based on appearance but could come from other sites I would think. Doesn't look like a primary pulmonary process to me. I guess I'd also want to exclude an epithelioid vascular tumor.

Dominic Spagnolo - Thanks for an easy one on which to finish! “Lymphangitis carcinomatosa” but I don’t know the nature of the malignancy, and whether the interstitial lung changes are a consequence of the extensive intralymphatic malignancy, or indicative of a separate pre-existing interstitial lung disease. The malignancy look like carcinoma with prominent “rhaboid” cells (?myoepithelial) rather than metastatic melanoma, alveolar soft part sarcoma, etc.

James Strauchen - Lymphangitic carcinoma with signet ring/rhabdoid cells.

Saul Suster - My case (this is one of the cases I presented at the International AMR Symposium in Tel-Aviv in July 2013, case No.40). My diagnosis on this case was that of epithelioid angiosarcoma of the pleura secondarily invading lung. The case was not without controversy. First, the bulk of the lesion involved the underlying lung. The pleural changes were quite minimal compared with the lung parenchymal involvement, but some of the sections showed a very thickened pleura with obvious angiosarcoma tracking into the underlying lung and with gradual transformation into a tumor with epithelioid and rhabdoid features as observed in the lung. Immunohistochemical staining showed strong CD34 and CD31 positivity in the tumor cells, as well as positivity for vimentin and FLI-1. Stains for cytokeratin AE1/AE3, CK5/6, CK7, CK20, EMA, p63, S-100,

HMB45, AFP, PLAP, calretinin, HBME-1, D2-40, WT1, SMA, desmin, myogenin and TTF1 were negative. The main source of controversy arose from the fact that two world-class consultants who saw this case felt that it could fit better for a diagnosis of “high-grade epithelioid hemangioendothelioma” or (a more horrendous term!) “malignant epithelioid hemangioendothelioma”. This all stems from the work of our colleague and Club member, Dr. Brian Rubin, who has demonstrated that the distinctive translocation t(1;3)(p36;q25) can serve as a disease-specific marker of epithelioid hemangioendothelioma (Science Translational Medicine Vol.3, Issue 98:1-9, 2011). Thus, some of our faculty felt this would be better classified as malignant epithelioid hemangioendothelioma rather than as epithelioid angiosarcoma. I think this case might as well be half a dozen of this or six of the other, but science must move on. We have not been able to get the sample tested for the t(1;3) yet and are hoping Dr. Rubin might be interested in doing so. Regretfully, the patient expired 3 month after the surgery with disseminated disease. So it appears as if the jury is still out regarding whether there is a difference between “malignant epithelioid hemangioendothelioma” and “epithelioid angiosarcoma”.