

## **COMMENTS TO AMR SEMINAR #71**

### **CASE NO. 1 – CONTRIBUTED BY: Abbas Agaimy, M.D.**

**Phil Allen** – Diffuse thyroid lipomatosis with secondary amyloid goiter with due to familial Mediterranean fever. The only case of amyloid struma I have seen was due to rheumatoid arthritis. The patient developed transient thyrotoxicosis and laryngeal stridor which forced the thyroidectomy to relieve the airways obstruction. The patient was a member of the pathology department in Adelaide about 40 years ago. She did not have an associated thyroid lipomatosis and the amyloid was much more obvious than in this case.

**Ira Bleiweiss** – Fatty thyroid. The amyloid is certainly not obvious.

**Alberto Cavazza** – Very nice case and instructive discussion, particularly on the combination of amyloid goiter and thyroid lipomatosis. Further comment from my colleague Maria Cecilia Mengoli: in dealing with a similar case, we were surprised by the macroscopic appearance of the thyroid that mimicked a lipomatous tumor. Our patient was affected by systemic amyloidosis with chronic renal failure. As you said the presence of diffuse lipomatosis should alert us of the possibility of an underlining “amyloid struma”, that sometimes may be not immediately appreciable on H&E.

**Kum Cooper** – Thank you Abbas for the great review. I recently saw two cases. One in our department associated with long standing amyloidosis and the other in Franco Fedeli’s seminar in Genoa.

**Göran Elmberger** – Great case. Also wonder about pathogenesis of fatty infiltration...

**Franco Fedeli** - Amazing case; very impressive lipomatous degenerative changes of the thyroid parenchyma. I saw in consultation a case of amyloid goiter in chronic renal failure without adipose tissue. In this case the amount of adipose tissue is impressive. This lesion is a typical consequence of Mediterranean fever with amyloidosis.

**Maria Pia Foschini** – Very interesting case of diffuse lipomatosis of the thyroid associated with amyloid goiter.

**Masaharu Fukunaga** – Thank you very much for the beautiful case and discussion of this type of tumor Abbas. I have never seen this type of thyroid disease.

**Barbara Gazić** – Very interesting case, never seen before. We see a lot of thyroid gland resections, but we have never seen amyloid goiter.

**Ondřej Hes** – Great case Abbas, never seen of course. Just want to share our recent experiences with Congo Red. We use it routinely for medical and transplant kidney. After years of using the customized recipe, we were not able to obtain proper staining. It was red but without green birefringence.....after a couple of weeks we are back, however we were not able to determine what was wrong.....Our advice- always use positive control and look at it both in normal and polarized light.

**Thomas Krausz** – Historically, I remember rare thyroid cases with focal fatty “metaplasia”, but nothing like this. This entity could easily be a diagnostic pitfall.

**Thomas Mentzel** – Thanks a lot Abbas for this interesting case, however, I have no sensible idea for the reasons of this coincidence...

**Markku Miettinen** – Agree on amyloid goiter with fat.

**Fredrik Petersson** - Diffuse lipomatosis with amyloid deposition/goiter. I am also eagerly awaiting the discussion on whether the lipomatosis is incidental or causally related to the amyloid (or vice versa..). Why is the goiter developing so rapidly??

**Murray Resnick** – Great case. The pathophysiology of the lipomatosis process is indeed intriguing. I read that there are theories that it may be related to metaplasia of stromal fibroblasts as a response to tissue hypoxia or that this is a developmental anomaly as fat is included in the thyroid gland during embryogenesis. Neither sounds terribly convincing.

**Brian Rubin** – I wanted to call this fatty atrophy of the thyroid. What a strange and cool case – great discussion.

**Saul Suster** - Great case. Can't explain the association between amyloid deposits and fatty metaplasia.

**Paul Wakely** – Have encountered amyloid deposition within the thyroid as part of systemic amyloidosis, but never with this degree of lipomatous metaplasia. I have no insight as to the reason(s) for this combination [lipid plus amyloid] being deposited in the same organ.

**CASE NO. 2 – CONTRIBUTED BY: Ofer Ben-Izhak, M.D.**

**Phil Allen** – Progressive multifocal leukoencephalopathy due to JC virus in a patient with B cell lymphoma treated with rituximab in complete remission after mirtazapine treatment. A very instructive and superbly worked-up case. Thanks for the contribution. It's lucky that I do not try to do neuropathology.

**Ira Bleiweiss** – So glad I don't do neuropathology.

**Alberto Cavazza** – In my very limited experience in this field, I thought of a viral infection due to the nice viral inclusions. I was interested to know your more specific diagnosis and the educational comments.

**Kum Cooper** – Thank you Ofer for this beautiful example of PML. The intranuclear inclusions are very evident in your case. Sometimes they are difficult to find. Another feature may be pleomorphic reactive astrocytes.

**Göran Elmberger** – Very interesting and well-presented case. Inclusion bodies are striking!

**Franco Fedeli** - Never seen in my life a case like this one. It is certainly one of the worst complication from Rituximab treatment in low grade lymphoma patients.

**Maria Pia Foschini** – Progressive multifocal encephalopathy. Interesting and classical case. It is not frequent to see so well the inclusion bodies.

**Masaharu Fukunaga** – Thank you very much for the interesting case, Ofer. Comment is very informative.

**Barbara Gazić** – I asked our lymphoma team clinicians if they ever had a case of PML after Rituximab or anti CD30 treatment and their answer was no. Great case. We've learned something new.

**Thomas Krausz** – What a coincidence, I just saw very similar viral inclusions in a renal transplant biopsy.

**Thomas Mentzel** – What a terrible disease!

**Markku Miettinen** – Thank you for this excellent teaching case. I have almost no experience on this entity.

**Fredrik Petersson** - My slide a bit faded. PML. Very important and instructive case for those of us who have to do brain frozens with no hardcore neuropathology background. For me it was hard to appreciate all the macrophages on H&E. Thanks for this case!

**Murray Resnick** – Nice example.

**Brian Rubin** – Very interesting! I don't do neuropathology so I've never seen a case of this before.

**Saul Suster** – Very rare and interesting case – thanks for sharing it!

**Paul Wakely** – Not being a neuropathologist, this is the 1<sup>st</sup> case I've seen of this entity. The eosinophilic intranuclear inclusions are obvious.

**CASE NO. 3 – CONTRIBUTED BY: Gerald Berry, M.D.**

**Phil Allen** – Atypical thymoma with prominent nucleoli and frequent intranuclear inclusions. The things I interpret as inclusions look like the intranuclear vacuoles seen in some soft tissue tumours. I have never seen this appearance in thymomas previously but I hardly see any thymic pathology.

**Ira Bleiweiss** – Agree. Inclusions are striking.

**Alberto Cavazza** – I agree. Never noticed so many nuclear inclusions in thymoma.

**Kum Cooper** – Thank you Gerry. Is this what used to be called a well differentiated thymic carcinoma?

**Göran Elmberger** – Absolutely remarkable. Nuclear inclusions, pseudoinclusions or pseudo pseudoinclusions? I suspect pseudoinclusions. Nice reference paper on these matters from JKC Chan 2010. Quick literature search revealed two papers mentioning pseudoinclusions in metaplastic thymomas but no further thoughts on mechanism.

**Franco Fedeli** - Very strange case. Thank you for sharing with us: I am waiting for comments from the very experienced specialists Saul Suster and Juan Rosai.

**Maria Pia Foschini** – Atypical thymoma with strange intranuclear inclusions. The neoplastic cells have also intracytoplasmic vacuoles, some of them contain red blood cells and lymphocytes. I do not know the meaning. At the beginning I had interpreted them as features of vascular differentiation.

**Masaharu Fukunaga** – Atypical thymoma, I have never seen this type of tumor. Thank you very much.

**Barbara Gazić** – We have some cases of B3 thymoma, but we didn't notice intranuclear inclusions. Thank you anyway for thymoma, never enough practice with them. We don't see many.

**Thomas Krausz** – I don't recall seeing intranuclear inclusions/cytoplasmic pseudo-inclusions in such a number in a thymoma before, but, why not...

**Thomas Mentzel** – Interesting case – was there any previous treatment causing the unusual nuclear changes?

**Markku Miettinen** – Thymoma, B3 variant, with large cells and some atypia.

**Fredrik Petersson** - Cytologically atypical epithelioid thymic neoplasm with 0 mitotic activity (hence not thymic carcinoma) intimately admixed with lymphocytes and plasma cells. Background of cyst formation, and hemorrhage; was any necrosis present? I found this reference: Thymoma with prominent cystic and hemorrhagic changes and areas of necrosis and infarction: a clinicopathologic study of 25 cases. Moran CA, Suster S. Am J Surg Pathol. 2001 Aug;25(8):1086-90. Saul, does this fit?

**Brian Rubin** – Very scary cytology. I haven't seen a case like this before.

**Saul Suster** – Very nice case of atypical thymoma (WHO B3) with the rare feature of intranuclear pseudoinclusions. I have not seen this before in B3 thymomas but these inclusions are very common in the so-called "metaplastic" thymoma (originally described as thymoma with pseudosarcomatous stroma). When we described those tumors, we interpreted the vacuoles and pseudoinclusions as a degenerative phenomenon and a sign of senescence.

**Paul Wakely** – Nice example of atypical thymoma. Are those inclusions PAS+, i.e. glycogen?

**CASE NO. 4 - CONTRIBUTED BY: Hugo Dominguez Malagón, M.D.**

**Phil Allen** – Metaplastic carcinoma simulating a desmoid tumour, left breast. I have seen a case of "nodular fasciitis" of the breast that recurred. The radiologists diagnosed cancer and so did we, after we did a keratin stain. Fortunately, I only saw the case after it had recurred because I could not tell it from fasciitis in the haematoxylin and eosin stain.

**Ira Bleiweiss** – Agree with low grade fibromatosis-like carcinoma. Very rare lesion which I've only seen twice before. Thanks for the best example yet.

**Alberto Cavazza** – I agree. Nice example of an entity that occasionally can be a real diagnostic challenge.

**Kum Cooper** – Thank you Hugo for the example of fibromatosis-like carcinoma (metaplastic carcinoma). When I encounter tumors like these I request every cytokeratin we have including high molecular weight keratins. The other feature I learnt from Chris Fletcher years ago was how these metaplastic carcinoma “wander” through the lobules (which this does as well). All the best in your retirement. We will miss you!

**Göran Elmberger** – Good case. Spectrum of what in breast is called metaplastic carcinomas and in other organs spindle cell carcinoma, sarcomatoid carcinoma etc is wide and this is probably one of the more treacherous variants. Great reminder!

**Franco Fedeli** - Spindle cell neoplasms in the breast are always very difficult to diagnose. You can find both benign and malignant lesions. Fibromatosis vs metaplastic carcinoma is one of the most challenging diagnoses and, like in this case, it is always very tricky. In this case nuclear atypia is remarkable.

**Maria Pia Foschini** – Fibromatosis-like metaplastic carcinoma of the breast: this is an interesting and rare type of metaplastic breast carcinoma. It is usually considered of low-malignancy, but the present case showed a quite aggressive behavior. The mitotic rate is quite high, and unusual for this type of tumor, thus explaining the rapid and widespread recurrence.

**Masaharu Fukunaga** – A nice case, Hugo. My first impression was fibromatosis. Fibromatosis-like metaplastic carcinoma of the breast, I agree.

**Barbara Gazić** – Nice case of metaplastic carcinoma, not misdiagnosed at our department any more, but we also had some pitfalls in the past.

**Ondřej Hes** – Thank you Hugo, for me always a challenge to evaluate spindle cell lesion in the breast especially on frozen section (mostly designated as “scar” by surgeons) and it is always a scary moment for me.

**Thomas Krausz** – Nice example.

**Thomas Mentzel** – Thanks for paying attention to this important entity not to be mixed up with a mesenchymal neoplasm.

**Markku Miettinen** – Agree on metaplastic carcinoma, based on Hugo’s immunostudies. Would be impossible to call this without immunostains (or concurrent differentiated Ca component).

**Fredrik Petersson** - Fibromatosis-like, agree, but in some areas a bit too wild for fibromatosis; focal necrosis on my slide. Dx predicated on IHC.

**Murray Resnick** – Great example.

**Brian Rubin** – Very pretty case of something I’ve actually seen a few times.

**Paul Wakely** – Thank you, Hugo. I’m so sorry to see you retiring from the club. We have all benefited from your insight, your contributions and your friendship.

#### **CASE NO. 5 – CONTRIBUTED BY: Cyril Fisher, M.D.**

**Phil Allen** – Dedifferentiated lipoma-like liposarcoma with pleomorphic liposarcoma-like dedifferentiation, pelvic retroperitoneum and left obturator internus, with pulmonary metastases and death 20 months after initial diagnosis in a female aged 26. Despite the prognosis implied in the classification, she only lasted 20 months. How much trust should we put in MDM 2?

**Ira Bleiweiss** – Agree. Liposarcoma.

**Alberto Cavazza** – Very nice and educational case, particularly regarding the differential diagnosis between dedifferentiated and pleomorphic liposarcoma and the utility of MDM2.

**Kum Cooper** – Thank you Cyril for sharing this case. It was a pleasure to hear Dr. Khin present this case at USCAP. I remember when Chris (his group) first presented their series at USCAP (around 2009). I commented on the microphone that they were just “killing me”!!! I now understand that there is a prognostic difference!

**Göran Elmberger** – Great case and discussion. By the way beautiful nuclear pseudoinclusions!

**Franco Fedeli** - Dedifferentiated homologous liposarcoma. Some years ago I shared with a group of pathologists involved in an Italian slide seminar a case where we still had the low grade component in the same slide (MDM2+).

**Maria Pia Foschini** – Dedifferentiated liposarcoma with lipoblastic differentiation. This case shows a great variety of features encountered in liposarcoma.

**Masaharu Fukunaga** – It looks like pleomorphic liposarcoma. Homologous differentiation in dedifferentiated liposarcoma, I agree. Thank you, Cyril, for the nice case and detailed comment.

**Barbara Gazić** – A tumor looking like pleomorphic liposarcoma and MDM2 amplified, it is most probably dedifferentiated liposarcoma with homologous lipoblastic differentiation - very interesting case with an excellent discussion for the less experienced members of the club.

**Thomas Krausz** – Agree with diagnosis, but somehow, I haven't seen dedifferentiated liposarcoma in such a young patient before.

**Thomas Mentzel** – Many thanks and this case raises interesting questions in regards to the classification of lipogenic neoplasms. Of course, we can label the neoplasm as a dedifferentiated liposarcoma with pleomorphic liposarcoma-like differentiation. Given the pleomorphic liposarcoma-like areas, we can also discuss that the neoplasm represents a dedifferentiated liposarcoma undergoing further progression to a higher-grade (pleomorphic liposarcoma) sarcoma. Pleomorphic liposarcoma seems a heterogeneous group including cases of pleomorphic liposarcoma per se and cases of ALT/dedifferentiated liposarcoma undergoing further progression (but keeping characteristic MDM/CDK4 amplification).

**Markku Miettinen** – Liposarcoma, low to intermediate grade, with hibernomatous differentiation. Necrosis but low mitotic rate, by formal criteria would be intermediate grade. Most people now believe that MDM2 amplification would classify this type of tumor into well-diff/dediff liposarcoma category. Because of high atypia and necrosis – dediff, probably a better diagnosis.

**Fredrik Petersson** - Pleomorphic – bizarre liposarcomatous cytology and necrosis. Low mitotic activity. It would have been interesting to see how high – and in what cells Ki-67 expression was detected. I have a vague idea that the very bizarre cells are too abnormal to be biologically malignant and perhaps a “biological end stage” in an extremely genetically unstable malignant tumor. Convincing Diagnosis and Discussion. Of note, dedifferentiated LS can be very bland. (Petersson F. Dedifferentiated liposarcoma of the deep (paralaryngeal) soft tissue: Lessons learnt from a case with a partly deceptively benign appearing dedifferentiated component. *Head Neck Pathol.* 2014 Jun;8(2):171-7.)

**Murray Resnick** – Fascinating case. The possible association with chemotherapy induced differentiation is interesting. Has this phenomenon been observed in other cases post chemotherapy?

**Brian Rubin** – Histology certainly good for lipoblast rich pleomorphic liposarcoma. I agree that MDM2 gene amplification argues for dedifferentiated liposarcoma with homologous pleomorphic liposarcomatous differentiation. Very rare and interesting. Thanks Cyril!

**Saul Suster** – There is clearly a dedifferentiated liposarcoma component in this section alongside a tumor showing well-differentiated lipoma-like liposarcoma intimately admixed with pleomorphic cells that in my book qualify for pleomorphic liposarcoma. One possible interpretation here is that the “dedifferentiated non-lipogenic” (i.e., spindle) component is arising from the well-differentiated lipoma-like liposarcoma elements and that the latter is also giving rise to a pleomorphic liposarcomatous component. Why not? Everything is possible in the 5<sup>th</sup> dimension!

**CASE NO. 6 – CONTRIBUTED BY: Jerónimo Forteza, M.D.**

**Phil Allen** – Intensely sclerosed mesenteric large B-cell lymphoma (slide 6b) with full-thickness involvement of the small bowel (slide 6a). I think the intense sclerosis is due to the lymphoma rather than to an unrelated inflammatory sclerosing mesenteritis.

**Alberto Cavazza** – I agree. I tend to think the “IgG4-like” fibrosis is secondary to lymphoma, a well-known pitfall in small biopsies.

**Kum Cooper** – I agree the fibrosis is likely initiated by the lymphoma. In the previous classification there used to be an entity called “sclerosing (mediastinal) large B-cell lymphoma”.

**Göran Elmberger** – Interesting connection. Perhaps the sclerosing mesenteritis could be “burnt out” in sampled areas thus lacking evidence of IgG4?

**Franco Fedeli** – Very unusual location for this type of lymphoma. I think that fibrosis is related to the lymphoma. In fact, many types of lymphoma (follicular lymphoma, T-cell lymphoma and Hodgkin lymphoma) induce fibrosis.

**Maria Pia Foschini** – Large B cell lymphoma with reactive sclerosing mesenteritis. The component of sclerosing mesenteritis is very interesting and unusually associated with lymphoma. A biopsy limited to this component would be very difficult to correctly diagnose.

**Masaharu Fukunaga** – Pleomorphic large B cell lymphoma, I agree. The cause of the fibrosis is unknown.

**Barbara Gazić** – GIT is the most common extranodal site of DLBCL (esp. ileocecal region) and we think this is DLBCL of GIT and we don't think it arose from MALT lymphoma. Fibrosis could be the part of lymphoma. Did the patient receive RT for prostate adenocarcinoma? Could it also be the reason?

**Thomas Krausz** – I am not sure, but I would consider local cytokine production and the focal presence of fat necrosis for the fibrosis.

**Thomas Mentzel** – The presence of prominent fibrosis and sclerosis with cracking artefacts and inflammatory cells represents an interesting phenomenon indeed, probably caused and induced by the high-grade malignant B-cell lymphoma.

**Markku Miettinen** – Difficult to be sure of lymphoma without immunostains but agree with your documentation, definitely has sclerosing features like sclerosing mesenteritis/retroperitoneal fibrosis.

**Fredrik Petersson** – Predominantly epithelioid, obviously malignant tumor with an associated inflammatory component and prominent sclerosis. I was misled by the prominent fibro-inflammatory/sclerotic component. Looking at the slide after reading the IHC info (double hit lymphoma?), the malignant cells appeared much more lymphomatous.

**Murray Resnick** – It is quite remarkable how in areas the storiform fibrosis resembles that seen in IgG4 associated disease.

**Brian Rubin** – Agree with B-cell lymphoma with impressive retroperitoneal fibrosis. Not all retroperitoneal fibrosis is IgG4 related so I would guess it is related to the tumor or tumor therapy.

**CASE NO. 7 CONTRIBUTED BY: Ondřej Hes, M.D., Ph.D.**

**Phil Allen** – TFE3-NONO Xp11 translocation renal cell carcinoma in a female aged 86. Oh for the uncomplicated days of Dr Grawitz! (Paul Grawitz, 1850-1932, initially assistant to Virchow. His handlebar moustache was enormous).

**Ira Bleiweiss** – Also glad I'm not a GU pathologist. There are too many new renal cell carcinoma variants now.

**Alberto Cavazza** – Thanks for sharing this unusual tumor. I learned to consider the possibility of a translocation carcinoma of the kidney even in the elderly!

**Kum Cooper** – Thank you Ondra for this beautiful example of NONO-TFE3 RCC. Recently (May AJSP) Thomas Krausz described a similar translocation in a sinonasal PECOMA.

**Göran Elmberger** – Any translocation specific treatment options on the way?

**Franco Fedeli** - Psammoma bodies-papillary architecture association is strongly suspected for translocation RCC even in the presence of a beautiful clear cell cytology.

**Maria Pia Foschini** – Xp11 translocation renal cell carcinoma with established TFE3-NONO; interesting case, showing two very different components.

**Masaharu Fukunaga** – Xp11 translocation renal cell carcinoma with established TFE3-NONO. A beautiful case and detailed comments. Thank you Ondrej.

**Barbara Gazić** – We don't have experience with renal tumors..... so we cannot comment.

**Thomas Krausz** – I am wondering whether the focal non-papillary nests with higher nuclear grade, more mitoses and areas of necrosis is a kind of dedifferentiation. Our local expert Tatjana Antic was so pleased to see your case. She then showed me a melanotic variant with ARID1B-TFE3 fusion from her collection (Antic T. Am J Surg Pathol 2017; 41:1576-1580).

**Thomas Mentzel** – A very nice case underlining the substantial changes in modern classification of renal cancer!

**Markku Miettinen** – Papillary clear cell ca with calcification, good for TFE3 fusion tumor.

**Fredrik Petersson** – Very interesting tumor!! I was initially contemplating a clear cell RCC with RAT-like areas. (Petersson F, Michal M, Hes O. Renal cell carcinoma with areas mimicking renal angiomyoadenomatous tumor/clear cell papillary renal cell carcinoma. Hum Pathol. 2013 Jul;44(7):1412-20). Very deceptive that TFE3 IHC was only focally positive!! How about broad spectrum cytokeratins? Weak and patchy? Negative??

**Murray Resnick** – Nice case and discussion.

**Brian Rubin** – Thanks for this case and excellent discussion. Interesting that gene fusions are being found more commonly in epithelial cancers.

#### **CASE NO 8. – CONTRIBUTED BY: Jason Hornick, M.D., Ph.D.**

**Phil Allen** – PEComa with TFE3 gene rearrangement, right nasal cavity. I wonder if any malignant melanomas have TFE3 gene rearrangements.

**Ira Bleiweiss** – Ouch. Awful.

**Alberto Cavazza** – Thanks for sharing this very nice case. On morphology, I thought alveolar soft part sarcoma was in the differential.

**Kum Cooper** – Thank you Jason for sharing this case. Following on my comment on case 7 (TFE3-NONO), I wonder what the fusion partner was in your case?

**Göran Elmberger** – Important and always difficult differential diagnosis for general pathologists. Good to know about emerging knowledge on genetical aspects.

**Franco Fedeli** - Pecoma in nasal cavity is very unusual in my experience. Another tumor with the TFE3 gene rearrangement (like the aforementioned case number 7, but completely different).

**Maria Pia Foschini** – PEComa with TFE3 gene rearrangement. Very interesting case in an unusual location. PEComa arising in the nose have been rarely described, and I am not aware of their molecular characterization. Thank you for sharing this case!

**Masaharu Fukunaga** – Thank you, Jason, for the beautiful case and concise comments of PEComa with TFE3 gene rearrangement.

**Barbara Gazić** – We recognized PECOMA and we learned that PEComas fall into two main genetic groups: those with TSC2 gene mutations/deletions and those with TFE3 gene rearrangements. Thank you!

**Ondřej Hes** – Great case!! I've recently encountered TFE3 rearranged renal cell carcinoma with HMB45 positivity in consultation. Tumor was very strange, more resembled t6;11 RCC than Xp11.2 (TFE3).....real challenge and PECOMA was one of my differential diagnoses (however morphology of my case was very "carcinomatous").

**Thomas Krausz** – Very nice case. A couple of years ago we had a case of sinonasal pigmented PEComa with *NONO-TFE3* fusion (Am J Surg Path 2017; 41:717-722)

**Thomas Mentzel** – Many thanks, and it's interesting that dermal PEComa that often shows the same clear cell morphology as the enclosed case lacks TFE3 rearrangement (Histopathology 2013;63:122-129).

**Markku Miettinen** – Agree that studies support PEComa. Here it mimics clear cell (myoepithelial) carcinoma.

**Fredrik Petersson** - Great, short sweet and convincing case! Clear cytoplasm with also rhabdoid-like features. In part a bit RCC-like initially. On my ddx-list was a clear cell myoepithelial carcinoma.

**Murray Resnick** – Great case. Some areas really resemble RCC at low power.

**Brian Rubin** – Nice case of clear cell PEComa with TFE3 gene region rearrangement. Good point about the lack of muscle markers in this variant.

**Paul Wakely** – With all that clear cell change, I was thinking myoepithelioma from the H&E alone – that is, until I read the results of your stains.

**Saul Suster** - Thank you for sharing this case; very easy to miss on H&E. PEComa now joins the growing family of translocation-associated tumors that can show different faces and morphology depending on the site and the precursor cells in which the genetic abnormality occurs.

#### **CASE NO 9. – Michal Michal, M.D.**

**Phil Allen** – Right paratesticular region pancreatic analogue solid pseudo-papillary neoplasm (4.8 cm), male aged 32. I think Michal has a strong case for this diagnosis.

**Ira Bleiweiss** – Wow, I've never heard of this. Not sure how you came up with that diagnosis.

**Alberto Cavazza** – Very nice case and up-to date discussion. Further comment from my colleagues Maria Cecilia Mengoli: We believe that SPN of the pancreas, ovary, testis, and also microcystic stromal tumor and signet-ring stromal tumor in the ovary and analogously in the testis probably belong to the same family of "β-catenin mutated tumors", sharing some morphologic features and the constant nuclear immunohistochemical expression of β-catenin and mutation of CTNNB1 (Applied Immunohistochem Mol Morphol 2017;25(10):e95-e99).

**Kum Cooper** – Thank you Michal. I like this newly described tumor of the para-testis. I enjoyed the presentation in Krakow too.

**Göran Elmberger** – Great case. Great work behind establishing new "analogue" links.

**Franco Fedeli** - Dear Michael, this case reminds me of the pancreatic-type solid pseudopapillary neoplasm of the testis – previously called signet-ring stromal tumor of the testis - which I presented in AMR Stockholm 2012.



**Maria Pia Foschini** – Pancreatic analogue solid pseudopapillary neoplasm arising in the paratesticular location. This is again a very unusual and interesting case. I did not know this entity; it is important to know that it can arise also in organs other than the pancreas.

**Masaharu Fukunaga** – What a great case of pancreatic analogue solid pseudopapillary neoplasm in the pretesticular location! Thank you, Michal. I have a similar case of the testis which shows signet ring cell proliferation.

**Barbara Gazić** – Very interesting, excellent case and of course your comments!

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

**Thomas Mentzel** – What a spectacular case, many thanks!

**Markku Miettinen** – Not totally identical with the pancreatic tumors, would also consider Sertoli cell tumor with signet ring cell features (although negative inhibin noted). Sertoli cell tumors, at least their ovarian counterparts, may also have beta-catenin mutations (based on 1 case experience, which may be insufficient).

**Fredrik Petersson** - After Krakow, how can I forget?? Astute.

**Murray Resnick** – Extraordinary case. Was not aware that pancreatic SPN may contain a signet ring component.

**Brian Rubin** – Wow! That's a spectacular case and interesting discussion.

**Saul Suster** – Thank you for sharing this new entity.

#### **CASE NO. 10 – CONTRIBUTED BY: Michal Michal, M.D.**

**Phil Allen** – Penile analogue of stratified mucin producing intraepithelial lesion (SMILE) of the cervix with a squamous and glandular phenotype in an HIV+ 56-year-old. These cases are getting curiozier and curiozier.

**Ira Bleiweiss** – Why isn't this squamous cell carcinoma?

**Alberto Cavazza** – Fantastic case, I completely ignored this entity in the male.

**Kum Cooper** – Michal I have only diagnosed "SMILE" in the cervix. Recently there was a paper with invasive SMILE. My slide only has invasive carcinoma (squamous and glandular) without an intraepithelial component. Thanks for sharing this case.

**Göran Elmberger** – Important to know. Another successful "analogue" history from M.M.!

**Franco Fedeli** - It really seems to be a variant of basal cell carcinoma with mucinous secretion. Very rare and tricky case.

**Maria Pia Foschini** – Penile analogue of stratified mucin-producing intra-epithelial lesions (SMILE) of the cervix. Interesting HPV related type of adenocarcinoma.

**Masaharu Fukunaga** – This case is also a great case. Penile analogue of SMILE of the cervix. Thank you very much for the case, Michal.

**Thomas Krausz** – Our departmental expert on SMILE (Dr. R. Lastra. Am J Surg Pathol 2016 40:262-269) was very pleased to see this case. So was I.

**Thomas Mentzel** – Does the glandular differentiation represent a metaplastic differentiation in an invasive squamous/basaloid cancer?

**Markku Miettinen** – Nice case, had no clue on this.

**Fredrik Petersson** - Blew my mind. I think there is invasion on my slide.

**Brian Rubin** – I've never heard of this, which shouldn't really surprise me. Thanks for the very unusual case.

**Paul Wakely** – Rather than a "lesion", because of its infiltration would it be better to classify this neoplasm as a form of adenosquamous carcinoma Michal?

**Saul Suster** - Was not familiar with this. Thank you for the contribution.

**CASE NO. 11 – CONTRIBUTED BY: Markku Miettinen, M.D.**

**Phil Allen** – Intramuscular myxoid liposarcomas with extensive necrosis, proximal thigh. I agree with Markku that most retroperitoneal liposarcomas with extensive myxoid change are well differentiated lipoma-like liposarcomas with myxoid matrix. I have often wondered if anyone ever checked the sections of the tumour illustrated in figure 15-38 on Page 506 of the latest edition of Enzinger. That illustration of an alleged large retroperitoneal myxoid liposarcoma had also appeared in most of the previous editions of that textbook.

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – Thanks for sharing the nice case and the useful information.

**Kum Cooper** – Thanks Markku. There was a recent study of five cases of primary myxoid liposarcoma in the abdomen. I recall the paper was from the East.

**Göran Elmberger** – Nice case.

**Franco Fedeli** - Myxoid liposarcoma with extensive necrosis: Could so many lipoblasts at the periphery of the specimen be related to the treatment effect?

**Maria Pia Foschini** – Myxoid liposarcoma with extensive necrosis. Interesting case. Some areas show features reminiscent of chondroid differentiation.

**Masaharu Fukunaga** – Myxoid liposarcoma with extensive necrosis. I think differential diagnosis between well differentiated and myxoid liposarcomas is not easy in this situation.

**Thomas Krausz** – The treatment-induced lipomatous differentiation is striking and may cause diagnostic pitfall.

**Thomas Mentzel** – A nice case of myxoid liposarcoma with prominent necrotic changes, however, in the periphery characteristic features are observed at least focally.

**Fredrik Petersson** – I have never seen a case with post radiotherapy changes. The vascular changes are quite distinct. On my slide, focally a limited condensation of small round cells (mitotically active) at the periphery. Very early high-grade/round cell transformation?

**Brian Rubin** – I love it when I see a history of intramuscular thigh mass. I feel like I have a chance to recognize it. Of course, I agree with the stated diagnosis of myxoid liposarcoma with extensive necrosis.

**CASE NO. 12 – CONTRIBUTED BY: Cesar A. Moran, M.D.**

**Phil Allen** – Myxopapillary ependymoma-like tumour with adjacent noncaseating granulomas, upper lobe of right lung. I would be surprised if this solitary lung tumour is a metastasis. Does the patient also have sarcoid?

**Ira Bleiweiss** – ???

**Alberto Cavazza** – Spectacular case! I understand the original diagnosis of carcinoid, but I suspect stains were consistent with myxopapillary ependymoma. In the surrounding lung there is quite a prominent granulomatous reaction: depending on clinico-radiological correlations, the latter can be incidental or clinically significant (sarcoidosis, infection, aspiration and so on).

**Kum Cooper** – Cesar, I showed this to our lung pathologist and GI pathologist who independently think this a neuroendocrine of likely pancreatic origin.

**Göran Elmberger** – Wow! I only found one case report of primary pulmonary ependymoma by Crotty 1992 and I find it vague due to previously treated small cell carcinoma in the same lobe and death shortly after diagnosis from “cerebral hemorrhage”. No autopsy performed. Posterior mediastinal cases with overgrowth have been described. Metastases are also described but usually with anaplastic morphology. Exact location? I had an interesting case of liver metastases from dedifferentiated extraneural filum terminale myxopapillary ependymoma to the liver but that also looked very poorly differentiated. This case looks well differentiated – benign! Primary??

**Franco Fedeli** - Classic morphology of the lesion, but very unusual site! There is a granulomatous sarcoid-like lesion at the periphery of the specimen in my slide.

**Maria Pia Foschini** – Myxopapillary ependymoma, primary site undetermined. Interesting case, very similar to those seen in the cauda. Staging is undoubtedly important, but as you all know, similar cases can be primary of the lung (Yust Katz S, et al. Ependymomas arising outside of the central nervous system: A case series and literature review. J Clin Neurosci. 2018 Jan;47:202-207).

**Masaharu Fukunaga** – A challenging case, myxopapillary ependymoma, primary site unknown. Thank you, Cesar.

**Barbara Gazić** – Difficult case, never seen this before in the lung.

**Thomas Krausz** – Looking at the slide, I understand the differential diagnostic consideration of carcinoid tumor.

**Thomas Mentzel** – A difficult diagnosis in this location (you have to think on it...)

**Markku Miettinen** – No wonder it was called originally carcinoid, this mimics carcinoid (looks like a grade 2 tumor, an atypical carcinoid). No immunostains were reported but I suppose there was something to go against a pulmonary NET (keratins, synaptophysin absent?). GFAP has been also reported in epithelial neuroendocrine tumors. I agree with Cesar that if ependymoma, it is likely metastatic.

**Fredrik Petersson** - I thought carcinoid, BUT it appears peripheral and there was something ependymomatous about it; nuclei polarized away from vessels. For sure also papillary structures. The myxoid component is limited. Very challenging! Btw, the text book wisdom of central location for pulmonary carcinoids may not hold true. (Meisinger Q et al. AJR Am J Roentgenol. 2011 Nov;197(5):1073-80. CT features of peripheral pulmonary carcinoid tumors.). Ependymomas may occur in ovarian teratomas. Could this be a germ cell “equivalent”? On my slide also distinct sarcoid-type granulomas.

**Brian Rubin** – I thought myxopapillary ependymoma but I didn’t think they arose in the lung or that they metastasized.

**Saul Suster** – I agree with Cesar that this looks like a classic myxopapillary ependymoma of the cauda equina. I’m assuming the diagnosis was supported with immunostains (GFAP/CD99+). If you get a history please let us know. It would be a highly unusual case if this were a primary in the lung, but I suppose it would be equally unusual to represent a metastasis (although more likely).

**Paul Wakely** – First time I see this, Cesar.

### **CASE NO. 13 – Kyle Perry, M.D.**

**Phil Allen** – Mast cell sarcoma after radiation therapy infiltrating voluntary muscle, mandibular region in a patient with previous lower extremity liposarcoma and prostatic adenocarcinoma. I must have missed these in the past. I would never have thought of a mast cell tumor on the basis of the H&E stain.

**Ira Bleiweiss** – This looks rhabdoid to me.

**Alberto Cavazza** – Thanks for sharing this extremely unusual case. Impossible for me, but it is nice to remember to consider the (unlikely) possibility of a mast cell neoplasm in pleomorphic malignancies.

**Kum Cooper** – Wow, thanks Kyle. Myeloid sarcoma (AMR # 69) and now a mast cell sarcoma!

**Göran Elmberger** – That's a very clever diagnosis to come up with. Expanding the spectrum of BFUM tumors and CUO's...

**Franco Fedeli** - Mast cell sarcoma. Very interesting case. I would put also epithelioid angiosarcoma in the differential diagnosis. What about CD31, CD 34 and ERG?.

**Maria Pia Foschini** – Mast cell sarcoma. Interesting case, very rare in the mandible!

**Masaharu Fukunaga** – This is my first time to see mast cell sarcoma, thank you for the beautiful case and comments, Kyle.

**Barbara Gazić** – We also thought about plasmacytoma in the differential, could be positive for CD117 but your other IHC results support mast cell sarcoma. It's a very interesting case, of course never seen before at our department.

**Thomas Krausz** – I looked at this case without the discussion and I had a broad differential diagnosis including metastatic dedifferentiated liposarcoma. Then I read the discussion, what a surprise, congratulations on the superb diagnosis. I hope I will recognize it next time.

**Thomas Mentzel** – A very difficult case, given that neoplastic cells do not look like mast cells.

**Markku Miettinen** – Hard to believe mast cell sarcoma. But this is because I have never seen this kind of mast cell sarcoma, we have a lot of mastocytomas but they all look like mast cells, although they are often spindled.

**Fredrik Petersson** - OMG. Lost for words. How many rounds of immune before you nailed it? Great case!

**Murray Resnick** – Interesting case. It is remarkable that the pathologist at the outside hospital had the foresight to order a mast cell marker.

**Brian Rubin** – Great case.

**Saul Suster** – Fantastic case and thank you for contributing it! It actually looks very similar to the case of mast cell sarcoma that was presented by Dr. Wakely at the recent Surgical Pathology Evening Specialty Conference at USCAP in Vancouver this year.

**Paul Wakely** – I contributed a case to AMR seminar #62 of systemic mastocytosis that presented as a sarcomatous soft tissue mass near the scapula. Morphologically, it resembled undifferentiated pleomorphic sarcoma, and I mistakenly diagnosed it as such until a subsequent bone marrow biopsy revealed the true diagnosis. As you say Kyle, true mast cell sarcoma without evidence of systemic mastocytosis is exceedingly rare. My congratulations to whomever thought of the entity and made that diagnosis. I had never heard of this tumor arising in a patient already burdened with a liposarcoma and a prostatic adenocarcinoma. Truly extraordinary case!

**CASE NO 14. – CONTRIBUTED BY: Fredrik Petersson, M.D.**

**Phil Allen** – Keratin-positive sarcoma with possible vascular differentiation, deltoid muscle, female aged 17. I too thought there was some vascular differentiation in the H and E stain, but the endothelial markers are apparently equivocal. I am confident that it is not an Enzinger type true epithelioid sarcoma and I am not personally convinced that proximal type epithelioid sarcoma is a genuine entity. I am concerned about the pleomorphism and the mitotic activity in this tumor. I understand that epithelioid sarcoma-like hemangioendothelioma and pseudomyogenic hemangioendothelioma are synonyms.

**Ira Bleiweiss** – Epithelioid sarcoma.

**Alberto Cavazza** – To my non-expert eyes, this tumor is malignant, and my differential diagnosis is between epithelioid sarcoma and pseudomyogenic hemangioendothelioma but, clearly, I am interested in the opinion of the experts.

**Kum Cooper** – Thank you Fred for this challenging case. Before I read your report, I went through the same DD: PMHE and ES. But on morphology I settled on proliferative myositis, given the entrapment of muscle cells, vascularity, microcystic degeneration and extravasation of red blood cells. Then I read you IHC and keratin was positive, and my heart sank since that is positive in PMHE but the vascular markers don't support the latter (given the results from your consultants). Then I read your follow-up and am now convinced that the proof is in the follow-up: proliferative myositis! So, what about the keratin positive? Well if you go back to the early literature, myofibroblasts can be keratin positive! Thank you again, I really enjoyed this case!

**Göran Elmberger** – Sorry Fredrik. No big help from me. I thought cytoplasm was rich and blue – cells reminding me of reactive myofibroblasts. Also, your own differential of epithelioid hemangioendothelioma if supported by vascular markers would not be a bad alternative.

**Franco Fedeli** - Based on pure morphology I would also consider the diagnosis of a CK+ Proliferative Fasciitis.

**Maria Pia Foschini** – Very unusual lesion. I agree to favor epithelioid sarcoma.

**Masaharu Fukunaga** – Thank you very much, Fredrik for the challenging case, comments and differential diagnoses. My diagnosis is proliferative fasciitis.

**Barbara Gazić** – I would end up with atypical epithelioid and spindle cell neoplasm of uncertain malignant potential. It would be interesting to see IHC for vascular markers.

**Thomas Krausz** – This is difficult; however, I am not convinced that this is a sarcoma. I favor an unusually florid variant of pseudosarcomatous condition (proliferative fasciitis/myositis family) with dominance of ganglion-like cells. Regarding the keratin expression, see reference by M. Miettinen. Am J Surg Pathol 2012; 36:1404-1409.

**Thomas Mentzel** – A nice case and I think that the diagnosis of pseudomyogenic hemangioendothelioma (initially called "epithelioid-sarcoma-like hemangioendothelioma") is correct. The tumor cells should show nuclear staining for FOSB as well due to underlying characteristic molecular changes.

**Markku Miettinen** – Cannot say what it is, but I agree with a potentially low-grade (myofibroblastic) tumor. A large fusion gene panel might help. It has some resemblance to proliferative fasciitis/myositis although too atypical. Also in the differential are IMFT (ALK-negativity is noted), and even myxoinflammatory fibroblastic sarcoma. Any of these can be also keratin-positive and many have distinct fusions.

**Brian Rubin** – The histology is good for pseudomyogenic/epithelioid sarcoma-like hemangioendothelioma but without vascular marker expression or genetics or genetic surrogates it's probably not classifiable. In my opinion epithelioid sarcoma-like HE and pseudomyogenic HE are the same entity. The different names emphasize different aspects of the histology but represent the histologic spectrum of the same thing. All cases of pseudomyogenic HE/epithelioid sarcoma-like HE that I've tested harbor SERPINE1-FOSB gene fusions that are the result of the t(7;19) translocation. See Walther C et al., J Pathol, 2014;232:534-40. FOSB IHC can be used as a surrogate for the gene fusion – see excellent paper with Jason Hornick as senior author: Hung YP et al. Am J Surg Pathol. 2017;41:596-606.

**Paul Wakely** – I may be naïve on this one Fredrik, but after 2 years with no local recurrence and no metastases in this 17 y/o woman, I think this is a florid example of proliferative fasciitis despite your IHC results.

**Saul Suster** - I believe this lesion is malignant; there are numerous abnormal and atypical mitoses scattered throughout. The cells contain inclusion-like nucleoli reminiscent of myxoinflammatory fibroblastic sarcoma. The strong keratin positivity, however, favors an epithelioid sarcoma.

**CASE NO. 15 – CONTRIBUTED BY: Murray Resnick, M.D.**

**Phil Allen** – Lymphoepithelioma-like hepatocellular carcinoma. I am not surprised that the EBER was negative. This tumour does not resemble the lymphoepithelial type of nasopharyngeal carcinoma, which is always associated with the Epstein-Barr virus.

**Ira Bleiweiss** – Agree.

**Alberto Cavazza** – Nice case and discussion.

**Kum Cooper** – I have not seen this variant of HCC before Murray. Interesting that the trabecular pattern is still maintained. Thank you.

**Göran Elmberger** – Good case with unusual morphology. PDL1 interesting point.

**Franco Fedeli** - Hepatocellular carcinoma, lymphoepithelioma like variant: never seen a case like this EBER in-situ neg. It would be noteworthy to investigate immunohistochemical markers for hepatocellular carcinoma (HSP70, GPC3 and GS).

**Maria Pia Foschini** – Hepatocellular carcinoma, lymphoepithelioid variant. Interesting case. Most of extra-oral lymphoepithelioid carcinomas are not related to EBV infection.

**Masaharu Fukunaga** – Lymphoepithelial type HCC, there are numerous bizarre giant cells with lymphoid background Thank you, Murray.

**Barbara Gazić** – A nice case, thank you for sharing it.

**Thomas Krausz** – Superb case, I did not realize until now that lymphoepithelioma-like carcinoma can occur in the liver.

**Thomas Mentzel** – A nice case of a rare entity.

**Markku Miettinen** – Looks very good for lymphoepithelial-like carcinoma. Looks like it is of hepatocellular origin based on arginase-positivity.

**Fredrik Petersson** - I think the term "lymphoepithelioma-like" for various carcinomas with a significant inflammatory component is perhaps not the best. The term lymphoepithelioma was originally defined by Schmincke and Ewing as a presumed tumor entity of lymphoepithelial, i.e. tonsillar-type organs, which are the most frequent in harboring virally driven carcinomas. The marked cytological pleomorphism seen in the presented tumor really does not correspond very well to a "real" (virally related) lymphoepithelial carcinoma, which are cytologically most frequently very uniform and in line with this, harbor relatively few genetic alterations. A similar "lymphocyte-rich" phenomenon, as seen in the tumor presented, was described in a paper on RCC a few years ago by me, Michal and Ondra. (Lymphocyte-rich renal cell carcinoma: an unusual histomorphologic manifestation of a tumor that is not part of lynch syndrome. Appl Immunohistochem Mol Morphol. 2011 Dec;19(6):519-27.)

**Brian Rubin** – Nice case.

**Saul Suster** – This tumor is straying somewhat from my concept of lymphoepithelioma-like carcinoma. There is too much pleomorphism and variability in nuclear size and shape, pleomorphic nuclei with multinucleation, and the nuclear chromatin does not show the typical vesicular chromatin pattern and prominent single eosinophilic nucleoli. Many malignancies can harbor a prominent lymphoid component but we generally reserve the term “lymphoepithelioma-like carcinoma” for tumors that close resemble poorly-differentiated nasopharyngeal carcinomas. Why is this not simply a poorly-differentiated hepatocellular carcinoma with prominent lymphoid stroma?

**Paul Wakely** – Thank you for presenting this unusual variant of HCC which I had not seen previously.

**CASE NO. 16 – CONTRIBUTED BY: Ady Yosepovich, M.D.**

**Phil Allen** – Secretory carcinoma, left breast of a male aged 3 years. Thanks for this instructive case. I do not see much breast pathology.

**Ira Bleiweiss** – Of course I agree with this. No other kinds of breast carcinoma in a 3 year old.

**Alberto Cavazza** – Thanks for sharing this very nice example of an unusual tumor.

**Kum Cooper** – Thank you for this educational/instructional case. I did get to male breast and carcinoma. And the write-up is very nice indeed!

**Göran Elmberger** – Seen this sometimes in salivary glands (MASC) but not in breast that seems to be less common location. Interesting with age distribution, a fact I was not aware of.

**Franco Fedeli** – Mammary-like secretory carcinoma (MASC) is the most frequent breast malignant neoplasm of the infancy and childhood. Very good teaching case with extensive discussion.

**Maria Pia Foschini** – Secretory carcinoma in a 3-yr old boy. This is a very typical case of secretory carcinoma of the breast. It can occur both in children as well as in adults, and both sexes can be affected. Prognosis is usually good in young patients, while it can be aggressive in adults.

**Masaharu Fukunaga** – Secretory carcinoma, agree. Thank you Ady for the beautiful slide and very informative comments.

**Barbara Gazić** – We saw 2 or 3 cases of secretory breast carcinoma but all in adults. I think radiologists in our institute would not perform core needle biopsy in a 3 year-old child; FNAB would be the first approach and then surgery.

**Thomas Krausz** – Thank you very much for sharing this very nice example with us.

**Thomas Mentzel** – Many thanks for this rare case that looks more solid than the (very) few secretory carcinomas we have seen in the skin. Did you stain the case for MUC4 as well?

**Markku Miettinen** – Secretory carcinoma of breast, low-grade; nice case.

**Fredrik Petersson** - Looks exactly like the classical and originally described mammary analogue secretory carcinoma of salivary glands, where secretory carcinomas are much more common than in the breast. The spectrum of MASC has subsequently been dramatically expanded. One example: A New Hitherto Unreported Histopathologic Manifestation of Mammary Analogue Secretor Carcinoma: "Masked MASC" Associated with Low-grade Mucinous Adenocarcinoma and Low-grade In Situ Carcinoma Components. Petersson F, Michal M, Kazakov DV, Grossmann P, Michal M. Appl Immunohistochem Mol Morphol. 2016 Oct;24(9):e80-e85.

**Brian Rubin** – Cool case and excellent discussion. It's interesting the ETV6-NTRK3 fusions are found in both secretory carcinomas and congenital fibrosarcoma/cellular mesoblastic nephroma.

**Saul Suster** – Beautiful example of secretory carcinoma of breast – we don't get to see these very often.

**Paul Wakely** – Just from reading the history and before picking up the slide, I was thinking this was going to be an example of either myeloid sarcoma, or rhabdomyosarcoma since the patient is so young. I had no idea this carcinoma could arise in a 3-year old.

**CASE NO. 17 – CONTRIBUTED BY: Barbara Gazić, M.D., Ph.D.**

**Phil Allen** – Primitive myxoid mesenchymal tumour of infancy, subcutis, paraspinal region in a 10 month old girl. This is the first case I have had shown to me. No doubt I have missed them in the past. I wondered about a myxoid dermatofibrosarcoma protuberans but did not consider infantile fibrosarcoma until after I had checked the patient's age. Thanks for the contribution.

**Ira Bleiweiss** – ???

**Alberto Cavazza** – Thanks for sharing this very unusual and educational case.

**Kum Cooper** – Welcome to the group Barbara. What an entrance with this excellent case! Have read about this tumor and this is my first view of a “live” slide. The BCOR ITD are expanding rapidly as you explain in your write-up (and soon to be published HG endometrial stromal sarcoma).

**Göran Elmberger** – Great and rare case. Thanks!

**Franco Fedeli** - Impressive and very rare case. In my opinion, it looks very similar to Clear Cell Sarcoma of the Kidney on morphology.

**Maria Pia Foschini** – Primitive myxoid mesenchymal tumor of infancy. Very interesting and unusual case. Thank you for sharing it!

**Masaharu Fukunaga** – I have never seen this type of tumor, primitive myxoid mesenchymal tumor of infancy. Thank you very much for this particular lesion, Barbara.

**Thomas Krausz** – I am so pleased to know that the molecular “soul” (BCOR) of primitive mesenchymal tumor of infancy has been identified. It certainly will help to arrive at a definitive diagnosis in histologically difficult cases.

**Thomas Mentzel** – Many thanks for sharing this case of a rare and recently described entity, unfortunately, I have no experience with this neoplasm.

**Markku Miettinen** – Sarcoma with myxoid features. Barbara reports BCOR-positivity, could it also have a BCOR fusion?

**Fredrik Petersson** – I was not aware of this. Looking at the slide I was struggling with infantile fibrosarcoma and perhaps an unusual variant of plexiform fibrohistiocytic tumor (predominantly fibroblastic/not so plexiform). Thanks for a great and educational case! Read up on it and the tumor can apparently metastasize.

**Brian Rubin** – Awesome. I’ve read about this entity but never seen a case.

**Saul Suster** - Thank you for sharing this case with us – first case I see of this entity!

**Paul Wakely** – Wow! My ignorance regarding unusual pediatric neoplasms is worse than I thought. The branching capillary network at low power made me consider myxoid LPS when I first picked the slide up.

**CASE NO. 18 – CONTRIBUTED BY: Saul Suster, M.D.**

**Phil Allen** – Unusual, presently undiagnosed, multinodular, sclerosing right ovarian stromal tumor with amianthoid foci, female aged 56. I have no idea what this is either Saul.



**Ira Bleiweiss** – As my son would say, IDK (I don't know).

**Alberto Cavazza** – I have never seen a lesion like this before and I am not able to add anything to your "unusual sclerosing ovarian stromal tumor".

**Kum Cooper** – Sex-cord stromal tumor with granulosa cell tumor (luteinized). FOXL2 IHC/mutation will be helpful to confirm this morphological impression Saul, also if this is GCT then the estrogens would have contributed to the FIGO 1 endometrial endometrioid carcinoma.

**Göran Elmberger** – Sorry not my strongest area. Sertoli, Sertoli-Leydig? Wolffian duct? Inhibin, Melan A, SF1?

**Franco Fedeli** - It reminds me of the pancreatic-type solid pseudopapillary neoplasm in the ovary. In your case, the tumor is only vimentin and CD10 positive. What about  $\beta$ -Catenin?

**Maria Pia Foschini** – Unusual variant of sclerosing ovarian stromal tumor. Unfortunately, my experience in ovarian tumors is too little to add suggestions!

**Masaharu Fukunaga** – A challenging case, I have never seen this kind of ovarian tumor. My impression is ossifying fibromyxoid tumor. It may be sex-cord and stromal cell tumor.

**Barbara Gazić** – Steroid cell tumor?

**Thomas Krausz** – Yes, I also favor sclerosing stromal tumor.

**Thomas Mentzel** – Wow, what an interesting and distinct looking lesions – I`m really looking forward to the comments of the club members!

**Michal Michal** – I would be interested whether the tumor was immunohistochemically Beta-catenin positive and had mutation in Beta-catenin gene. It seems to me that it might be another primary ovarian solid pseudopapillary tumor of the ovary (Vikram Deshpande, Esther Oliva, Robert H. Young, MD. Am J Surg Pathol 2010;34:1514–1520).

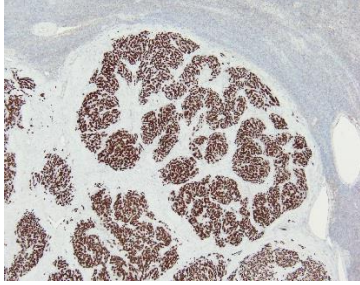
**Markku Miettinen** – Agree on sex cord stromal tumor. Could it be a variant of Sertoli cell tumor combining fibroma-like elements? Inhibin and calretinin would also be of interest.

**Fredrik Petersson** - Never seen this. Initial thoughts around sex-cord-stromal tumor and solid adenomatoid tumor, but IHC not much "to go on". My ears are wide open for the comments.

**Murray Resnick** – Would probably perform more sex cord markers such as inhibin and WT1. Looks to me like some sort of thecoma variant.

**Brian Rubin** – Could it be a PEComa? Should be HMB45 positive if that's what it is. Kind of reminds me of an epithelioid PDGFRA-mutant GIST of the stomach too but the tumor is in the ovary. Those can be KIT weak/negative but are DOG1 positive. This is what happens when you ask a soft tissue pathologist about ovarian tumors!

**Saul Suster (My case)** – Upon receiving the comments from the members I requested a few additional stains on this case. Stains for inhibin, calretinin, HMB45 and Melan-A were negative in the tumor cells, which does not support a sex cord stromal tumor or PEComa. Stains for beta-catenin showed strikingly strong nuclear positivity (see below), and WT1 showed focal dot-like paranuclear cytoplasmic positivity. In reviewing the paper cited by Michal Michal (Deshpande et al. Am J Surg Pathol 34:1514, 2010), there is a close similarity between this tumor and the images depicted in that paper. Given the absence of any markers associated with ovarian sex cord or stromal cells, I believe the best explanation is that suggested by our friends Michal Michal and Franco Fedeli that this corresponds to a pancreatic-type solid pseudopapillary tumor. Such tumors stain for CD10 in >90% of cases. I think I will have to agree with Drs. Michal and Fedeli that this most likely corresponds to this unusual extrapancreatic entity.



Beta-catenin stain.

**CASE NO. 19 – CONTRIBUTED BY: Saul Suster, M.D.**

(Case contributed by Dr. Francisco Mucientes, University of Concepcion, Chile).

**Phil Allen** – Large (12 cm), poorly differentiated malignant tumor centered outside the rectum involving prostate and rectum, male aged 49. Could this be an ectopic spermatocytic seminoma Saul?

**Ira Bleiweiss** – Saul, where do you find these cases?

**Alberto Cavazza** – Sorry, again no ideas. I tend to favor an undifferentiated sarcoma.

**Kum Cooper** – NKX3.1 to rule out prostate. Poorly differentiated with neuroendocrine differentiation (NSE/CD6)?

**Göran Elmberger** – Sorry, the morphology and cited IHC does not give much help. I always start off with CK, CD45, S100 and vimentin in cases like this not to miss the main line of differentiation. Dedifferentiated tumors occur as for example dedifferentiated malignant melanomas. Sometimes CUO protocols based on DNA/RNA gives better clues in cases like this. Somehow these molecules seem more stable in lineage than morphology and IHC according to my experience.

**Franco Fedeli** - Morphologically malignant melanoma cannot be excluded. I would try to immunostain the lesion for MITF and SOX10.

**Maria Pia Foschini** – Very highly aggressive tumor, negative for all markers tested. In these cases, even if morphology is not consistent, I would add markers of hematological malignancies.

**Masaharu Fukunaga** – Very tough case to make a diagnosis. Undifferentiated malignant tumor or clear cell sarcoma?

**Barbara Gazić** – Carcinoma with NE differentiation?

**Thomas Krausz** – PEComa is the most likely for me. Repeat appropriate immunos might help.

**Thomas Mentzel** – Looks like a high-grade neoplasm of unknown differentiation (in my slide vascular invasion is seen in the periphery). Given that wide spectrum keratin was reported to be positive, could this be an undifferentiated sarcomatous carcinoma?

**Markku Miettinen** – Malignant epithelioid neoplasm. I also like the PEComa possibility (malignant in this case), although seems difficult to verify this based on negative HMB45. Could also try TFE immuno and FISH. And a large fusion panel if possible.

**Fredrik Petersson** - High-grade malignant tumor. Does not look epithelial to me. Sarcoma? EWSR1-rearrangement?

**Murray Resnick** – May be worth ordering a GATA3 or p40 for urothelial carcinoma, although the keratin negativity would be unusual.

**Brian Rubin** – With the immunoprofile it's hard to put it into a diagnostic category. The pathology isn't that distinctive. Could it be a lymphoma? I'd run a CD43 IHC if it hasn't been done. IT might be a poorly differentiated granulocytic sarcoma.

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

**Phil Allen** – What about cellular angiofibroma Saul?

**Alberto Cavazza** – Difficult for me. Ischemic fasciitis would be my first consideration and I would ask for possible causes, but I may be easily wrong.

**Kum Cooper** – DD: SFT (myxoid/atypical), atypical cellular angiofibroma.

**Göran Elmberger** – Pattern looks familiar, but I am not sure. LGFMS?? Perineurial??

**Franco Fedeli** – It reminds me of an angiofibroma of the female tract. I ignore if this kind of tumor has been described in men.

**Masaharu Fukunaga** – Solitary fibrous tumor, angiofibroma or angiofibroma-like tumor.

**Thomas Mentzel** – Angiofibroma of soft tissue.

**Markku Miettinen** – Low-grade mesenchymal neoplasm. Because of a subtle fatty element, ?atypical, could consider one of the potential forms of dedifferentiated liposarcoma, so MDM2 studies would be of interest. If this does not pan out, an odd SFT or a (new) fusion tumor could be considered.

**Michal Michal** – Hemangioblastoma of soft tissues?

**Fredrik Petersson** - Difficult. Fibroblastic something neoplastic with a prominent vascular component and superimposed reactive changes. I am eagerly awaiting the soft tissue experts' views.

**Murray Resnick** – Would order a STAT6 to rule out a solitary fibrous tumor. S-100 to exclude a nerve sheath tumor.

**Brian Rubin** – Not sure what this is. I'd favor solitary fibrous tumor (giant cell variant). Low-grade fibromyxoid sarcoma, PEComa, or unusual angiofibroma of soft tissue with atypical/round cells are other thoughts. I need immuno to figure this out!

**Saul Suster – My case:** this is a peculiar **schwannoma**. The tumor was well-circumscribed and encapsulated without evidence of invasion, hemorrhage, necrosis or mitotic activity. IHC showed nuclear and cytoplasmic positivity for S-100 protein and focal positivity for bcl-2. Stains for CD56, bcl-1, CD34, desmin, cytokeratin AE1/AE3, EMA, SMA and Stat 6 were negative. MIB-1 was also negative in the tumor cells. The entire tumor showed this peculiar degenerative appearance with prominent stromal and perivascular hyalinization and focal strands of single-cells reminiscent of extraskeletal myxoid chondrosarcoma. In light of the strong and convincing S-100 protein positivity, a diagnosis of schwannoma with peculiar degenerative changes was favored.