COMMENTS FOR AMR SEMINAR #76

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

Phil Allen – Undiagnosed sarcoma with a biphasic SMARCA4 deficient rhabdoid alveolar component colliding with a histologically atypical hemosiderotic fibrohistiocytic component, subcutis, left foot in a 54-year-old male with rheumatoid arthritis.

I don't think the histology matches acral myxoinflammatory fibroblastic sarcoma, nor pleomorphic hyalinising angiectatic tumor nor hemosiderotic fibrolipomatous tumor while the witches brew of cytogenetic and other newly established test results makes for an uncertain interpretation. I wonder if the patient is immune suppressed from rheumatoid treatment. What is really needed now is the ability to collect a decent series of tumors that are histologically similar to this one and to investigate them for any shared features. Where is the AFIP when we need it? Its soul tried to march on while its body lies a-mouldering above ground, possibly because it would cost too much to bury.

Ira Bleiweiss – Very rhabdoid indeed.

Alberto Cavazza – Fascinating and unusual case, with a great discussion.

Kum Cooper – Abbas this is what the millennials would call a "sick" case. Outstanding review of the HFLT/PHAT/MIFS story from 1990. I still recall the debate in the mid-2000s at USCAP from the two "stables" both lined up in different lanes awaiting the microphone...fascinating to watch! In the end they were both correct! Thank you for sharing this excellent educational case.

Göran Elmberger – Great case. So many important take home messages in a unique tumor. Thanks Abbas!

Franco Fedeli – This is a very rare case. For the treatment, It would be interesting to see if the BRAF mutation; fusion or amplification has been found exclusively in MIFS and not in HFLT.

Cyril Fisher – Remarkable case, thanks Abbas. As noted in e, it is apparent that high grade undifferentiated sarcomas emerging from lower grade lesions (?dedifferentiation) can assume a variety of patterns - fibrosarcoma or myxofibrosarcoma-like, pleomorphic and now rhabdoid SMARCA4-deficient tumors. Genetic analysis would be of interest.

Masaharu Fukunaga – Thank you very much for the interesting and impressive case, which have been analyzed Histologically, the undifferentiated area seems to be epithelioid sarcoma.

Thomas Krausz – Superb, highly educational, diagnostically challenging case (agree with diagnosis). My first impression, before reading your excellent discussion, was malignant melanoma with both spindle and epithelioid/rhabdoid components. However, reanalyzing the case, the pigment is not melanin and the diagnostic features of HFLT/PHAT, adjacent to the rhabdoid component, are apparent. The IHC study gives valuable result in solving the puzzle.

Brandon Larsen – Fascinating case. I have yet to encounter my own case of "sarcoma ex HFLT/PHAT", but this is certainly a convincing example. The epithelioid/rhabdoid morphology of the high-grade component resembles the SMARCA4-deficient thoracic sarcomas that I've encountered. It makes me wonder how many cases of epithelioid sarcoma I've seen where I missed the HFLT or PHAT in the background.

Jesse McKenney – My first thought was "de-differentiated" MIFS. Agree … high grade sarcoma with rhabdoid features (proven SMARCA4 deficient) arising in background of HFLT. Great case!

Thomas Mentzel – What a case, many thanks Abbas! To be honest I would probably miss or underestimate the peripheral part of the lesion raising interesting questions regarding this form of transition.

Markku Miettinen – Agree. The tumor has a hemosiderotic fibrolipomatous tumor component. The high-grade epithelioid component is probably a progression component of that tumor. It is very epithelioid and mimics a carcinoma, but collision tumor seems even less likely.

Fredrik Petersson – Beautiful case. Erudite presentation. Both the relation between HFLT/PHAT and (high-grade) myxoinflammatory sarcoma and sarcomas deficient for SWI/SNF appear to be "hot topics".

Saul Suster – Thank you Abbas for this great case. In areas it resembles an alveolar soft part sarcoma, only with more striking atypia.

CASE NO. 2 – CONTRIBUTED BY: Gerald Berry, M.D.

Phil Allen – Mediastinal water-clear parathyroid adenoma.

I attended a parathyroid lecture by Ben Castleman in Adelaide in the mid-sixties. He had earlier described primary clear cell parathyroid hyperplasia and was also the author of the first AFIP parathyroid fascicle. He said in Adelaide that since his 1951 article (Bull Hosp Joint Dis 12: 368-378, 1951), primary clear parathyroid hyperplasia seemed to have disappeared. However, I see that it still merits three pages (566-568) in Juan Rosai's latest thyroid/parathyroid fascicle. Ben Castleman's 1951 black and white illustration of the macroscopic appearances of primary clear cell parathyroid hyperplasia, which was published in colour in Ben's 1952 AFIP fascicle (plate III opposite page 61), still survives in colour in the latest fascicle (page 567), although slightly reduced in size from the original AFIP picture (AFIP accession number 218954). Interestingly, Ben was not entirely happy with his Adelaide trip because he thought the Australian College, which funded his visit, was a little parsimonious with the honorarium.

Ira Bleiweiss – Agree. Never seen this before, at least not that I can remember.

Alberto Cavazza – Unusual case in an unusual location. Nice example of endocrine/degenerative atypia.

Kum Cooper – Beautiful case Gerry! Thank you for sharing. Great story and great ending.

Göran Elmberger – Interesting case "wasserhelle" adenoma PT. Marked "endocrine atypia". Pseudo malignancy. Even large eosinophilic nucleoli probably corresponding to increased RNA synthesis, but I doubt cells are proliferating much as judged by completed cell cycling with mitoses and high Ki-67. Interesting phenomenon. Anyone understand the mechanism behind?

Franco Fedeli – The water clear cells might represent hyperfunction of the parathyroid cells.

Cyril Fisher – Water-clear parathyroid adenoma, with focal calcification, very pretty example.

Masaharu Fukunaga – Thank you very much for the impressive case of mediastinal water-clear parathyroid adenoma. Cells are markedly degenerated.

Thomas Krausz – Very nice example. I agree that despite the "random" nuclear pleomorphism, this is a benign parathyroid tumor (adenoma). The extensive clear cell change can lead to differential diagnostic considerations especially if one would miss the microscopic foci of more conventional parathyroid tissue.

Brandon Larsen – I've never seen nor heard of this variant before. Thanks for sharing. Some of that stroma is even a bit "amyloid-like". Interesting.

Jesse McKenney – Nice case!

Thomas Mentzel – A wonderful case of a variant of ectopic parathyroid adenoma with prominent degenerative cytological features!

Markku Miettinen – Agree on parathyroid adenoma with clear cell change.

Fredrik Petersson – Cytologically horrible, but no mitotic activity and non-infiltrative, i.e. adenoma. Interesting clinical history. Thanks.

Saul Suster – Spectacular H&E slide – eye candy for morphologists. Never seen this in the mediastinum.

CASE NO. 3 – CONTRIBUTED BY: Justin Bishop, M.D.

Phil Allen – Low-grade mucoepidermoid carcinoma with tumor associated lymphoid proliferation in 5 of 54 level 2 cervical lymph nodes, side not stated, possibly arising from a focus of heterotopic salivary gland tissue in one of the lymph nodes.

I quote from the Ellis and Auclair's fourth series AFIP fascicle: "...but without detailed clinical and surgical information, the (normal residual) lymphoid tissue is difficult to distinguish from a tumor-associated lymphoid proliferation." Review of all the organ imaging might help to resolve the problem in this case. I have trouble being confident about the endothelial lining of the subcapsular sinus story.

Ira Bleiweiss – Agree. Not sure I see cilia.

Alberto Cavazza – Very nice comment on cilia, I have never noticed them in mucoepidermoid carcinoma.

Kum Cooper – Thank you Justin for the lovely example from your recent publications. I did look for cilia since I thought this was going to be the HPV case! Great discussion. I did not realize that MEC can be p16 positive!

Göran Elmberger – Admit I missed beautiful cilia. Knowing about value of detecting increasing numbers of hallmark translocations and mutations in SGT tricky variants, I wonder if NGS might be the best platform, and if so, which platform and commercial assay that would do the job best? Regarding cilia I remember seeing those in PA's and WT's. Also, in old days when we used EM for CUO a lot of tumors showed few cilia's as for example prostate carcinomas and glioblastomas. Not so rare with that level of magnification. I guess in early embryology almost all cells needed to move around, and cilia was the perfect tool. Dedifferentiation? Too philosophical?? Thanks!

Franco Fedeli – Metastatic low grade mucoepidermoid carcinoma ciliated variant. Very interesting discussion on the significance of ciliated cells.

Cyril Fisher – Metastatic mucoepidermoid carcinoma with cilia, and areas of typical morphology, very nice example and discussion, thanks Justin.

Masaharu Fukunaga – I have never seen a case of MEC, ciliated type. My initial diagnosis was Warthin tumor. Thank you very much.

Thomas Krausz – I was not aware of the ciliated variant of mucoepidermoid carcinoma, thank you very much for submitting it, highly educational. The ciliated cells are indeed well differentiated, difficult to distinguish them from non-neoplastic ciliated cells. I assume that the ciliated cells also have the MAML2 alteration on FISH study.

Brandon Larsen – I wasn't aware that mucoepidermoid carcinomas can be ciliated, nor did I notice the cilia before reading your write-up, although I have to admit that I haven't been looking very closely for ciliated cells in these tumors! Looks like a straight-forward MEC in every other way, but I can see how this could be a problem in a small biopsy or FNA specimen without being aware of this fact. Thanks for making me aware of this.

Jesse McKenney – Interesting example of mucoepidermoid carcinoma…yes, I missed the cilia.

Thomas Mentzel – Great example of cystic mucoepidermoid carcinoma containing a ciliated cell component. Did you find the primary tumour in the meantime?

Markku Miettinen – Agree on cystic metastasis of low-grade mucoepidermoid carcinoma. Analogous to a cystic nodal metastases of squamous cell carcinoma.

Fredrik Petersson – Mucoepidermoid carcinoma, low-grade. Few ciliated cells on my section. Primary nodal? The combination of ciliated cells and MEC-like areas often seen in glandular odontogenic cysts.

Saul Suster – Great case! Convincing MEC; had no idea a ciliated variant existed! But it's very convincing. Truly a collector's item.

CASE NO. 4 - CONTRIBUTED BY: Ira Bleiweiss, M.D.

Phil Allen – Small, completely excised, recently appearing focus of an atypical cellular blue nevus in a 60-year-old female arising from a massive, deeply invasive blue nevus present since the age of 7.
I also have never seen a case like this before. I agree that the original tumor is a deeply invasive blue nevus with an attraction to breast ducts. I don't think the newly appearing nodule has metastasizing potential, but I don't really know. It's lucky that the new nodule has been completely excised. I would leave the sentinel lymph node in her sentry box to maintain the guard. Was the patient also Chinese? Could this nevus of Dr. Wu be similar to the nevi (I am not sure if that is the plural of naevus) of Ito and Ota?

Alberto Cavazza – Never seen something like this, thanks for sharing. I am concerned about the nodule being malignant (a melanoma arisen in a primary blue nevus of the breast), but if the experts classify this as an atypical blue nevus, I am happy.

Kum Cooper – Thanks Ira. The nodule is in my slide. Morphologically though it looked bland and along with the spindled component goes well for blue nevus. But the breast distribution/involvement is "wild". Sentinel lymph node likely has nevi in it too. Which would be a frozen nightmare!!

Göran Elmberger – Wow what a case. I am not an expert on this, but your diagnosis sounds reasonable given the nature of the cellular nodule i.e.: not to frequent mitoses, not pronounced atypia, no necrosis and expansile rather than infiltrative growth. I looked up an article illustrating similar cases where they suggest using cytogenetics to further resolve diagnosis. Multi FISH or CGH or perhaps today NGS profiling might be of use. Melanoma Arising in a Large Plaque-type Blue Nevus with Subcutaneous Cellular Nodules. Iwei Yeh, MD, PhD, Yuqiang Fang, MD, and Klaus J. Busam, MD. Am J Surg Pathol 2012;36:1258–1263).

Franco Fedeli – I think that the nodule would be better to consider a melanoma (mitosis are numerous) in a 60 Y.O. patient with a long history of "cellular blu nevus".

Masaharu Fukunaga – I prefer cellular blue nevus. Thank you, very much Ira.

Thomas Krausz – Fascinating case, thank you very much for submitting it. I agree, it has histologically two different melanocytic components: 1. heavily pigmented dendritic melanocytic lesion ramifying in septa and perilobular distribution, consistent with "common" blue nevus and 2. a "nodule" of hypopigmented, cellular, spindle cell melanocytic proliferation with brisk mitotic activity with a differential diagnosis between atypical cellular blue nevus and melanoma developing from a blue nevus. In order to solve the differential diagnostic dilemma, it would be important to review all the previous biopsies and also consider molecular study to see whether there are additional molecular alterations beyond those one can demonstrate in blue nevi (GNAQ, GNA11). On the basis of the clinical history and size of the lesion provided I suspect that the cutaneous tumor is a "plaque-type blue nevus" which is typically large and can infiltrate into underlying tissue, like breast. I have never seen primary blue nevus in the breast, but the heavily pigmented dendritic component one can see in this case in the breast, reminds me to blue nevus of prostate.

Brandon Larsen – The nodule of interest was not present on my slide. In any event, I've never seen such a lesion in the breast. Strange case. It would be hard to argue if the clinicians wanted to perform a sentinel lymph node biopsy, just to be safe, but I'm no expert in atypical cellular blue nevi!

Jesse McKenney – I probably would have classified this descriptively as atypical melanocytic proliferation in blue nevus.

Thomas Mentzel – Many thanks, and for me the nodule is very suspicious for malignant melanoma arising in a long standing, multicentric naevus blue. I´ve seen a similar case of malignant melanoma arising in a patient with Naevus Ota, melanosis and multiple blue naevi that also showed *GNAQ and BAP1* mutations.

Markku Miettinen – Yes, a cellular blue nevus, in which the non-pigmented component has atypia and mitoses (uncertain biologic potential, need to follow-up).

Fredrik Petersson – Not very high mitotic activity on my section and the atypia is not more than I can accept in an atypical cellular blue nevus. The background dendritic melanocytic process is a real "melanocytosis".

Saul Suster – Very convincing, and disquieting.

CASE NO. 5 – CONTRIBUTED BY: Fatima Carneiro, M.D., Ph.D.

Phil Allen – Epithelioid malignant mesothelioma, omentum and peritoneum. I wonder if she has an asbestos history.

Ira Bleiweiss – Agree.

Alberto Cavazza – In my set of slides, n. 5 corresponds to n. 6 and vice versa. Nevertheless, I agree: nice example of epithelioid mesothelioma with deciduoid features, not exceptional in peritoneal mesothelioma.

Kum Cooper – Thank you Fatima. My slide has a solid focus of very bland looking cells with scattered giant cells and peripheral lymphocytes. After looking at slide 6 I realize that this is the benign skin lesion (Case 6). Other thoughts include reticulohistiocytosis.

Göran Elmberger – Reciprocal switch from case six. Omental tissue with beautiful deciduoid malignant mesothelioma.

Franco Fedeli – Deciduoid mesothelioma was first described in 1985 by Talerman in a female peritoneum.

Masaharu Fukunaga – It seems to be epithelioid granulomatous lesion. No mitotic figures are found but cytologic atypia is prominent. Thank you very much for the wonderful case.

Ondřej Hes – Case 5 and Case 6 are mislabeled…

Case 5 is necrobiotic xanthogranuloma in my set of slides and case 6 is mesothelioma. But it was easy to sort them out ☺. Both great cases indeed

Thomas Krausz – Agree with diagnosis.

Brandon Larsen – Agree…a rather beautiful example of epithelioid peritoneal mesothelioma. Thanks for sharing.

Jesse McKenney – Nice case of epithelioid mesothelioma. (My slides 5 and 6 were mislabeled as each other).

Thomas Mentzel – The slide listed with Case 5 shows the features of Case 6 with a subcutaneous xanthogranulomatous lesion. Cases of necrobiotic xanthogranuloma arising at the extremities are rather rare but well-documented. However, I´ve found the case quite difficult because I did not see cholesterol clefts and no plasma cell rich inflammatory infiltrate.

Markku Miettinen – Agree on malignant epithelioid mesothelioma.

Fredrik Petersson – Nice classical deciduoid morphology.

Saul Suster – Oncocytic mesotheliomas (aka, deciduoid mesothelioma) can be harder to diagnose than conventional ones. Very nice case!

CASE NO. 6 – CONTRIBUTED BY: Fatima Carneiro, M.D., Ph.D.

Phil Allen – Necrobiotic xanthogranuloma with paraproteinemia, forearms and face.
Thanks for this excellent case. I have not seen one before.

Ira Bleiweiss – Wow. Very concerning for malignancy but no mitoses.

Alberto Cavazza – In a silent clinical scenario I would probably miss the diagnosis. Interesting case!

Kum Cooper – Thank you Fatima. I think my slide labels were transposed. This is the epithelioid malignant mesothelioma.

Göran Elmberger – Ok switch from case 5. Histiocytosis with giant cells of Touton and Langhans type. I note deep necrobiotic zone. Cytomorphology not unlike Langerhans cells but without eosinophilia and obviously with IHC better in favor of non-Langerhans cell histiocytosis. New to me as well as connection with gammopathy. Obviously of great importance. Thanks!

Franco Fedeli – I didn't know this disorder and the association with monoclonal gammopathy.

Cyril Fisher – Necrobiotic xanthogranuloma, other diagnoses excluded by the immunohistochemistry.

Masaharu Fukunaga – A wonderful and interesting case of necrobiotic xanthogranuloma. It looks like epithelioid mesothelioma. It could be a pitfall.

Thomas Krausz – Agree that this is a histiocytic infiltrate. The section is rather pale; hence, I could not analyze the texture of the cytoplasm properly, but foamy character is limited to rare cells. I assume microorganism stains are negative. In addition to xanthogranuloma, in the context of monoclonal gammopathy I would also consider "crystal storing histiocytosis" in the differential diagnosis.

Brandon Larsen – Nice case of NXG. Thanks for sharing.

Jesse McKenney – Interesting clinical association! (My slides 5 and 6 were mislabeled as each other).

Thomas Mentzel – The slide listed with Case 6 shows the features of Case 5 with a malignant epithelioid neoplasm.

Markku Miettinen – Agree on benign histiocytic proliferation.

Fredrik Petersson – Very, very focal "necrobiosis" on my slide. History helpful! Thanks.

Saul Suster – Rare and difficult lesion – looks like a metastasis from the previous case! (I'm kidding).

CASE NO. 7 CONTRIBUTED BY: Fatima Carneiro, M.D., Ph.D.

Phil Allen – Primary angiomatoid (malignant) fibrous histiocytoma with two proximate lymph nodal metastases, hilum of right lung.

I always put "(malignant)" in brackets in my diagnoses of this tumor because it can metastasize. Once I had a young child with a facial angiomatoid (malignant) fibrous histiocytoma. The referring pathologist accepted the modern implied benign name but agreed to investigate an enlarged occipital lymph node which, on excision, contained metastatic tumor. I wouldn't have looked too good if I hadn't warned of the small metastasizing potential. It's a pity that fibrohistiocytic names were all the rage at the time Enzinger recognised this specific tumor. His metastasis rate (approx. 17%) was probably due to the highly selected nature of the AFIP material. More of the metastasizing cases would have been referred by puzzled pathologists while other non-metastasizing cases may have been hidden under unlikely diagnostic aliases and could still lie filed in the bowels of the atom bomb proof AFIP building.

Alberto Cavazza – Spectacular case. I have seen just another case primary in the lung, in the collection of Tom Colby.

Kum Cooper – This is spoiling us. Great neat case. Thank you, Fatima!

Göran Elmberger – Wow! That's a unique and challenging case. Even after reading the diagnosis I had trouble recognizing hallmark lesion of pseudovascular spaces in my section. Intratumoral high vascularity and fresh hemorrhage I could see. It is great that molecular confirmation can help in diagnosis of such rare tumors and it is of great importance to be aware that primary lung AFH do occur. Given the rarity of primary AFH perhaps it would be more common to find cases metastasizing to the lung even if this also must be a very rare occurrence. Metastases would probably be multifocal so in present case primary lung tumor is more probable. I remember my first and only case of metastasizing cellular dermatofibroma to the lung. It presented as a multicystic lesion first suspected to represent LAM. Took a while till I found primary skin tumor on shoulder skin of that young man. The skin tumor had undergone three partial resections with local recurrences in another hospital. Tom Colby helped me to verify that case. After that case more than one dermatologist have complained that I report margins on those kind of skin lesions and even argued that DF/FH is a non-neoplastic reactive lesion.

Franco Fedeli – Angiomatoid fibrous histiocytoma of the lung. In this case the inflammatory component is extremely represented.

Cyril Fisher – Very interesting case. It would be of interest to know the partner gene. Of the endobronchial cases we published (AJSP2012;36:883-8) one had *EWSR1-ATF1* and one *EWSR1-CREB1*. Recently (myxoid) AFH with *EWSR1-CREM1* fusion has been recognised (e.g. AJSP 2019; 43:1622-1630).

Masaharu Fukunaga – I agree with your diagnosis. The orientation of the slide is not clear, but some area shows typical feature of angiomatous fibrous histiocytoma. Vascular invasion with lymphoid cuffing is very interesting. Thank you very much.

Thomas Krausz – I have seen only one case of AFH in the lung before. A related entity with the same genetics under the term "primary pulmonary myxoid sarcoma" has also been described.

Brandon Larsen – Great case. I often struggle with pulmonary "fibrohistiocytic" lesions and it's always nice to see good examples of angiomatoid FH with FISH confirmation.

Jesse McKenney – Great example. We have been seeing a run of the pulmonary myxoid sarcomas with EWSR1 rearrangements.

Thomas Mentzel – Many thanks for this rare case of an angiomatoid fibrous histiocytoma arising at the lung. At least for me positive staining of tumour cells for caldesmon is unusual.

Markku Miettinen – Agree on angiomatoid FH, may be just part of the same tumor, not nodal metastasis.

Fredrik Petersson – Wow!

CASE NO 8. – CONTRIBUTED BY: Alberto Cavazza, M.D.

Phil Allen – Persistent, florid, ectopic deciduosis, omentum, and pelvis, in a 29-year-old still lactating woman biopsied three years after delivery. The three-year follow-up after the biopsy strongly supports the diagnosis.

Ira Bleiweiss – Agree.

Kum Cooper – Thank you Alberto for re-visiting this case. Another thought? Have you done an ALK IHC and/or FISH? IMTs have been described in the post-partum so I was just wondering.

Göran Elmberger – Great case. Mimicker. Prolonged breast feeding also have risks!

Franco Fedeli – Interesting proliferation that, in this case, mimicks malignancy.

Masaharu Fukunaga – Ectopic decidual change is not rare, however I have never seen such a case. Without history of deciduoid malignant mesothelioma or other spindle cell tumor might be considered. Thank you very much for the excellent slide.

Thomas Krausz – Agree with diagnosis.

Brandon Larsen – Alberto, this is an amazing case. I must admit that I didn't think of deciduosis. I really wondered if this might represent an epithelioid or deciduoid variant of IMT, but my impression might be influenced by a case of IMT with peritoneal dissemination that I encountered recently. Without knowing the immunoprofile, I might've gone down the wrong road with FISH testing, but it's hard to argue with the ER result and clinical outcome. Thanks for sharing.

Jesse McKenney – Very interesting case!

Thomas Mentzel – To be honest I was thinking on a myxoid myogenic neoplasm, however, the immunohistochemical stains are convincing.

Markku Miettinen – Yes, deciduoid tumor. Could also think of a low-grade endometrial stromal tumor.

Fredrik Petersson – Very tricky. The mucinous component led me into a completely different track. Worried about trophoblastic neoplasm, but as stated, no mitotic activity of significance.

Saul Suster – In the absence of the history would have been very difficult to make the diagnosis of deciduosis. The cells look more histiocytic than decidual, and the extensive inflammatory infiltrate admixed with the epithelioid cells is not something I would expect to be associated with decidual reaction.

CASE NO 9. – CONTRIBUTED BY: Göran Elmberger, M.D.

Phil Allen – IGg4-related salivary gland disease (Kuttner), right submandibular gland. Thanks for the very detailed and informative discussion.

Ira Bleiweiss – Agree. Beautiful case.

Alberto Cavazza – A very nice example of an entity in vogue. Elastic stain can really be useful to detect a subtle obliterative phlebitis, like in your case.

Kum Cooper – Thank you Goran for sharing this illustrative educational case.

Göran Elmberger – My case. Sorry for long description. Just summing up for teaching files.

Franco Fedeli – IgG4-related salivary gland disease is an important macroscopic cancer mimicker.

Cyril Fisher - Kuttner tumor, very nice example.

Masaharu Fukunaga – A beautiful case of IgG4-related Salivary gland disease. Thank you very much for the very informative comments, Goran.

Thomas Krausz – Agree with diagnosis, very nice case. Excellent discussion.

Brandon Larsen – Agree with diagnosis. Thanks for sharing.

Jesse McKenney – A real case of IgG4!

Thomas Mentzel – Many, many thanks for the nice case and the detailed discussion!

Markku Miettinen – Nice fibroinflammatory tumor, a well-documented IgG4-associated case.

Fredrik Petersson – Classic case. The list of manifestations of IgG4 sclerosing disease still increasing. We have had cases of IgG4 related Hashimoto thyroiditis, aortitis etc. Some older published cases of meningeal Rosai-Dorfman and inflammatory meningioma may be IgG4 related.

Saul Suster – Very classical example; thank you.

CASE NO. 10 – CONTRIBUTED BY: Franco Fedeli, M.D.

Phil Allen – CIC-DUX4 undifferentiated round cell sarcoma, subcutis, left forefoot. The subcutaneous location would be most unusual for Ewing's sarcoma, further evidence that it is different from Ewing's.

Ira Bleiweiss – Agree. Nice case.

Alberto Cavazza – Very interesting entity and discussion!

Kum Cooper – Thank you Franco for this great example. Nice teaching case.

Göran Elmberger – Great case. Challenge for CUO work up protocol subsite SBRCT! Need the molecular tools! Fortunately, our NGS kit Arrow have DUC included in fusion panel.

Cyril Fisher – CIC-DUX4 rearranged sarcoma, very nice case. The mild pleomorphism, occasional myxoid change and WT1 with only focal CD99 help to distinguish this from Ewing sarcoma but molecular analysis is needed for diagnosis.

Masaharu Fukunaga – Undifferentiated small round cell sarcoma CIC-DUX4. Thank you very much for sharing the case, Franco.

Thomas Krausz – Nice case, molecular study is necessary for this diagnosis.

Brandon Larsen – Nice case of CIC-DUX4 sarcoma. Thanks for sharing.

Jesse McKenney – Nice example! In the days before CIC-DUX and BCOR, I remember when the pediatric oncologists used to get mad at us for diagnosing round cell sarcoma, NOS when EWSR1 FISH was negative.

Thomas Mentzel – Many thanks for sharing this nice example of a new entity. Do you have experience with the antibody ETV4 in these neoplasms? A number of cases are FISH-negative due to cryptic rearrangement as I have learned.

Markku Miettinen – Nice example of CIC-DUX4 sarcoma. DUX4 immunostain helps to pick these out.

Fredrik Petersson – CIC-DUX4 translocated ES/PNET-like undifferentiated/small cell sarcoma. There were few rosettes on my section.

Saul Suster – Nice case – thank you for sharing.

CASE NO. 11 – CONTRIBUTED BY: Maria Pia Foschini, M.D.

Phil Allen – Recurrent adenoid cystic carcinoma with high-grade solid basaloid transformation, left breast, 11 years after the initial excision.

One would have thought she was cured 10 years after the initial excision of the apparently typical adenoid cystic carcinoma. Has "dedifferentiation" gone out of favour in the breast while still enjoying popularity in bone and soft tissue? In this case, "transformation" seems to be morphologically more accurate.

Ira Bleiweiss – Agree. Quite the collision of a rare tumor and a common tumor.

Alberto Cavazza – Spectacular and convincing example of high-grade transformation in adenoid cystic carcinoma of the breast: never seen before this phenomenon in this location.

Kum Cooper – Maria thank you for this great case. We have seen ACC in the breast but not with HG transformation.

Göran Elmberger – Nice case with abrupt transition between adenoidcystic carcinoma classical and HGT component. HG also show some peculiar tendency to biphasic organization with palisading of smaller darker cells. It would be interesting to see the immunophenotype here. Odd case with long interval and ER positivity in recurrent but not primary tumor! Translocation markers in booth components? How can one understand ER positivity? Seems rather unlikely with collision tumor. I guess we always need consider patient history carefully since dedifferentiated (HGT) seem to occur in many different tumor types of different histogenetic lineages. Luckily genetic markers tend stick around even in the HGT components.

Franco Fedeli – In this tumor that is usually ER negative, it would be interesting to study the occurance of the positivity for ER in high grade transformation.

Cyril Fisher – Adenoid cystic carcinoma with high grade transformation, well demonstrated.

Masaharu Fukunaga – Agree. It shows additional anaplastic histologic features. Thank you very much for this nice case and discussion.

Thomas Krausz – Very instructive case.

Brandon Larsen – I don't believe I've ever seen an example of high-grade transformation of AdCC in the breast before. Thanks for sharing.

Jesse McKenney – Agree, "de-diff" adenoid cystic CA.

Thomas Mentzel – A very nice case showing transition from low-grade to high-grade ACC as we see it in the skin as well very rarely.

Markku Miettinen – Agree. Is it both mesenchymal and epithelial.

Fredrik Petersson – Unusual morphology for ACC – HGT, in that here seems to be multifocal presence of islands of low-grade abluminal neoplastic cells; p63-positive? The high-grade component appears to have acquired a luminal phenotype with ER+. That in itself not uncommon in SG Adcc- HGT where the high-grade component often is an AR+ salivary duct carcinoma.

CASE NO. 12 – CONTRIBUTED BY: _Masaharu Fukunaga, M.D.

Phil Allen – Uterine tumor resembling ovarian sex cord tumor, female aged 29. Thanks for this case Masa. I don't think I have seen one before. I note that the metastasis rate in Moore and McCluggage's series of 34 cases was 23.5% (8/34) in a follow-up time of 6-135 months (mean 39 months). It could rise even higher with longer follow up. On that basis, I can't see how the definite malignant potential of around 25% could be regarded as uncertain.

Ira Bleiweiss – Agree. Looks like sex cord tumor.

Alberto Cavazza – Great case and discussion, thanks!

Kum Cooper – Masa, this is an exceptional example with beautiful heterogeneity in morphological patterns. Thank you.

Göran Elmberger – Great case with variations in growth pattern and typical IHC! Interesting new molecular findings.

Franco Fedeli – A really good case. In differential diagnosis I would like to consider a pecoma.

Cyril Fisher – UTROSCT, very nice slide.

Masaharu Fukunaga – Uterine tumor resembling ovarian sex cord tumor (UTROSCT), my case.

Ondřej Hes – Great case. Very recently, series of *NF2* mutated renal cell carcinomas was published by Pete Argani (so far online Am J Surg Pathol)…some cases resemble this tumor...We presented in LA during USCAP "gonadoblastoma-like RCC"… (working on NF2 analysis right now). Our tumor is similar to cases from Argani series…could be here link to *NF2* mutations (however NF2 mutations are not uncommon in other malignant tumors)…and "sex cord-like morphology?" (I know it is a bit crazy idea).

Thomas Krausz – Very nice example. I had opportunity to study a few cases of UTRSCT before. They showed a broad histologic spectrum and had NCOA1-3 alteration. Few showed focal plasmacytoid/rhabdoid phenotype (molecular study on these is in progress). Detection of molecular alterations helps with the diagnosis.

Brandon Larsen – Agree with the diagnosis. I didn't realize that gene fusions have now been described in these tumors. Thanks for the helpful write-up.

Jesse McKenney – Nice example! Probably too many sex cord elements for GREB1 uterine tumor.

Thomas Mentzel – Many thanks. It has been mentioned that in addition multiple conventional leiomyomas have been detected. How often do we find an association of conventional uterine leiomyomas with a uterine tumour resembling ovarian sex cord tumour?

Fredrik Petersson – Spectacular and beautiful morphology. Thank you!

Saul Suster – Great case; very nice example. Thank you.

CASE NO. 13 – CONTRIBUTED BY: Thomas Krausz, M.D.

Phil Allen – Paratesticular desmoplastic small round cell tumor with metastases but without desmoplasia, male aged 22. I thought of rhabdomyosarcoma and mesothelioma but the diagnosis in this case is pretty well nailed down, despite the missing desmoplasia.

Ira Bleiweiss – Agree. Almost a theme for the seminar.

Alberto Cavazza – Very convincing example of a rare entity in a rare location.

Kum Cooper – Thomas you have such an enquiring mind. I would have stopped at EWS. Thank you for sharing this excellent educational case!

Göran Elmberger – Interesting case of atypically located DSRCT. Interesting references. The promiscuous gene!

Franco Fedeli – Very unusual location for this fascinating tumor. It could be an extension from retroperitoneal lesion as liposarcoma.

Cyril Fisher – Very nice case Thomas, really difficult to diagnose with so little desmoplasia and focal myxoid change. The location and immunophenotype are clues but both FISH and RT-PCR are essential for diagnosis.

Masaharu Fukunaga – Paratesticular desmoplastic small round cell tumor (DSRCT), a unique location and non-typical DSRCT histology. I learned a lot from this case, thank you Thomas.

Brandon Larsen – I don't think I would've ever thought about DSRCT at this location, particularly in the absence of desmoplasia. I'll have to remember this one for later.

Jesse McKenney – Unusual pattern of DSRCT.

Thomas Mentzel – Given the lack of prominent desmoplasia and the anatomic location its at least for me a very difficult case! Many thanks! Very, very rarely these neoplasms may be seen in soft tissues as well (Am J Surg Pathol 1999; 23: 1408-1413).

Markku Miettinen – Difficult to diagnose histologically, but convincingly documented by IHC and fusion.

Fredrik Petersson – Great case. Desmoplastic small round cell tumor sine desmoplasia!

Saul Suster – Hard case to diagnose without IHC.

CASE NO 14. – CONTRIBUTED BY: Brandon Larsen, M.D.

Phil Allen – E-cigarette or vaping product use-associated Acute Lung Injury (EVALI), wedge biopsy, male aged 63. A most instructive case. The vapers should be more susceptible to COVID-19, so I expect to see a combined EVALI/COVID-19 biopsy in the next AMR round.

Ira Bleiweiss – Clueless. Non-neoplastic lung is clearly not my fort*é*.

Alberto Cavazza – I thought at a bronchiolocentric acute lung injury, and an inhalation damage of some sort was my first idea, but I did not consider vaping. An aspiration was also in my differential diagnosis. Spectacular case, never seen before (or at least never recognized!).

Kum Cooper – It is amazing to see this case, Brandon, that has caused much public interest in the past several months. Thank you for sharing this precious slide and the excellent summary of the pathology and the social issues associated. I am humbled to own a glass slide of this evolving pathological entity!

Göran Elmberger – Nice update. Just had my first consult case in Umeå. My case was more in AFOP spectrum but still centrilobular airway centered. Dangerous stuff!

Franco Fedeli – This is a new disease that I heard of but have never seen such a case.

Cyril Fisher – Very interesting and informative. Many thanks, Dr. Larsen.

Masaharu Fukunaga – E-cigarette or vaping product use-associated acute lung injury (EVALI), this is very new to me. It is very interesting and thank you for the detailed comments.

Thomas Krausz – I haven't seen EVALI before. Thank you very much for the excellent discussion.

Jesse McKenney – Thanks for sharing the case… I never see medical lung.

Thomas Mentzel – Many thanks.

Fredrik Petersson – I thought "allergic alveolitis" (pardon the likely outdated terminology) first. Thank you for an enlightening case and educational comments.

Saul Suster – Nice case. We had a similar case here a few months ago. Similar findings.

CASE NO. 15 – CONTRIBUTED BY: Thomas Mentzel, M.D.

Phil Allen – Lipofibromatosis, subcutis, right thigh, male aged 5 months. Some of the cases that Enzinger used to call diffuse infantile fibromatosis were probably lipofibromatosis. It certainly looks like the edge of a dermatofibrosarcoma protuberans or possibly a non-calcifying variant of (juvenile) aponeurotic fibroma. Thanks for the contribution.

Alberto Cavazza – Very beautiful case and discussion.

Kum Cooper – Thank you, Thomas, for this great example. Nice write-up with the recent differential diagnostic expansion.

Göran Elmberger – Interesting. Another entity with molecular handle!

Franco Fedeli – In this case the lipomatous component was very exuberant.

Cyril Fisher – Nice case of lipofibromatosis in appropriate clinical context. The IHC is important to distinguish from NTRK-rearranged lipofibromatosis-like neural tumour.

Masaharu Fukunaga – Lipofibromatosis is rarely seen. Thank you for the interesting case and the fusion gene information.

Thomas Krausz – Agree with diagnosis. Highly educational case. In this particular case, the bland spindle cell component can be overlooked or mistaken for septae.

Brandon Larsen – Nice case of lipofibromatosis. Thanks for sharing.

Jesse McKenney – Nice example!

Markku Miettinen – Agree on lipofibromatosis. A fat-dominated tumor/tumor area.

Fredrik Petersson – Limited (but present!) (myo-)fibromatosis on my section.

CASE NO. 16 – CONTRIBUTED BY: Michal Michal, M.D.

Phil Allen – Paraurethral female prostatic carcinoma, female aged 73. I looked at the slide "blind" and couldn't work out how this straightforward prostatic carcinoma had tricked its way into the AMR club. I trust that the patient is not one of those increasingly common people who have discovered that gender is fluid rather than an immutable solid, subject of course to some male hormone therapy.

Ira Bleiweiss – Really? Wow.

Alberto Cavazza – Thanks for the rare case and the reference!

Kum Cooper – Michal this is a unique case. Thanks for sharing. Thank you for sharing your friend's book too.

Göran Elmberger – Wow! GG 4+4! Honors to Dr. Zaviacic and thanks for great book. Typical educational case from our friend in Pilzen with a great taste for interesting and important peculiarities.

Franco Fedeli – Skene adenocarcinoma. Thank you for showing us this very rare tumor with prostatic differentiation "Gleason (4+3)".

Cyril Fisher – Prostatic-type adenocarcinoma of Skene gland. Great PSA image.

Masaharu Fukunaga – Female adenocarcinoma form Skene glands, very beautiful case, Michal. I had a case of penis-like tubulosquamous polyp of the uterine cervix.

Thomas Krausz – Reading the book by Dr. Zaviacic, my understanding of the topic improved tremendously. Thank you very much for making the book available for us.

Brandon Larsen – I've never encountered this entity before. Great case, and also very helpful that the AMR club has posted a PDF copy of Dr. Zavaičič's book. Thanks for sharing.

Jesse McKenney – I looked at the slide without history and thought it was a funny prostate cancer in a TURP.

Thomas Mentzel – Many, many thanks and I think I´ve seen a poster at the USCAP dealing with few cases of this rare entity a couple of years ago.

Markku Miettinen – Nice case, really looks a little bit like prostate carcinoma.

Fredrik Petersson – !!! Dr. Zaviačič collected and analysed secretions for PSA and PSAP in an interesting way.

Saul Suster – Very interesting and educational. Thank you for sharing this rare finding.

CASE NO. 17 – CONTRIBUTED BY: Delia Perez-Montiel, M.D.

Phil Allen – Prostatic carcinosarcoma. Yet another tumor that I haven't seen before.

Ira Bleiweiss – Agree.

Alberto Cavazza – For some reasons, prostate is an unusual location for carcinosarcoma. Thanks for this rare case.

Kum Cooper – Thank you Delia for this unusual case. My slide also has osteoid production too.

Göran Elmberger – Great rare case with prognostic implications!

Franco Fedeli – Prostatic carcinosarcoma. An aggressive tumor with ominous prognosis.

Masaharu Fukunaga – Prostatic carcinosarcoma, I have never experienced this type of malignant tumor. Thank you, Delia, very much for sharing the case and detailed comments.

Thomas Krausz – Nice example, thank you very much.

Brandon Larsen – Agree with diagnosis. Great case.

Jesse McKenney – Very rare occurrence!!! Thanks for the example.

Thomas Mentzel – Many thanks for this nice example (given the molecular findings and the experience in other organs the term sarcomatoid carcinoma is probably more appropriate than carcinosarcoma).

Markku Miettinen – Agree, carcinosarcoma, with osteocartilaginous differentiation.

Fredrik Petersson – I have never seen such a case. Thank you!

Saul Suster – Nice case; have not seen this before.

CASE NO. 18 – CONTRIBUTED BY: Cesar Moran, M.D.

Phil Allen – Low-grade mucoepidermoid lung, female aged 12. A nice example.

Ira Bleiweiss – Agree. Another theme for the seminar.

Alberto Cavazza – As correctly pointed out, low-grade mucoepidermoid carcinoma of the bronchus is not exceptional in the pediatric population. Bronchoscopically, it tends to be confused with the even more common bronchial carcinoid.

Kum Cooper – Thank you, Cesar. You presented a similar case in Cambridge 1999!

Göran Elmberger – Beautiful classical case in unusual location. Age spectrum important to be aware of. No need for translocation markers!

Franco Fedeli – Low-grade mucoepidermoid carcinoma of the lung. I would like to put in the differential diagnosis of a secretory carcinoma of the salivary gland. Did you perform any molecular study?

Cyril Fisher – Low-grade mucoepidermoid carcinoma in unusual context.

Masaharu Fukunaga – Low-grade mucoepidermoid carcinoma of the 12-year old child. Mucinous epithelium, squamous cell-like epithelium and intermediate cells are observed.

Thomas Krausz – Nice example, thank you very much.

Brandon Larsen – Agree with diagnosis. A great example of MEC in a child.

Jesse McKenney – I see cilia!!!

Thomas Mentzel – Many thanks for sharing this rare pulmonary lesion.

Markku Miettinen – Agree on mucoepidermoid carcinoma, low-grade.

Fredrik Petersson – Agree, nice case. Some areas a bit infiltrative – intermediate grade pattern.

CASE NO. 19 – CONTRIBUTED BY: Brian Rubin, M.D.

Phil Allen – Probable "ectopic" lipoblastoma-like tumor, submucosa, left distal mainstem bronchus, male aged 38. I note that Michael Michal has just published a paratesticular lipoblastoma-like tumor (Histopathology 2020; 76:628-630) and I reckon I recently saw one on the left great toe of a male aged 16 (clinpath 37176-19K), although no one yet believes me. I am fairly confident that lipoblastoma-like tumor is not restricted to the vulva. I also suspect that previously reported "lipoblastomas" occurring in patients older than 10 were not lipoblastomas but rather a different fatty tumor now called lipoblastoma-like tumor. I will be interested in Ken Schoolmeester's opinion on this case and on the previously reported adult "lipoblastomas". Is Michael Michal related to Michal Michal?

Ira Bleiweiss – Very nice case. Never seen this before.

Alberto Cavazza – I agree, very unusual and difficult case. Once convinced this is benign, I suspect the distinction with a lipomatous hamartoma can be quite arbitrary (and practically irrelevant).

Kum Cooper – Thank you for sharing this unusual variant of this rare lesion.

Göran Elmberger – Interesting case. No personal experience from bronchial cases. Closest case of giant fibrovascular polyp originated from larynx protruding through mouth with nidus of mdm2 amplified well differentiated lipoma like LPS earlier submitted to this club. Definitively a role for molecular pathology here with FISH and NGS as good tools.

Franco Fedeli – The positivity for CD34 suggested to me that this tumor was a spindle cell lipoma but the molecular study in association with the absence of the ropey collagen was against my idea.

Cyril Fisher – Endobronchial lipoma with remarkable myxoid change, spindle cell content and rare molecular definition. Thanks, Brian, for an interesting discussion.

Masaharu Fukunaga – It is an excellent case mimicking malignant lipomatous tumor. My initial impression was myxoid liposarcoma. Thank you, Brian, for sharing this case.

Thomas Krausz – Intriguing case. Agree with diagnosis. Focally, the richly vascularized spindle cell component without fat cells reminded me pre-lipoblastic phase of embryonic fat development. Perhaps this is a lipoma with focal inhibition of lipogenicity.

Brandon Larsen – Like you, I've never seen a lipomatous lesion in the bronchus before. I can see why you sequenced it first…it's hard to argue with those molecular results. Thanks for sharing.

Jesse McKenney – Very difficult without sequencing result!!!

Thomas Mentzel – What an interesting case! Given the variation in size and shape of the lipogenic cells, the presence of slightly enlarged hyperchromatic nuclei, of scattered lipoblasts, and the mentioned CD34 positivity I was thinking (despite the small size of the lesion) on an atypical spindle cell lipomatous tumour.

Markku Miettinen – Spindle cell lipomatous tumor, low potential, unusual.

Fredrik Petersson – My initial consideration was clearly malignant, metastatic vs primary. Blown away by the genetics.

Saul Suster – Very unusual case. Has some features of spindle cell lipoma. Did you try bcl-2 in the spindle cell component? Spindle cell lipomas are characteristically positive for both.

CASE NO. 20 – CONTRIBUTED BY: Niels Rupp, M.D.

Phil Allen – Basaloid squamous cell carcinoma with NSD3-NUT fusion, inferior lobe, right lung.
A case like this with an ectopic (non-midline) location and a disease-free survival of 18 months makes me question the diagnostic specificity of NSD3-NUT. So many "specific" immunohistochemical stains have turned out to be not so specific after a few years and I fear that may also happen to the NSD3-NUT fusion finding.

Ira Bleiweiss – Agree.

Alberto Cavazza – Unusual case and very interesting discussion.

Kum Cooper – Nice case Paul.

Göran Elmberger – Great unusual case. Shows we need to test for NUTM1 on wide indications! Obviously important to make diagnosis and analyze molecular biology with identification of underlying translocation to make prognosis and predict therapy response on experimental protocols.

Franco Fedeli – NUT carcinoma. Thank you for the complete molecular discussion.

Cyril Fisher – Endobronchial NUT carcinoma, with *NSD3-NUT* fusion. The clinical and morphological spectrum of *NUT*-rearranged tumors is widening.

Masaharu Fukunaga – Nut carcinoma with NSD3-Nut fusion. Nice and informative comments.

Thomas Krausz – Highly educational case. Before reading the discussion, I thought this was a basaloid squamous cell carcinoma. The molecular finding surprised me. I will do molecular studies more frequently in the future on basaloid squamous cell carcinomas in order not to miss this type of NUT carcinoma.

Brandon Larsen – Agree with the diagnosis. I'm not sure I would've even thought to test for a NUT fusion in this case…probably would've just called it a keratinizing SqCC. I wonder how many cases like this have been missed in the past.

Jesse McKenney – Nice case with rather abundant squamous differentiation.

Thomas Mentzel – Great case, many thanks!

Markku Miettinen – Yes, NUTM1 rearranged carcinoma, poorly differentiated squamous cell ca with NUTM1 fusion.

Fredrik Petersson – How interesting; possible morphologic correlation with unconventional translocation partner and less atypical morphology. Still, the very abrupt keratinization and the very monotonous ("translocation-related") nuclei are there. The chromatin almost neuroendocrine. Thanks for this case.

Saul Suster – Very unusual to be this well differentiated for a NUT carcinoma; but I guess the morphology of these tumors shows a wide range.

CASE NO. 21 – CONTRIBUTED BY: _Paul Wakely, M.D.

Phil Allen – Chondomyxoid fibroma, left tibia. Thanks for the nice update. I had one in the craniofacial bones a few years ago and had some trouble "selling" it to the sceptics. It was a pity that Meredith's article (Am J Surg Pathol 2018;42:392-400) was not then available.

Ira Bleiweiss – Agree. Textbook example. I wrote a paper on s-100 on this once a very, very long time ago when I was seeing huge numbers of bone tumors during my residency at Mount Sinai. Seems like a century ago.

Alberto Cavazza – I have no experience in bone tumors, but I recognized this chondromyxoid fibroma, so it must be classic! A very nice case and discussion, thanks.

Göran Elmberger – Nice educational case. Also here are important molecular points. However, could not find this translocation marker or mutations in our preset NGS panels. Probably later developments for panels focused om bone pathology.

Franco Fedeli – Chondromyxoid fibroma. Recently we saw, in our Italian slide seminar, a case with cellular atypia that don't seem to impact with the prognosis.

Cyril Fisher – Chondromyxoid fibroma of tibia, nice slide thanks Paul.

Masaharu Fukunaga – Chondromyxoid fibroma. Mesenchymal chondrosarcoma may be included in the differential diagnoses.

Thomas Krausz – Agree with diagnosis. Nice example. Thank you very much for submitting it.

Brandon Larsen – I haven't seen a case of CMF for years. It's nice to see one now. Also didn't realize that CMF has a characteristic molecular abnormality. Good to know! Thanks**.**

Jesse McKenney – Classic histology for CMF!

Thomas Mentzel – Many thanks!

Markku Miettinen – Chondromyxoid fibroma, nice case.

Fredrik Petersson – Morphologic overlap with the spectrum of phosphaturic mesenchymal tumor. Clinical correlation! Nice to have a case of this uncommon neoplasm. Many thanks.