COMMENTS TO AMR SEMINAR #70

CASE NO. 1 – CONTRIBUTED BY: Volkan Adsay, M.D.

Volkan Adsay - I was the one who submitted this case, and I again apologize for its annoying nature. I still don't know how I would have even remotely considered this possibility if it weren't to the history and IHC. Annoying for us morphologists but I am hoping you will find it still interesting and educational.

Abbas Agaimy – Now we believe it Volkan, spectacular case, impossible to diagnose without clinical history, most unique in being a metastasis of a recently defined neuropath entity.

Phil Allen – Metastatic diffuse cerebral midline glioma (H3K27M mutant type) in omentum via a shunt, in a post stem cell transplant 44-year-old male with amyotrophic lateral sclerosis. Very educational. Many thanks. The poor patient had two nasty diseases plus the treatment. Is the conjunction of the two diseases coincidental?

David Ben-Dor – Hard to believe is an understatement. The shunt provides a believable mechanism for tumor spread. The question is how would you put all this together in a needle biopsy. Descriptively this looks like a spindle cell tumor which doesn't show the weird pleomorphism of glioblastomas- is this par for the course for this entity? This shows how much perspective and depth is afforded by genetic evaluation beyond the histology.

Ira Bleiweiss – You said it, Volkan but Hardtobelieve-oma is an understatement. This is truly bizarre. At low power, admittedly neuroid, but then I thought it looked like smooth muscle - neither of which make much sense either. I never knew this could occur.

Alberto Cavazza – I have no experience in neuropathology, but I think the diagnosis is very convincing and the case is clearly spectacular. Thanks for the educational case (and congratulations to Dr. Velazquez!).

Kum Cooper – Fascinating case Volkan. The history of GBM (along with the palisading necrosis) was the giveaway since I was aware of metastases to the abdomen via the shunt. This midline GBM of children with the specific H3 mutation was recently presented by one of our young faculty here at Penn. Thank you for sharing this excellent teaching case.

Hugo Dominguez-Malagón – Metastatic glioblastoma, the palisaded necrosis is still visible. I was ignorant of the variety of diffuse midline glioma H3K27M mutant. Nice discussion, thank you.

Göran Elmberger – Great case! Heard about gliomatosis peritonei but this was new to me.

Franco Fedeli - Amazing case; This entity is very rare at the age and the spread through the shunt is exceptional.

Cyril Fisher – Amazing case and pattern of behavior, new to me, and undiagnosable without background information. Thanks for great discussion.

Jerónimo Forteza Vila - Metastatic glioblastoma is a classic concept written in books but never seen one in my experience. This robust immunohistochemical and molecular study is confirmation of its existence.

Maria Pia Foschini – This is a rare case, but as the modern therapies allow a longer survival of glioblastoma patients, extracranial metastases can be encountered. We should remember graft-transmitted metastatic glioblastoma (Transpl Int. 1996;9(4):426-9).

Masaharu Fukunaga - It is very challenging and interesting. Volkan, thank you very much for sharing the case.

Ondřej Hes – Never seen, great case!! For sure GLB wouldn´t be my first (to be honest not even second and so) differential diagnosis from H&E.

Thomas Krausz – I was considering various entities (including sarcomatoid mesothelioma) but not glioblastoma, before reading the discussion. This is a highly educational case. It also shows the value of autopsy.

Thomas Mentzel – Wow, what a case! Many thanks for sharing this rare case, and many thanks for the great discussion.

Michal Michal – Uf, uf!! I had seen a few cases of recurrence of gliomas in the soft tissues of the head after operation of brain primary tumor in the eighties, but this is my first case!!

Markku Miettinen – Yes, it is hard to believe. But these gliomas have resemblance to MPNST in their histone 3 mutation, perhaps they are more prone to metastasize through peritoneal shunting than others.

Cesar Moran – I have never seen this before. In the past, I have seen metastatic ependymomas to the lung but not this tumor in this location. Was not familiar with the entity.

Fredrik Petersson - Malignant spindle cell neoplasm with multifocal necrosis. Low mitotic activity and fairly uniform nuclei. Metastatic GBM/gliosarcoma needs to be considered, but I would expect the cytological features to be more high-grade. After reading the convincing discussion and browsing through the new WHO neuropath book, I realize that my knowledge in this field has imploded into a void of almost nothingness.

Murray Resnick – Striking case. Very nice discussion.

Brian Rubin – Without history I would have thought of metaplastic carcinoma. I've seen a metastatic GBM to femur once but that is the only case I ever saw that left the CNS. Interestingly, it had the same pattern of necrosis as other GBMs.

Saul Suster - Pretty spectacular case Volkan – thank you for sharing it!

Paul Wakely – Boy, this one takes the cake. It's a 'rapazapadoma' if I've ever seen one. Thank you Volkan for your erudite explanation. I wonder, were these cells picked up on cytologic examination of the peritoneal fluid?

Ady Yosepovich - This is a fantastic case – I am not a neuro fan, our neuropathologist agrees with the diagnosis – she prefers "seeding" rather than "metastasis".

CASE NO. 2 – CONTRIBUTED BY: Phil Allen, M.D.

Volkan Adsay - I suspect that this deciduoid process will prove to be benign although a deciduoid mesothelioma will have to be a consideration. The findings that made me favor a benign process included the more quiescent cytology than deciduoid mesotheliomas. Additionally, the fact that surface mesotehelial cells are well preserved and not replaced by the proliferation also gives me this impression. Moreover, those black pigmented nodules (represented as clusters of macrophages here), which seem to show a specific distribution going hand-in-hand with the decudual nodules made me wonder about some sort of a preexisting endometriosis that has now become completely decudialized after pregnancy. I don't see the glandular component here though. Overall, I favor this to be benign decidual nodula

Abbas Agaimy – Pretty and colorful case, never seen before, great informative discussion. thanks.

David Ben-Dor – An unusual occurrence, at least this time with a happy ending (mother and child doing well). The decidual changes are obvious and given the location deciduoid mesothelioma jumped into my mind. Lipofuscin is also Ziehl Neelsen positive.

Ira Bleiweiss – Never seen this Phil, but then again, I only do breast. Very nice decidual reaction. I thought the pigment was hemosiderin so I'm surprised at your iron studies.

Alberto Cavazza – An exceptional case and a very convincing explanation. I have never seen this condition before.

Kum Cooper – Nope, never heard of it Phil. Great case. Only third in the literature!!! The decidua was straightforward with the history of pregnancy. In fact, I thought that this was hemosiderin secondary to hemorrhage (endometriosis in pregnancy). Thank you for sharing this super case.

Hugo Dominguez-Malagón – Peritoneal lipofuscinosis and deciduosis, I have never seen a similar case. By looking to the slide submitted two population of cells are seen, one consists of macrophages loaded with lipofuscin and related to damaged erythrocytes, immediately below there is a superficial decidual reaction of the adipose tissue. It can be postulated that the pigmented cell is secondary to bleeding with transformation into lipofuscin, and the decidual reaction the result of superficial damage and reparative reaction caused by the blood.

Göran Elmberger – New to me. Agree with descriptive diagnosis. No clue to pathogenesis.

Franco Fedeli - Deciduosis in pregnancy is not uncommon, but the association with peritoneal lipofuscinosis is very rare.

Cyril Fisher – Something else I have not seen or heard of! Striking appearance and fits the published description.

Jerónimo Forteza Vila - The macroscopic presentation of the lesion is interesting and surprising.

Maria Pia Foschini – Peritoneal lipofuscinosis and deciduosis. Very rare! I had never seen this.

Masaharu Fukunaga - A beautiful case with detailed comments. Extrauterine decidual change. I totally agree with Phil.

Ondřej Hes – We have few cases of deciduosis in appendix, never seen in association with lipofuscinosis. We have one case of focal lipofuscinosis (??) coming out from peritoneal surface of stomach.

Thomas Krausz – I looked at the case without reading the history or the discussion and favored peritoneal deciduosis but the unlikely deciduoid mesothelioma was also in my differential. I thought the pigment was going to be hemosiderin. I was a bit surprised to learn that it is lipofuscin. The excellent work-out of the case clarified all the issues. From time to time pigment-classification remains problematic, despite all my efforts with various histochemical stains. I haven't seen a case like this before.

Thomas Mentzel – Many thanks for this great case (I knew the term ceroid-lipofuscinosis only as a neural disease), very interesting.

Michal Michal – Nice case. I am sure that many of the pigmented histiocytes in between the nodules of endometriosis belong to the category of "Histiocytes with raisinoid nuclei". Reference: Michal M., Kazakov D.V., Dundr P., Michal M., Peckova K., Agaimy A., H., Havlicek F., Daum O., Dubova M., Michal M.: Histiocytosis with Raisinoid Nuclei: A Unifying Concept for Lesions Reported under Different Names as Nodular Mesothelial/histiocytic Hyperplasia, Mesothelial/monocytic Incidental Cardiac Excrescences, Intralymphatic Histiocytosis and Others. A Report of 50 Cases. American Journal of Surgical Pathology, 2016:40:1507-1516.

Markku Miettinen – Agree on peritoneal deciduosis, i.e., progesterone-influenced peritoneal endometriosis.

Cesar Moran – Interesting case. I recall having seen something similar in the past but cannot be sure.

Fredrik Petersson - Deciduosis. Did not really appreciate the lipofuscinosis first (I thought it was hemosiderin).

Murray Resnick – Remarkable case and very impressive gross picture. Explanation regarding rapid resorption of iron makes sense.

Brian Rubin – Fascinating case. I've never seen this condition before.

Saul Suster – Thank you for this rare case. We no longer work up cases with histochemical stains and this case would probably have been banalized as hemosiderin pigment by most. Lipofuscin is related to ceroid (breakdown product of hemoglobin) and Dr. Rywlin was a great fan of old-fashioned histochemical stains – he would surely have made the correct diagnosis!

Paul Wakely – First time for me Phil. Don't sign out gyn anymore.

Ady Yosepovich - Thank you for this interesting case, I was not aware of this entity.

CASE NO. 3 – CONTRIBUTED BY: David Ben-Dor, M.D.

Volkan Adsay – My top two considerations for this high-grade malignant epithelioid neoplasm were malignant melanoma versus clear-cell sarcoma of soft parts, although I would not be too surprised if this proved to be a peculiar sarcomatoid carcinoma or true sarcoma of other sorts. But my initial gut was really in favor of clear-cell-sarcoma of soft parts versus a melanoma.

Abbas Agaimy – Spectacular case in every aspect, David! if one should calculate down the probability of 5% from 1.2%, then getting 5% of the result and reducing it down to 6/131% then would arrive at zero before the end of the story. Thus, this is a unique case in every respect. Thanks for the comprehensive and very educational discussion, as always. Just to add one point on specificity of antibodies, Michal & I just have published a study in AJSP showing the vast majority of phosphaturic mesenchymal tumors being strongly SATB2 positive.

Phil Allen – Ulcerated osteosarcoma involving skin, soft tissues and distal end of the right first metatarsal bone in a male aged 83. I cannot tell from the circulated small photograph of the x-ray if the tumor arose from the bone, soft tissues or skin. I would be guided by the opinion of an experienced bone and soft tissue radiologist as well as by the clinical history and clinical examination. I don't think I have previously seen any small osteosarcomas of bone that ulcerated the skin. I suspect this is a primary osteosarcoma of either the soft tissue or skin.

David Ben-Dor – I plucked this out of the slide box and not realizing that it was mine my reaction was "what a weird case". If I started out with this slide I would not put carcinoma high on the list, if at all- I would first think about sarcoma or melanoma. Still osteoblastic sarcoma would be a stretch and the pink fibrillary deposits would look to me like keloidal collagen. I'm looking forward very much to the "crowd wisdom" on this.

Ira Bleiweiss – I would have called this a sarcomatoid carcinoma. I don't see convincing osteoid production in my slide.

Alberto Cavazza – Very nice case and interesting discussion (I was not aware of SATB2). To my untrained eyes the hyaline material looks fine for osteoid, but clearly I am not the right person to comment on it.

Kum Cooper – Thank you David. My slide did not have any obvious morphological osteoid formation. We do not have SATB2; although I wish we did since it is also a marker for colon carcinoma (useful for mets to the ovary).

Hugo Dominguez-Malagón – Diagnosed as osteosarcoma. I wander if a single test (which is in itself non-specific) can defeat a whole process of logical thinking!

Göran Elmberger – That was a tough one. I must say you sent the case to the right person. I am glad we got IHC and promising new markers. Clinical-radiological correlation! Good consults! Up to date IHC!

Franco Fedeli - Osteoblastic osteosarcoma: it is really interesting that some cases of melanoma in the fingers show osteoid tissue formation. (Brisigotti M, Moreno A, Llistosella E, Prat J. Malignant melanoma with osteocartilaginous differentiation. Surg Pathol 2:73-78, 1989)

Cyril Fisher – This hinges on the identification of malignant osteoid/bone formation confirmed in this case by SATB2. In this situation, sarcomatoid carcinoma with heterologous osteosarcoma also needs consideration, and it is debatable whether CK alone or the presence of two morphologically distinct areas is necessary for that diagnosis. Thanks for great discussion Dr Ben-Dor.

Jerónimo Forteza Vila - The osteoid is the clue for the diagnosis and this is supported by the immunohistochemical panel.

Maria Pia Foschini – Osteosarcomatous differentiation can be seen in carcinomas. In the breast, we can see tumors identical to bone osteosarcomas in the absence of any bone lesions, and these tumors behave in an intermediate fashion between carcinomas and sarcomas. I think that sometimes our techniques, both morphological and molecular do not allow a clear diagnosis!

Masaharu Fukunaga - It seemed to be spindle cell (sarcomatoid) carcinoma for me. However, surprisingly the diagnosis is osteoblastic osteosarcoma. Thank you very much for the very interesting case and sophisticated discussion,

David.

Thomas Krausz – Yes, differentiating hyalinized collagen from osteoid, like in this case, can be problematic. I am ordering the SATB2 antibody immediately. I remember one case where I diagnosed metastatic sarcomatoid carcinoma in bone because of keratin expression, which turned out to be keratin positive osteosarcoma; I certainly learned my lesson.

Thomas Mentzel – Great example of a rare superficially located extraskeletal osteosarcoma, and the mentioned antibody SATB2 is of great help in the diagnosis of these rare neoplasms.

Markku Miettinen – Agree on osteosarcomatous differentiation. In some cases, this could be a secondary phenomenon in a carcinoma or even melanoma.

Cesar Moran – Puzzling case as keratin positive tumor. On histology, I thought sarcoma but did not think osteosarcoma.

Fredrik Petersson - No osteoid on my section. I was thinking of some kind of Richter transformation mimicking sarcoma/melanoma. Scholarly discussion. I cannot help but wonder about the "multifocal positivity for SATB2". Could this not be an aberrant activation of that gene (and matrix production) in a sarcomatoid carcinoma?

Murray Resnick – Unique case. Will be interesting to see if the sensitivity and specificity of *SATB2* as a marker for osteosarcoma pans out.

Brian Rubin – This is an interesting case with a wonderful discussion but I'm not convinced that this lesion started off its life as an osteosarcoma. I have seen a couple of cases of squamous cell carcinoma with a dysplastic, in-situ component that developed into beautiful osteoblastic osteosarcoma in the invasive component. Based on the clinical situation, ulceration, and keratin staining, I wonder if this isn't a case of metaplastic squamous cell carcinoma with heterologous osteosarcomatous differentiation.

Saul Suster – May be that there is true osteosarcomatous differentiation in this tumor but based on the clinical presentation I believe it is highly unlikely that this may actually represent an osteosarcoma. A sarcomatoid carcinoma would make much more sense in this context. Regarding the SATB2 antibody, we have started to see cases that were called osteosarcoma because of positivity for this marker which turned out to be other conditions on closer examination or upon complete resection of the lesion. In this context, I would caution that before any single IHC marker is embraced as an infallible and specific marker, we need to give it at least 5-10 years in the market before we can gain sufficient experience with it. Our past experience has shown time and again that all IHC markers eventually turn out to have exceptions and are never as "specific" as initially touted. We need to embrace the lessons of years past and again become surgical pathologists instead of "immunoperoxidologists".

Paul Wakely – Before I read the history and discussion on this case, I was thinking this probably represents sclerosing epithelioid fibrosarcoma. I think the jury is still out regarding the real specificity of SATB-2.

Ady Yosepovich - Thank you David for this unusual case and brilliant discussion

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

Volkan Adsay – I get the impression that this is a granular cell tumor although it is unusually well circumscribed (especially the ones in breast that I had seen had a lot more infiltrative-appearing edges). Some of the areas with nested growth pattern is also somewhat unusual to my eyes but nevertheless that will be my top choice here.

Abbas Agaimy – Very tricky case that represents a true pitfall both on imaging and at frozen. Thanks Ira.

Phil Allen – Well circumscribed granular cell tumor, skin of breast. Neurofibromas can be both well circumscribed or locally infiltrating, as can benign cutaneous histiocytomas and even nodular fasciitis. Pathology seems to abound with entities that occasionally slip out of bounds, like teenagers.

David Ben-Dor – the histology does look obvious but a biopsy from the breast of a young woman would have an automatic scare factor built in- who wants to miss a diagnosis and be made a fool of on the front page of the New York Times? The different implications of the exact situation (breast parenchyma vs subcutaneous) are interesting. Was it mobile? I wonder why it would be hard when arising in the breast- it must provoke a desmoplastic reaction in that location. Assuming the lesion was superficial I wonder why this went the route of mammography-core biopsy and wasn't treated simply as a cutaneous tumor and removed by a plastic surgeon. This reminds me of an FNA labeled "supraclavicular mass". Assuming it was a supraclavicular lymph node it made me suspicious of a metastasis from an intra- abdominal mass. The FNA showed epithelial tumor which seemed unusually bland for any kind of metastasis. The mass was eventually excised and turned out to be a benign sweat gland tumor of the skin. Sometimes things are what they are.

Alberto Cavazza – An interesting consideration for a quite typical case. Granular cell tumor can occur in other locations, and I think in general it tends to be more infiltrative than here.

Kum Cooper – Granular cell tumor.

Hugo Dominguez-Malagón – Granular cell tumor of the breast skin, nice case, no experience.

Göran Elmberger – Beautiful case. Not so common. At least cytological features are the same… Interesting observation.

Franco Fedeli - Granular Cell Tumor usually is not so well circumscribed like this one case.

Cyril Fisher – Very nice example of granular cell tumour.

Jerónimo Forteza Vila - The different patterns of growth depending on the location of tumor are very interesting. I don´t know similar cases.

Maria Pia Foschini – Interesting case! We have some cases of lobular carcinoma of the breast that are very similar to granular cell tumor (Am J Surg Pathol. 1995 May;19(5):553-62).

Masaharu Fukunaga - Granular cell tumor of the skin, I appreciate your comments, Ira

Thomas Krausz – Agree with diagnosis. Nice example.

Thomas Mentzel – Thanks, and yes, there are a number of neoplasms showing a different growth pattern. Whereas spindle cell lipoma of the subcutis is encapsulated, rare dermal spindle cell lipoma is ill-defined and infiltrative. Schwannoma is an encapsulated lesion, but if arising in the sinonasal tract and the nasopharynx it is unencapsulated (Mod Pathol 1997; 10: 777-784).

Markku Miettinen – Agree on granular cell tumor, a nice example.

Cesar Moran – Nice case.

Fredrik Petersson - Granular cell tumor. Agree.

Brian Rubin – Agree with diagnosis of granular cell tumor.

Saul Suster – Granular cell tumors can sometimes occur in unexpected locations and can throw you for a loop, especially when they are atypical. We recently published our experience with such cases presenting in soft tissues (Stemm M et al. Typical and atypical granular cell tumors of soft tissue: a clinicopathologic study of 50 cases. Am J Clin Pathol 148:161-166, 2017).

Ady Yosepovich - Thank you Ira for this teaching example, the CNB of these tumors can be very tricky. It may be that not all granular cell tumors are the same in terms of their biological behavior – maybe there is some kind of "grading system" or "atypical variants". As I recall they can be locally aggressive and warrant complete excision in the breast as the show "invasive pattern of growth" thought they are considered "benign".

CASE NO. 5 – CONTRIBUTED BY: Alberto Cavazza, M.D.

Volkan Adsay – I believe this is fundamentally a necrotizing granulomatous lesion. I don't see overt evidence of malignancy, but there are scattered atypical cells that warrant recuts to exclude a subtle infiltrate. If malignancy has been excluded with additional levels, then a specific infectious process can be investigated with AFB/GMS, before moving on to non-specific granulomatous prostatitis. Infarction of prostate can have foci like this too. This slide also shows nice illustration of that Gauze artefact.

Abbas Agaimy – Beautiful example of GPA, a diagnosis with significant clinical impact if recognized or missed either, thanks for sharing.

Phil Allen – Necrotising inflammation without vasculitis or giant cells, prostatic core biopsy in a patient with Wegener's granulomatosis. I could not make the diagnosis on the slide alone. The clinical history, radiological findings and serology clinch the diagnosis.

David Ben-Dor – on its own merits and knowing the location I would assume it to be granulomatous prostatitis. Without knowing the location or the diagnosis I thought of one of the necrotizing granulomatous lesions from the skin- maybe necrobiosis lipoidica. Churg Strauss can show up in unexpected places and I thought I saw a few eosinophils. I submitted a case of GIST appearing on prostatic needle biopsies to a previous seminar so unexpected diseases can show up in that material. I don't think it's wise to rush to the diagnosis what we used to call Wegener's granulomatosis based only on histology without clinical support.

Ira Bleiweiss – Necrotizing areas, as you say, not well-formed granulomata, but very instructive case. I recently saw a case of Wegener's in breast, luckily accompanied by history of Wegener's.

Kum Cooper – Instructive case. Necrotizing granulomatous inflammation of prostate. No obvious vasculopathy. Great case.

Hugo Dominguez-Malagón – Wegener in the prostate, impossible for me.

Göran Elmberger – Didactic case. Good reminder. As in sinonasal tract it is difficult to make a confident tissue based diagnosis on small biopsy material. Still as you stress is a very important differential diagnosis that could save lives if discussed…..in the prostate!

Franco Fedeli - GPA-Wegener's granulomatosis: Clinical findings are very helpful in this unique and interesting case.

Jerónimo Forteza Vila - Thank you for sharing this amazing case. It is a very good case of clinicopathological correlation. Rhinitis is one of the key diagnostic points for Wegener Disease.

Maria Pia Foschini – Thank you very much for sharing with us this interesting case. In prostatic biopsy, it could be misdiagnosed for an intense non-specific inflammation.

Masaharu Fukunaga - Granulomatosis with polyangiitis, a great case! I have never seen this type in the prostate. I thank you very much for sharing the case.

Ondřej Hes – Great case, I haven´t read the diagnosis first and suggested that it may be the so-called BCGitis, which is pretty common in our institution in patients treated by BCG vaccine (immunomodulation in patients with urothelial carcinoma).

Thomas Krausz – Yes, I observed the necrotizing foci focally involving a blood vessel, but I was not sure what was going on, though I considered infection. Reading the excellent discussion, of course, the features make sense.

Thomas Mentzel – A great but difficult case indeed.

Markku Miettinen – Extensively necrotic, with granulomatous inflammation, challenging for a definitive diagnosis.

Cesar Moran – I do not think I had seen WG in the prostate. Very nice case.

Fredrik Petersson - Necrosis, vasculitis and MNGC - Wegener's granulomatosis. Never seen in the prostate before.

Brian Rubin – Interesting discussion.

Saul Suster – Thank you for sharing – never seen Wegeners in the prostate!

Ady Yosepovich - This is one of the cases that reminds me why I chose to be a pathologist. Thank you for this extraordinary case.

CASE NO. 6 – CONTRIBUTED BY: Kumarasen Cooper, M.D

Volkan Adsay – I wondered about a PMT (phosphoturic mesenchymal calcifying tumor). If this were in the G.I. tract, based on the clear cells, compartmentalization, sclerosis, and osteoclast-like giant cells, I would've also considered the possibility of a GI neuroectodermal tumor ("clear cell sarcoma of GI type", on which AMR group is the main author, and I will defer to them if this truly resembles so). In the neck, also considering the calcifications (of amorphous depositions) a medullary thyroid carcinoma becomes a consideration as well I suppose, as it does for any peculiar neoplasm in this region. There are foci with more monotonous cells in a nested pattern, which might go along with this impression of medullary carcinoma too.

Abbas Agaimy – Nice case of mesenchymal chondrosarcoma, thanks for the update Kum.

Phil Allen – Mesenchymal chondrosarcoma, soft tissues, right side of neck. It's not a textbook case but I agree there is some calcified chondroid tissue at the interface between the round cells and the less cellular calcified areas.

David Ben-Dor – It looks to me that there's a lot of osteoid material. I didn't see much cartilage. For my money, the cells in and of themselves could be lymphoma (which wouldn't make sense in the context).

Ira Bleiweiss – Agree.

Alberto Cavazza – I agree, but I have nothing clever to add.

Hugo Dominguez-Malagón – Mesenchymal chondrosarcoma. Sorry I missed that, no hemangiopericitomatous pattern in a small cell tumor and no islands of well differentiated cartilage. I thought it was a chondroblastoma.

Göran Elmberger – I assume the new markers were positive. In my slides, difficult to find hyaline cartilage but at least focally a definitive bluish tint that could help in the correct diagnosis.

Franco Fedeli - The chondroid component is usually scanty in mesenchymal chondrosarcoma.

Cyril Fisher – Looks like extraskeletal myxoid chondrosarcoma with unusual appearance of cartilage (possibly related to fixation as suggested). Thanks Kum.

Jerónimo Forteza Vila - This is a malignant sarcoma where the cartilaginous areas are difficult to recognize. The specific mutation helps to assure the diagnosis.

Maria Pia Foschini –This case is very interesting as the cartilaginous areas are not so well evident.

Masaharu Fukunaga - Extraskeletal mesenchymal chondrosarcoma vs. sclerosing epithelioid fibrosarcoma. The prominent mineralization and Ewing-like areas indicate mesenchymal chondrosarcoma. Thank you very much, Kum.

Thomas Krausz – Agree with diagnosis.

Thomas Mentzel – A nice but difficult example of rare extraskeletal mesenchymal chondrosarcoma.

Markku Miettinen – Metastatic medullary carcinoma with prominent amyloid would have been my first choice. Did not see cartilage; amyloid-like material is associated with an osteoclastic reaction. Tumor shows vascular invasion not typical of sarcoma. However, if the tumor was keratin-negative, then another interpretation is more appropriate.

Fredrik Petersson - I pass on this one. Eagerly awaiting the discussion from the soft tissue resources.

Murray Resnick – Very nice example.

Brian Rubin – Agree with diagnosis of mesenchymal chondrosarcoma. This can be a very difficult diagnosis when there is minimal primitive cartilage formation.

Ady Yosepovich - Extraordinary case, thank you for sharing

CASE NO. 7 CONTRIBUTED BY: Göran Elmberger, M.D., Ph.D.

Volkan Adsay – The findings in this case reminded me of the old days when we used to see ruptured silicone implants in the breast fairly commonly. In fact, the sclerosis pattern and those lipocyte like large vacuoles which are irregularly distributed really do look like the silicon (or similar inert substance) ingestion to the tissues. For this reason, I suspect this patient may have had injections or some other means of getting foreign substance to this area that is leading to this reaction.

Abbas Agaimy – Penile silicon reaction, benign lesion but with significant clinical consequences, thanks Göran for sharing the slides and the fine discussion

Phil Allen – Sclerosing silicone reaction in an 80-year-old Thai's penile skin clinically simulating a carcinoma and treated by penectomy. Many years ago in the States, they were using paraffin for penile and breast augmentations. The genteel and eloquent Englishman, Professor Bill Symmers, who also published a multivolume and popular pathology textbook in the '60s and '70s, used to entertain pathologists in the colonies with his lecture entitled "Curiosa et exotica." The advertising flyers occasionally substituted the X with an R, which always boosted attendances. The British National Health Service did not knowingly support his performances and certainly never established a British centre for penile diseases.

David Ben-Dor – No one thought of doing a biopsy? The cases we've seen come with a history and consisted only of the affected tissues and not total resection. I've seen this from time to time, mostly in immigrants to Israel from the ex-Soviet Union (this term reveals my age!). I'm used to seeing giant cells in this material and their absence is curious. In this slide the silicone must have leached out during processing. I remember seeing bladder biopsy material full of empty spaces with a foreign body reaction. I assumed it to be fat necrosis until we came to the conclusion that it was air insufflated into the bladder before cystoscopy. Apparently this latter situation is a very rare occurrence. It's easy to forget that air is a foreign body when it infiltrates into soft tissues.

Ira Bleiweiss – Goran - I recognized this as a silicone reaction right away - very similar to breast - but then I read your short summary/location. History first, surgery second!

Alberto Cavazza – Beautiful example of silicone pseudotumor, with an instructive history.

Kum Cooper – Thanks Goran. Good to see you at USCAP. I have also seen this in the face too to enhance structural features. Thank you for the exhaustive reference list.

Hugo Dominguez-Malagón – Silicone reaction in penis, never though it existed in that location.

Franco Fedeli - Silicone reaction after injection has been seen everywhere in the last 20 years.

Cyril Fisher – Striking example of silicone reaction without typical giant cell response.

Jerónimo Forteza Vila - Interesting case for good surgical practice.

Maria Pia Foschini –Very sad story! But it is important to know!

Masaharu Fukunaga - It is very interesting. Silicone reaction, silicone pseudotumor should be included in differential diagnosis in a penis or breast mass.

Ondřej Hes – Very nice, we also have such cases in our registry. For me, identical lesion can be seen in paraffin injection (we have few cases in registry), however grossly they were not cancer mimickers.

Thomas Krausz – I have seen this pathology only in the breast before. Thank you for submitting it.

Thomas Mentzel – Nice and impressive case, but how ignorant are clinicians?

Michal Michal – There are dysplastic even changes of differentiated PeIN type in the basal layer of the penile epithelium. Was the patient psychiatrically checked-up?

Markku Miettinen – Agree on sclerosing lipogranuloma caused by mineral oil/silicone injections.

Cesar Moran – Well, what can one say – trying to be 18 at 80 was the first mistake, and second, the surgeon who took care of this man.

Fredrik Petersson - Foreign body reaction. I thought of oil granuloma / paraffinoma.

Murray Resnick – Wow! Talk about aggressive surgeons….

Brian Rubin – Sad case. Silicone reactions are always interesting and potentially hazardous. Never saw one involving the penis before.

Saul Suster – Very unfortunate case of medical malpractice!

Paul Wakely – Although tempted, I am going to refrain from making any sarcastic remarks about silicone injections into this part of the body. Some of that hyalinized material certainly reminds me of amyloid deposition.

Ady Yosepovich - We must establish a penile tumor board!!! This is a perfect example of how dangerous surgeons can be when left alone with the patients….

CASE NO 8. – CONTRIBUTED BY: Giovanni Falconieri, M.D.

Volkan Adsay – This seems to fit very well to adenomatoid odontogenic tumor (adenoameloblastoma" based on picture matching in publications. Never seen one.

Abbas Agaimy – Very nice description of a rare lesion with complex DDx, thanks Falco.

Phil Allen – Adenomatoid odontogenic tumor, maxilla, female aged 10. I have never seen one before but it seems to have come straight out of the textbook. Thanks for the contribution Falco. Sorry to hear that you are retiring from the club. I trust that I will not catch the tendency because today is my birthday.

David Ben-Dor – At first glance and without paying attention to the location I thought it looked sertoliform. There is a lot of amyloid-like material here which can be seen in another jaw tumor, calcifying epithelial odontogenic tumor (also known as Pindborg tumor). It's interesting that in the duct like foci lined by columnar cells there is no reverse polarization seen in ordinary ameloblastomas.

Ira Bleiweiss – Adamantinoma.

Alberto Cavazza – Giovanni, very nice case and discussion! Never seen before.

Kum Cooper – I agree with you Falco that this is an adenomatoid odontogenic tumor. I saw a handful of these tumors in Africa (black patients). And as you say F>M and maxilla is the favored site. The descriptive term we used in those days for this tumor was "congeries of tubules". I am sad that you have retired from the AMR group but wish you well in your retirement. You have been a good friend and I will miss you!

Hugo Dominguez-Malagón – AOT, agree, very nice case, thank you Giovanni.

Göran Elmberger – Beautiful case. Was lucky to see one myself not long ago in Örebro.

Franco Fedeli - Adenomatoid Odontogenic Tumor: wonderful example of this rare entity.

Cyril Fisher – Adenomatoid odontogenic tumor; very nice slide thanks Dr Falconieri

Jerónimo Forteza Vila - Knowing this benign entity in important.

Maria Pia Foschini – Very typical case! Thank you for sharing with us this rare and interesting tumor. It is important to know, as it can simulate clinically and sometimes also on small incisional biopsies an ameloblastoma.

Masaharu Fukunaga - Adenomatous odontogenic tumor, this is first time I see one. Thank you, Falco. This case resemblesovarian sex-cord tumor with annular tubules.

Thomas Mentzel – Great case in the field of ENT pathology.

Markku Miettinen – Agree on adenomatoid epithelial odontogenic tumor. I think it is a neoplasm.

Cesar Moran – Not very familiar with this entity. Thanks for sharing this case.

Fredrik Petersson - Adenomatoid odontogenic tumor. Agree with the diagnosis.

Brian Rubin – Beautiful case and I agree with diagnosis. As for whether these lesions are true neoplasms or hamartomas, I'd have to go with a true neoplasm.

Ady Yosepovich - Very unusual, thank you for this case.

CASE NO 9. – CONTRIBUTED BY: Franco Fedeli, M.D.

Volkan Adsay – This looks like Kimura to me.

Abbas Agaimy – Pretty example of Kimura's disease, concise discussion, thanks Franco for sharing this beautiful slide.

Phil Allen – Kimura's disease, cervical lymph node. I couldn't see any polykaryocytes of the Warthin-Finkeldey type (Am J Surg Pathol 1988;12, 846). In Hong Kong, I have seen the disease diagnosed on fine-needle aspiration cytology. I have only seen one case in a Caucasian living in Australia. Thanks for the contribution.

David Ben-Dor –Nice slide. Once you become aware of them the eosinophilic infiltrates are impressive. We have in the lab one of the multiple volumes of Bernard Ackerman's differential diagnosis in dermatopathology series where, as was stated regarding this case, that angiolymphoid hyperplasia and Kimura's disease are totally different entities and that the abnormal vessels which are integral to the pathology of the former are absent in the latter, but the vasculature is still prominent in this slide

Ira Bleiweiss – Agree.

Alberto Cavazza – I agree, very nice case and discussion. Recently I have seen a similar case in an Italian patient.

Kum Cooper – Kimura's disease. I saw this case with Franco in Italy.

Hugo Dominguez-Malagón – Kimura disease, diseases affecting Orientals and Eskimos are relatively frequent in my country, native Mexicans are genetically related due to migration through the Behring strait.

Göran Elmberger – This man was certainly not from Istanbul. Nice case!

Franco Fedeli - My case

Cyril Fisher – Kimura's disease. Nice example

Jerónimo Forteza Vila - The eosinophilic infiltrate is crucial for the correct diagnosis.

Maria Pia Foschini – Very interesting and rare case. I had never seen it before, thank you for sharing!

Masaharu Fukunaga - Thank you very much for sharing this beautiful case. It is a typical case of Kimura' disease. Dr. Kimura was a professor of Department of Pathology, our university (Jikei University). In the original paper Kimura's disease is not a lymph node but a soft tissue lesion. Another histologic feature of this disease is the presence of irregular shaped or multinuclear giant cells in the germinal centers, these are seen in this slide.

Thomas Krausz – Very nice example, thank you

Thomas Mentzel – A wonderful example of this rare (outside asia) disease.

Markku Miettinen – Agree on Kimura disease. Also present are floccular eosinophilic deposits in the follicles.

Cesar Moran – Nice example.

Fredrik Petersson - Kimura's disease. Nice case. We see it quite frequently in Malaysia.

Murray Resnick – Excellent example.

Brian Rubin – Great case of Kimura disease.

Saul Suster – Very nice and classical example. I've been collecting cases like this for several years and I believe I probably have more than 6 occurring in non-Oriental patients. Very rare.

Ady Yosepovich - Thank you for this great teaching case.

CASE NO. 10 – CONTRIBUTED BY: Jeronimo Forteza Vila

Volkan Adsay – I think this has some ABC (aneurysmal bone cyst) type changes but the ABC may be secondary due to an infiltrate. I think radiologic correlation to rule out a more sinister bone tumor (including an osteosarcoma) would be necessary. I also wondered about an unusual renal/hyperparathyroid process contributing to this.

Abbas Agaimy – Solid variant ABC, agree with diagnosis, thanks. Any USP FISH done?

Phil Allen – Aneurysmal bone cyst, right vertebral arch of T9. An excellent example. One can see how they used to be confused with giant cell tumors of bone.

David Ben-Dor – Thanks. Looks like a textbook case with all the classical features.

Ira Bleiweiss – Agree. Aneurysmal bone cyst.

Alberto Cavazza – I agree, thanks for sharing this beautiful case.

Kum Cooper – Agreed solid ABC. Thanks for the great example.

Hugo Dominguez-Malagón – Agree with ABC, in my slide is predominantly cystic but it may be completely solid. It can be primary and monoclonal or secondary to other bone tumors.

Göran Elmberger – Impressive yet very illustrative case of ABC including blue bone. Just read translocation t(16;17) is common in this lesion making it a real neoplasm to my mind.

Franco Fedeli - Aneurismal bone cyst (solid variant) with typical location. High proliferative activity of the benign-appearing proliferative spindle cells, often with fairly abundant mitoses, associated with benign giant cells and immature bone production are the features of this pseudosarcomatous hyperplastic lesion.

Cyril Fisher – Aneurysmal bone cyst, solid variant

Maria Pia Foschini – Thank you for sharing this interesting lesion. ABC can be very difficult to diagnose on small incisional biopsies. In addition, ABC can present as an extra-skeletal lesion.

Masaharu Fukunaga - ABC, solid variant. Thank you very much for the slide and images.

Thomas Krausz – Agree with diagnosis, solid focally.

Thomas Mentzel – Very convincing example of aneurysmal bone cyst arising in a young male patient.

Markku Miettinen – Nice aneurysmal bone cyst, with solid and cystic components.

Cesar Moran – Good example.

Fredrik Petersson - Aneurysmal bone cyst. Always nervous about the possibility of a secondary ABC (giant cell tumor, osteoblastoma, chondroblastoma, OS). Sampling !!!!

Brian Rubin – Nice example of aneurysmal bone cyst.

Paul Wakely – Beautiful example of ABC showing islands of so-called 'blue bone' scattered about.

Ady Yosepovich - Thank you for this interesting case.

CASE NO. 11 – CONTRIBUTED BY: Maria Pia Foschini

Volkan Adsay – The pale nuclei with striking overlapping reminded me of a Merkel cell carcinoma. Since EL syndrome is known to have small cell carcinoma of lung, that may be a safer bet here, but based on morphology alone, I would have wondered about Merkel cell carcinoma and investigated that possibility accordingly.

Abbas Agaimy – Great case of recurrent of MCC, most likely primary in lymph node and presenting with paraneoplastic syndrome, a combination of rare events.

Phil Allen – Primary Merkel cell carcinoma, axillary lymph node in a patient with Lambert-Eaton myasthenia and clinically apparent cerebellar degeneration. I had a similar axillary primary but without the myasthenia and neurological signs only a few months ago. I had considerable difficulty convincing some of my colleagues that a lymph node primary is permitted and even now, I do not think they truly believe it. I will have to treat them with this case.

David Ben-Dor – Blue tumor the diagnosis of which depends on immunohistochemistry and context. In this case the context favored small cell of the lung and it was perspicacious of the pathologist to order the CK20. I wonder how widespread the use of the antibody to the Merkel cell virus is even in the large academic centers. I once submitted a

case of Merkel cell carcinoma which presented in the jaw and afterwards a presumably primary tumor was found in the scalp. I thought the jaw location was strange even as a secondary from the scalp tumor.

Ira Bleiweiss – Very nice Merkel cell ca. I've seen several but never primary in node or with paraneoplastic syndrome.

Alberto Cavazza – Very unusual case, both for the association with a paraneoplastic syndrome and for its location as primary in a lymph node (clearly a diagnosis of exclusion).

Kum Cooper – An instructive case. Intranodal MCC. Not heard of that before. I thought it was metastatic small cell neuroendocrine carcinoma from the lung (which E-L-S patients can get). Did you perform TTF-1 and polyoma virus IHC? CK7/CK20 is odd; since MCC is CK 20 positive.

Hugo Dominguez-Malagón – Merkel carcinoma primary of lymph node, other possibility is a "vanishing" primary. The PNS is interesting.

Göran Elmberger – Remarkable case. Occurrence of polyoma virus makes me wonder if metastasis from skin primary with spontaneous regression might be an alternative explanation. This phenomenon is well described in the literature.

Franco Fedeli - Merkel Cell Carcinoma (primary in lymph-node): very unusual presentation, could be excluded the possibility of a secondary lesion from regressed cutaneous primary tumor?

Cyril Fisher – Merkel cell carcinoma primary in lymph node. I was unaware of this paraneoplastic syndrome.

Jerónimo Forteza Vila - In this case, immunohistochemical panel is very important to determine the diagnosis.

Masaharu Fukunaga - Thank you very much for the case of Merkel cell carcinoma in the lymph node. I have never seen lymph node primary cases. Histology is very beautiful.

Thomas Krausz – The "milky" histologic appearance still helps me favor Merkel cell carcinoma among others, on H&E.

Thomas Mentzel – An interesting case of rare intranodal Merkel cell carcinoma – did tumour cells show a reduction of H3K27me3 (Busam KJ et al. Mod Pathol 2017)? Was the expression of INI1 retained?

Markku Miettinen – Agree on Merkel cell carcinoma based on your studies.

Cesar Moran – Really? primary in lymph node? or perhaps axillary soft tissue primary with extension to lymph node? Wonder what Dr. C. Toker would have said about the issue of primary lymph node tumor?

Fredrik Petersson - Metastatic small cell carcinoma? Merkel cell carcinoma?? On my sections the lymph nodal tissue not very obvious.

Brian Rubin – Fantastic case. Not sure I've ever seen a case of Merkel cell CA primary to lymph node or one that caused a paraneoplastic syndrome. Very cool.

Saul Suster – I have seen cases before of primary Merkel cell carcinoma (the Toker tumor) arising in head and neck lymph nodes and as a primary in the parotid. I believe it was Dr. Vincenzo Eusebi, former Chief of Pathology at Dr. Foscini's Department who first described this in AJSP. We don't have the papilloma virus antibody in our department; we rely on H&E, history and a combination of chromogranin and CK20 for the diagnosis.

Ady Yosepovich - Thought this is small cell Ca.

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

Volkan Adsay – Something in the Brenner spectrum? (or one of its relatives) associated with cystic changes and accompanying stromal changes?
Abbas Agaimy – Pretty gynandroblastoma, thanks Masa for the fine contribution.

Phil Allen – Gynandroblastoma, left ovary in a female aged 67. I am amazed by the WHO technological advances that now make tumors invisible.

David Ben-Dor – The sertoli component is clear cut though in a different context I wonder if it would be wise or necessary to rule out carcinoid (sorry- well differentiated neuroendocrine). I thought that in juvenile granulosa cell tumor the cells were large with eosinophilic cytoplasm -what I didn't notice on this slide. It would be interesting to surmise how long this patient had the tumor even if it didn't come to clinical attention until recently.

Ira Bleiweiss – Agree. Nice case

Alberto Cavazza – I agree, thanks for sharing this very nice case.

Kum Cooper – Fascinating tumor Masa. I have never seen one before…only read about it. Great to catch up with you at USCAP.

Hugo Dominguez-Malagón – Gynandroblastoma, a collector's case. Thank you Masaharu.

Göran Elmberger – Seems to fit with descriptions. What is the reason for omitting it in the new WHO?

Franco Fedeli - Gynandroblastoma: Sertoli component is very limited.

Cyril Fisher – Gynandroblastoma or mixed sex-cord stromal tumor, very rare, nice to see.

Maria Pia Foschini – It is a very rare tumor, in addition my experience in gynecologic pathology is very limited. I wonder why it disappeared in the last WHO blue book.

Masaharu Fukunaga - My case, gynandroblastoma. I am afraid that some slides contain only tiny foci of Sertoli cell tumor.

Ondřej Hes – Never seen this! Thank you very much for sharing!!

Thomas Krausz – The granulosa cell tumor is relatively straight forward; however, my confidence level (without immuno-stain) in recognizing the Sertoli cell component was not high.

Thomas Mentzel – Nice case, I`ve never seen one….

Markku Miettinen – Also thought of granulosa cell tumor with fibroma features.

Cesar Moran – Nice case. Another tumor cured by pathologists as it has disappeared from WHO.

Fredrik Petersson - My slide quite weakly stained. Sex cord – stromal neoplasm. Looks benign. Sertoli cell differentiation? Did not get the juvenile GCT component. Thank you.

Brian Rubin – So what happened to gynandroblastoma in the new WHO classification? Where did it go?

Saul Suster – Breaking news in Fox news channel: "Rare ovarian tumor cured by the WHO – most recent fascicle indicates this tumor has now disappeared!"

Paul Wakely – What a lovely case of a rare entity, Masaharu.

Ady Yosepovich - Never saw one before, thank you for this example.

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

Volkan Adsay – I will be looking forward to the experts' view on the prognostication of this struma and whether/ how to report that infarction/necrosis type of change. There are also foci with subtle PTC nuclear features it seems but I am not sure it fully qualifies.

Abbas Agaimy – Nice example of struma ovarii with features suggestive of follicular carcinoma, thyroid type. As always superb discussion, thanks Thomas.

Phil Allen – Well differentiated follicular thyroid carcinoma with pulmonary metastases arising in struma ovarii. The only criterion I trust for the diagnosis of well differentiated follicular thyroid carcinoma is the presence of distant metastases. Like Thomas, I would not have made a diagnosis of malignancy without knowledge of the multiple pulmonary metastases.

David Ben-Dor – As the saying goes, when the going gets tough the tough get going. Thomas is certainly a tough guy. I checked the Robboy et al 2009 reference in pubmed and my understanding of the abstract was that there is really no foolproof way to diagnose malignancy in cases like this purely on the basis of the histology of the ovarian mass. I would find it very difficult to make a definitive diagnosis of vascular invasion in this case- I see follicles pressing against the thin walled vessels but can't be certain if they're definitely inside; I prefer to see the tumor unequivocally deforming the wall and protruding into the lumen. I wonder what was meant by "toughening of the criteria" for vascular invasion. To me the most sane procedure would have been to biopsy the lung lesions to confirm malignancy and if positive then do total thyroidectomy. But another hackneyed saying is that the proof of the pudding is in the eating so the diagnosis of malignancy was verified at the end.

Ira Bleiweiss – Agree but wow - a 13 year old girl with a 19cm struma. I would not have had greatest confidence in diagnosing malignancy but obviously it is.

Alberto Cavazza – I am not competent enough to have a firm opinion on this difficult case. In the absence of lung nodules, probably I would be descriptive just as you did, suggesting a close follow-up, and I would not be able to make a firm diagnosis of malignancy in this young patient (even if particularly necrosis and vascular invasions are clearly worrisome features). Very instructive case, and I am curious to know the opinion of the experts.

Kum Cooper – Thomas I was also at struma ovarii. I could not make a morphological diagnosis of carcinoma on this section. Then I showed it to Zubair Baloch who called it poorly differentiated carcinoma arising in a follicular variant of papillary carcinoma. Then I gave him the full history!!!

Hugo Dominguez-Malagón – Malignant ovarian struma, in my slide there are also areas with an insular pattern, necrosis and vascular invasion.

Göran Elmberger – Interesting case and discussion. I agree on everything. Perhaps still, I would have been hedging a carcinoma diagnosis if given only the present slide. In thyroid gland criteria, capsular invasion and lymphovascular growth exist but they are only partly transposable to the ovary. In addition, this type of undermining indentation/infiltration of vessels without any type of thrombus or reactivity is to me not quite convincing of vascular invasion. However, our morphologic criteria are far from perfect as indicated by the "entity" of benign metastasizing thyroid follicular adenoma. Perhaps a molecular definition might solve or at least help the situation.

Franco Fedeli - I saw a case of omental secondary lesion from malignant struma ovarii once. Not easy to find the parenchymal infiltration, but in this case the vascular invasion is very well documented.

Cyril Fisher – Of course we have the benefit of hindsight, but I would likely have termed this carcinoma based on the necrosis and vascular invasion.

Jerónimo Forteza Vila - Because of the intravascular tumor growth it´s worth considering this lesion as a follicular carcinoma. The necrosis is not so worrysome, it could be the consequence of ischemic factors.

Maria Pia Foschini – This is a difficult case, especially as the patient is very young. Indeed, the presence of pulmonary metastases confirm the malignant nature of this tumor. On the other hand, the tumor itself with the mitotic figures, necrosis, and vascular invasion should be considered malignant.

Masaharu Fukunaga - A very interesting and challenging case. Thank you very much for the deep discussion, Thomas. My impression is struma ovarii without clinical information.

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

Markku Miettinen – Struma ovarii with atypical features, cannot rule out malignancy.

Cesar Moran – I'm not so sure about follicular carcinoma; likely I would not have made that diagnosis in real time.

Fredrik Petersson - Proliferative struma ovarii, angio invasion? – very very worrisome for follicular carcinoma. Superb case. Good clinicopathological correlation. Thank you, Thomas.

Murray Resnick – Quite a dilemma. I do not think I could call this outright malignant without the clinical history of pulmonary nodules or molecular studies to back me up.

Brian Rubin – Impressive case. I wouldn't have confidently been able to call this case malignant without the clinical history.

Saul Suster – Very interesting and challenging case, Thomas. I would have not gone beyond a diagnosis of struma ovarii with areas of ischemic infarction on the submitted slide. I could not find any convincing evidence of vascular invasion in my slide. My suggestion would be to biopsy one of the lung lesions to confirm the diagnosis. It seems unusual that the pulmonary lesions would have not responded to the radioactive iodine treatment.

Paul Wakely – To answer your question Thomas, I would have probably diagnosed 'struma ovarii' only if there were no pulmonary nodules.

Ady Yosepovich - Fantastic case, thank you for this excellent discussion

CASE NO 14. – CONTRIBUTED BY: Anais Malpica, M.D.

Volkan Adsay – This seems to be a poorly differentiated adenocarcinoma, and I think I would have performed neuroendocrine markers and MSI markers. Secondary involvement from an adjacent GI cancer (with medullary like features) may be a consideration too, and MSI (and perhaps CDX2) may help in that regard as well. One of the reasons I would do MSI is that, if there is a loss indeed, it could give the oncologists to hang their hat on, even if we cannot tell the primary location specifically.

Abbas Agaimy – A case of LCNEC with focal glandular differentiation, agree. Any recommendation for cutoffs to define MANEC in the GYN tract? Similar to the GI cases

Phil Allen – Large cell neuroendocrine carcinoma with focal glandular differentiation, uterine cervix. Thanks for the encyclopedic discussion.

David Ben-Dor – That this is carcinoma - and a pretty ugly looking one at that- is a no-brainer but if the criteria for neuroendocrine differentiation are nuclear and if the nuclei in the large cell variant don't show the typical features of NEC then on what basis are you supposed to order the appropriate immunostains? I had a cytologically typical small cell neuroendocrine carcinoma of the cervix (sad case- a young woman who was already diagnosed with Hodgkin's disease; she also had limited survival) on which I did CK20 which turned out positive; the case was included in Glenn McCluggage's 2010 paper cited among the references. The stain using antibody specifically against the Merkel cell virus was negative.

Ira Bleiweiss – I would not have thought of this a neuroendocrine based on the slide alone.

Alberto Cavazza – I agree, nice case and comment. I remember I have seen a couple of LCNEC of the uterine cervix, and both were pure (without a glandular or squamous component).

Kum Cooper – Thank you Anais. Nice case. I have not seen LCNC of the cervix with glandular differentiation. I agree that an IHC panel is required to confirm that diagnosis. Enjoyed your talk at USCAP.

Hugo Dominguez-Malagón – Large cell (high grade) neuroendocrine carcinoma of the cervix. Nice case.

Göran Elmberger – I believe it is not easy to make the diagnosis without IHC. Perhaps somewhat discrete chromatin pattern for grade and a hint of NE architecture. Guess only way to pick up is to screen all poorly differentiated large cell carcinoma with NE IHC panel. Does it matter? Some textbooks claim similar prognosis for usual poorly differentiated adenocarcinomas or adenoca with NE-differentiation. Similar discussion in pulmonary pathology… Good case to bring up discussion and awareness!

Franco Fedeli - Large Cell NE Carcinoma: Thank you for sharing this wonderful case.

Cyril Fisher – Large cell neuroendocrine carcinoma of cervix, very interesting case

Maria Pia Foschini – Glandular differentiation can be seen in NE carcinomas, especially in the GI tract. I wonder, in the present case, if the glandular elements showed true exocrine (EMA?) together with neuroendocrine markers, leading to a divergent differentiation of the same cells.

Masaharu Fukunaga - Large cell neuroendocrine carcinoma of the cervix. Anais, thank you very much for the case.

Thomas Krausz – Agree with diagnosis.

Thomas Mentzel – An interesting case! Is the focal glandular differentiation of importance?

Markku Miettinen – High-grade neuroendocrine carcinoma of the cervix.

Cesar Moran – Coming from Anais I better keep my mouth shut ☺.

Fredrik Petersson - High grade adenoca, ? Biphenotypic, LNEC component ??, These were my initial thoughts. Thank you for very educational case.

Murray Resnick – Striking case. Is p16 uniformly strongly positive in neuroendocrine carcinoma of the cervix?

Brian Rubin – Very nice case with some good teaching points.

Ady Yosepovich - Agree with the diagnosis, highly aggressive tumor.

CASE NO. 15 – CONTRIBUTED BY: Alberto Marchevsky, M.D.

Volkan Adsay – Mucoepidermoid carcinoma. Compact, circumscribed growth at the major bronchus junction is a nice illustration of the good old (extinct) "bronchial adenoma" concept?

Abbas Agaimy – It seems I missed this slide!

Phil Allen – Looks like a mucoepidermoid carcinoma to me.

David Ben-Dor – there was no diagnosis given at least at the time I looked at the slides. I'll venture that this is a mucoepidermoid carcinoma arising in the bronchial glands. Nice slide.

Ira Bleiweiss – ???

Alberto Cavazza – I think it is a low-grade mucoepidermoid carcinoma of the bronchus, a low-grade malignancy frequently occurring in young people. Unfortunately, sometimes it requires a major surgery for its central location. A nice case, if I am correct!

Kum Cooper – Good to chat with you at USCAP Alberto (as always). Mucoepidermoid carcinoma. FISH for MAML2. I shared this case with Charuhas Deshpande who also came to the same conclusion.

Hugo Dominguez-Malagón – The discussion is incomplete, my impression is acinic cell carcinoma r/o mucoepidermoid.

Göran Elmberger – Combining my two favorite areas! Mucoepidermoid carcinoma.

Franco Fedeli - Salivary gland-type mucoepidermoid tumor (low grade), in my opinion.

Cyril Fisher – Mucoepidermoid carcinoma.

Jerónimo Forteza Vila - This lesion could be a mucoepidermoid carcinoma derived from a teratoma. I have never seen this lesion before, so that I am not confident with my opinion.

Maria Pia Foschini – This is an interesting case of mucous producing tumor with no atypia. I discussed it with my colleagues, and we favor the diagnosis of mucinous adenoma of the peri-bronchial glands; differential diagnosis: well differentiated, low grade mucoepidermoid carcinoma.

Masaharu Fukunaga - Mucoepidermoid carcinoma of the bronchus.

Thomas Krausz – Mucus gland adenoma with some acinic differentiation versus low-grade mucoepidermoid carcinoma.

Thomas Mentzel – The neoplasm looks like a relatively well-differentiated mucinous carcinoma.

Markku Miettinen – Low-grade carcinoma of salivary gland type, favor mucoepidermoid carcinoma; also, considered mammary analogue secretory carcinoma.

Cesar Moran – This looks to me like a mucous gland adenoma. The other consideration is the obvious mucoepidermoid carcinoma but I think it is important to determine the extent of this tumor.

Fredrik Petersson - Looks like mucoepidermoid carcinoma to me.

Murray Resnick – Could this be a mammary secretory analogue carcinoma? Some variant of an acinic tumor?

Brian Rubin – ?Mucoepidermoid carcinoma.

Ady Yosepovich - Mucoepidermoid carcinoma?

CASE NO. 16 – CONTRIBUTED BY: Thomas Mentzel, M.D.

Volkan Adsay – Mesenchymal neoplasm with a distinctive look that makes me think it may be a product of some translocation of some sorts. In the background tissue there seems to be a peculiar nerve which may be representative of the underlying phenomenon but that is under a bubble in my slide and that is why I cannot tell whether that is just reactive or something more serious than that (as a predisposing factor to this neoplasm?).

Abbas Agaimy – I too would call it "I don´t knowoma", I believe, Thomas, that I have seen a similar lesion the beginning of this year which I too have called it similarly, reminiscent somewhat of some angiofibromatous proliferations but lacking any line of differentiation. If I recall correctly also in my case there were scattered stromal

lymphocytes, I do not know what they mean and what this lesion is, but likely ones that harbors yet unidentified peculiar gene fusions.

Phil Allen – Undiagnosed epithelioid and spindle cell perivascular tumor, soft tissues of chest wall. I don't think I have seen one like this before. I assume the HMB-45 is negative (PECOMA). If the tumor bed could be more widely excised without causing much morbidity, re-excision might be justifiable. Otherwise, careful follow-up might be in the patient's best interests.

David Ben-Dor – May be a fascinoma.

Ira Bleiweiss – Reminds me of meningioma but....

Alberto Cavazza – The cells reminded me those of ossifying fibromyxoid tumor, but immuno seems against it and most important if you and Dr Fletcher have not considered this possibility, it is probably not that! No idea.

Kum Cooper – Reminds me of Saul's case from the previous seminar. Residents and fellows look in disbelief when I tell them that even the experts don't know everything!! That is why the Italians call these "*impossible cases*"!

Hugo Dominguez-Malagón – Sorry, I don't know any intelligent answer. Meningioma/perineurioma?, Solitary fibrous tumor?, myoepithelioma?

Göran Elmberger – I would try HMB45.. and probably everything else in the box.

Franco Fedeli - For me it morphologically resembles a low grade endometrial stromal tumor … but … he is a man!!!??

Jerónimo Forteza Vila - This is an atypical, probably malignant epithelial tumor, with negative immunohistochemical study. A bigger panel could be helpful. Maybe an ultrastructural study could be useful.

Maria Pia Foschini – This is a tumor with well defined-margins, composed of uniform cells arranged in whirling nodules. Cells are quite regular, with central nuclei and minute nucleoli. Mitoses are rare. Your immunostainings exclude most of mesenchymal or epithelial tumors. Personally, I would add some more melanocytic markers, as melanocytic tumors can present a wide variety of morphological patterns. In addition, as a remote hypothesis, I would add progesterone receptor, as some features (the whirling nodules) are reminiscent of meningioma. Meningiomas are benign tumors, but, on rare occasions, even if they have a benign looking pattern, they can give rise to extracranial metastases.

Masaharu Fukunaga - A challenging case, thymoma?

Ondřej Hes – Unfortunately, never seen a case like this.....

Thomas Krausz – I am also stuck…, would love to know the solution, though. A remote suggestion: cellular undescribed variant of ossifying fibromyxoid tumor with neither ossification nor myxoid matrix?

Markku Miettinen – Low-grade mesenchymal neoplasm, unclassified. Perhaps should put this case for a comprehensive fusion search.

Cesar Moran – !!!!!

Fredrik Petersson - I also do not know. On H&E I thought of a small cell – neuroblastoma-like schwannoma. I wonder if Michal will pull out something from his sleeve…

Murray Resnick – Based on the morphology and immunoprofile I could not come up with any ideas. My soft tissue colleague Dr. Hart suggested running PECOMA markers (MELAN-A, HMB-45 and some other smooth muscle markers despite the SMA negativity).

Brian Rubin – I would have thought perineurioma or unusual non-ossifying variant of ossifying fibromyxoid tumor. I guess you could check for a *PHF1* gene fusion. Unfortunately, I see things that look classifiable but that I can't classify

quite frequently. It's quite humiliating. I'll keep an eye out for more of these. We should call them Mentzeloma's if we can't figure out what to call them.

Saul Suster – Sorry I'm unable to be of help with this. The lesion looks benign and "fibrohistiocytic" to me. I would consider a deep juvenile xanthogranuloma. Any histiocytic markers done (CD68, CD163, FXIIIa)?

Paul Wakely – Wish I could be of more help. It looks somewhat myopericytomatous, and even reminds me of a follicular dendritic cell tumor.

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

Volkan Adsay – I thought there were areas of Nicholson phenomenon that led me to embryonal rhabdomyosarcoma possibility here.

Abbas Agaimy – Nice example of Müllerian adenosarcoma with sarcomatous overgrowth and rabdo diff. Thanks for sharing.

Phil Allen – Uterine adenosarcoma with sarcomatous stromal overgrowth. I don't think the rhabdomyoblastic differentiation is very impressive in the H&E stain.

David Ben-Dor – I'm missing the biphasic aspect. Mostly there is immature stroma but there are elongated cells with pink cytoplasm consistent with the striated muscle component but I'm having difficulty convincing myself that they're actually striated. Did I miss any spiral arterioles?

Ira Bleiweiss – Agree.

Alberto Cavazza – I agree, nice case.

Kum Cooper – Thank you Delia for this nice example of Mullerian adenosarcoma. I had to go back to identify the rhabdomyoblastic differentiation. Yes, it is there!

Hugo Dominguez-Malagón – Mullerian adenosarcoma, I agree, nice case. Welcome to the AMR Delia!

Göran Elmberger – Rare case. Nice. Difficult ddx vs EST with glands. Wonder if glands would be FISH positive with t(7;17).

Franco Fedeli - Adenosarcoma with sarcomatous overgrowth and rhabdomyoblastic differentiation: I have seen a case like this. Same Age. As in this case the glandular component was very scanty.

Cyril Fisher – Adenosarcoma with stromal overgrowth and rhabdomyoblastic differentiation

Maria Pia Foschini – Interesting case, thank you for sharing this case with us.

Masaharu Fukunaga - Adenosarcoma with sarcomatous overgrowth. Thank you, Delia for sharing this great case.

Thomas Krausz – This is the youngest patient with this tumor-type I have ever seen. I had difficulty to identify the rhabdomyoblasts on H&E.

Thomas Mentzel – Nice example of a rare entity.

Michal Michal – I did not have the adenomatous component in the slide.

Markku Miettinen – Endometrial carcinosarcoma vs. adenosarcoma with maturing skeletal muscle differentiation, treatment effect? In the near absence of glands hard to decide, which one.

Cesar Moran – Interesting case.

Fredrik Petersson - I did not appreciate the bland epithelial component, but when I went back to the slide, it was there!

Brian Rubin – Great example of adenosarcoma with sarcomatous overgrowth.

CASE NO. 18 – CONTRIBUTED BY: Santiago Ramón y Cajal, M.D.

Volkan Adsay – Stroma appears to be a part of this malignancy in some foci. If so, then, carcinosarcoma? (pulmonary blastoma, if connected to lung?). I guess clear cell pattern and the resemblance to pneumocytes in the adenocarcinomatous areas may also suggest a pulmonary blastoma?

Abbas Agaimy – Pretty case of sclerosing hemangioma of lung. Was beta-catenin stained? Nuclear?

Phil Allen – Sclerosing pneumocytoma, right lung. I hardly see any lung cases and if I do, I invariably have to consult a lung specialist. Unfortunately, my younger colleague, Doug Henderson, has already retired, which is great pity because I always enjoy twisting his old tail around rare lung lesions. Tom Colby's retirement from the Club is also a great loss.

David Ben-Dor – I certainly wouldn't want to be in a position where I would have to diagnose this on the basis of a needle biopsy and can fully sympathize with the initial diagnosis. However when you look carefully at the cells they do have a delicate cytology. But the variegated appearance, architectural complexity and vacuolated cells which could lead one to mistake them with signet ring cells, are worrisome unless you can think of the diagnosis. There didn't seem to be any clinical or radiological indication that this was a lung tumor. The AFIP does mention that these tumors "can adhere to neighboring structures such as the pericardium". Was it obvious to the surgeon that this was a lung tumor? Or did the pathologist have to figure it out on his own? Also from the AFIP- there are often cholesterol clefts and scroll like laminated structures that I didn't notice in this slide.

Alberto Cavazza – Great case! I missed the diagnosis because of the mediastinal location, but in retrospect this is clearly a sclerosing pneumocytoma. I can add just a couple of comments: 1) a few cases have loco-regional lymph node metastases, and a case is reported with a gastric localization, but as far as I know no patient ever died of this tumor; 2) apparently both superficial and interstitial cells are neoplastic (they both can be present in lymph nodes).

Kum Cooper – Thank you Santiago this is an exceptional instructional case. I recall John Chan writing about this pitfall many years ago in Ad.Anat.Pathol. This would be a frozen section nightmare!

Hugo Dominguez-Malagón – Pneumocytoma (sclerosing hemangioma), completely agree, rare cases are associated to Gardner syndrome with alteration of the WNT pathway and expression of beta-catenin.

Göran Elmberger – Beautiful case. Challenge on frozen. Only case I have seen before ended up with pneumonectomy after frozen dx of mesothelioma.. (at another hospital..)

Franco Fedeli - Sclerosing Pneumocytoma; in this case the differential diagnosis from mesothelioma is very difficult in the H&E staining.

Cyril Fisher – Sclerosing Pneumocytoma; very nice example, many thanks

Jerónimo Forteza Vila - This case has been studied exhaustively. It is difficult to reach the correct diagnosis, which can be misinterpreted with a malignant tumor.

Maria Pia Foschini – This is a very difficult case, diagnosis should be suspected especially in small pre-operative biopsies performed in young patients.

Masaharu Fukunaga - Sclerosing pneumocytoma. An excellent educational case. Thank you, Santiago for the case and clear-cut discussion

Thomas Krausz – Nice example. Yes, it can be easily misdiagnosed on frozen section or on small biopsies. Despite the TTF1 immunoreactivity, I still do not fully understand what the "interstitial" polygonal cell population in this tumor is trying to do.

Thomas Mentzel – A great example of this rare benign neoplasm.

Markku Miettinen – Agree that that TTF1-positivity takes it to pneumocytoma from a consideration for a papillary mesothelioma.

Cesar Moran – Very interesting location. I had seen this tumor in the anterior mediastinum only once before as a mediastinal tumor without lung involvement, which raises all sort of questions regarding origin – thymus? Really pneumocytoma? From where in the mediastinum?

Fredrik Petersson - Agree. Excellent case! Great pitfall. Clues to the diagnosis radiology + age. In this case the tumor is huge!

Murray Resnick – Great example. Excellent discussion.

Brian Rubin – Very interesting case and something I haven't really seen very often. I wondered about papillary thyroid CA but totally forgot about sclerosing pneumocytoma.

Saul Suster – This is a truly difficult case which morphologically does fit for the diagnosis of pneumocytoma, but clinically is hard to conceive as such. Other than postulating ectopic lung tissue in the mediastinum or embryologically displaced pneumocytes, it would be very hard to explain. I have never seen this tumor in this location. Have you tried beta-catenin staining to support your diagnosis? Pneumocytomas are universally positive for this marker.

Paul Wakely – Beautiful case!

Ady Yosepovich - From the first glance looks like placenta.. Never saw this before, thank you for this case.

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

Volkan Adsay – High grade sarcoma. Ovarian cortex like monotonous cellularity with dense hypercellular appearance, along with some of the associations with the vessels reminded me of an MPNST.

Abbas Agaimy – Great Case Brian, Having seen only a single case very long ago now I have a pretty slide in my collection, thanks Brian for sharing this case, great discussion.

Phil Allen – Spindle cell type of adamantinoma arising in osteofibrous dysplasia, right mid tibia, with pulmonary metastases. We presently have a case in this hospital which looks to me like a massive, sclerosing, poorly differentiated adamantinoma of the tibia with pulmonary metastases. The only catch is that the cells are clear and a number of pathologists maintain it is a secondary clear cell carcinoma, although clinically, the massive tibial tumor is the primary.

David Ben-Dor – I guess this is "not morphologically difficult" if you do a lot of bone pathology. On low power examination the tumor invades as cohesive nests befitting an epithelial neoplasm but the cytology doesn't look particularly epithelial. The gross photo is gruesome.

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

Kum Cooper – Thanks Brian for the classic example. In fact, some areas truly resemble ameloblastoma.

Hugo Dominguez-Malagón – Adamantinoma of the tibia, beautiful case, thank you…

Göran Elmberger – Thanks for sharing this unusual case.

Franco Fedeli - Classic Adamantinoma: The prominent spindle cell component lets us strongly consider the possibility of monophasic synovial sarcoma

Cyril Fisher – Adamantinoma of long bone. Thanks, Brian, for the informative discussion.

Maria Pia Foschini – This is a rare tumor, and diagnosis is very difficult especially when the lesions is mainly composed of spindle cells.

Masaharu Fukunaga - A very beautiful case of adamantinoma. Thank you, Brian, for the detailed discussion.

Thomas Krausz – Brian, even though you say "this case is not morphologically difficult", before reading your excellent write-up, I considered a few things in my differential. The history of osteofibrous dysplasia, of course does help. For me this case is highly educational, so thank you for submitting it. I would have never thought that adamantinoma in a long bone can be so enormous in size.

Thomas Mentzel – Many thanks Brian for this wonderful case.

Markku Miettinen – Nice case of adamantinoma with spindle cell features.

Fredrik Petersson - Malignant spindle cell neoplasm. SS? MPNST?, were my initial thoughts. Excellent presentation and discussion.

Murray Resnick – Excellent case and nice comprehensive discussion.

Brian Rubin – My case. Hope you enjoyed it!

Saul Suster – Pretty spectacular case! Even for people who routinely do bone pathology this would be a difficult case given the massive size and the spindle cell features.

Paul Wakely – What a sad story. If he only would have agreed to appropriate treatment in a timely manner, then those lung nodules might not be present now. Thank you for a wonderful case illustrating the morphologic spectrum of adamantinoma.

Ady Yosepovich - Thank you for sharing this extraordinary case.

CASE NO. 20 – CONTRIBUTED BY: Manual Sobrinho Simoes, M.D.
(This case was studied by Dr. Irene Gullo, a Resident in our Department)

Volkan Adsay – My prediction is that this is the type of case that Drs. Asa or Livolsi will call PTC but some of the other gurus may not. I will be very curious to hear the opinions of our experts. The multinodularity is okay for PTC but I thought it had more the features of a goiter type nodularity. Nevertheless, the nuclear changes are of the type that some experts would qualify as PTC, I think.

Abbas Agaimy – Excellent example of emerging entities learned from recent genetic studies. It seems that the single gene single tumor theory is vanishing. I presented recently a case of adenomatous goiter probably related to Cowden syndrome (PTEN mutation), now DICER1-related adenomatous goiter as well, so different diseases with shared organ manifestations, albeit surely with differences in morphological details.

Phil Allen – I call all minimally angio-invasive follicular thyroid tumors benign, and am likely to be right 99% of the time. So far, I have not got one wrong but I have reported less than 100 cases. As the occasion demands, I wheel out this argument in an attempt to guide the surgeons' and oncologists' hands away from aggressive treatment.

David Ben-Dor – I see aside from normal thyroid parenchyma, some encapsulated follicular nodules focally with papillary like structures but otherwise the nuclei look small and condensed and don't show the features of papillary carcinoma (in my opinion). Then there are variably sized well circumscribed follicular nodules with dark colloid in the lumens and whose lining cells have enlarged clear nuclei. Are the smaller nodules breaking off from the largest one,

thus invasive, or are they independent? Or maybe one nodule transected by fibrous bands? Maybe this is semantic but it could have diagnostic significance. On multiple attempts I think there is one focus that I'll accept as vascular invasion. If the nuclei fit the criteria for papillary then it would be the follicular variant of papillary or- if you're not convinced of the invasion, maybe an example of what is now called NIFTP. The possibility of a third intermediate group?- challenging diagnostically. There are enough problems with two types we already have!

Alberto Cavazza – Very interesting case and comments about this genetic syndrome.

Kum Cooper – Thank you for this DICER-1 associated thyroid carcinoma. Did the patient have pulmonary cysts?

Hugo Dominguez-Malagón – Well differentiated thyroid carcinoma in the context of DICER1 syndrome, a new one for me.!

Göran Elmberger – Case with great story! Looking forward to further spanking.

Franco Fedeli - Papillary Carcinoma Follicular Variant (infiltrative), in my opinion.

Jerónimo Forteza Vila - I agree with the diagnosis.

Maria Pia Foschini – Interesting case. I was not aware of DICER1 syndrome. Is it related to the rhabdomyosarcoma also?

Masaharu Fukunaga - This is the first time I see well differentiated thyroid carcinoma in DICER 1 syndrome. Thank you very much for the very rare case. I often have problems making a diagnosis of follicular carcinoma, interpretation of vascular invasion is very difficult.

Thomas Krausz – This is superb. I must admit, I did not know about the thyroid and *DICER1* association. Thank you very much for educating me.

Thomas Mentzel – What a great case, many thanks indeed. For me the thyroid neoplasm looks like the follicular variant of papillary thyroid carcinoma.

Markku Miettinen – I thought of papillary carcinoma, with a prominent follicular component, but agree that this a probably better considered a separate entity by its genetic association.

Cesar Moran – I thought follicular variant of papillary carcinoma.

Fredrik Petersson - Initially, I was surprised by the age in relation to the multiple nodules present. The section was not easy to spatially orientate, but I could not see any unequivocal vascular invasion. Thanks for succinct discussion.

Murray Resnick – Thanks for submitting this case and enlightening us with the DICER story.

Brian Rubin – Didn't realize there was an association with DICER1 syndrome and thyroid neoplasms of any type! I need to read about this fascinating connection.

Saul Suster – Thank you for the enlightening discussion about DICER-1 mutations and thyroid nodules. Here in Milwaukee we are very conservative with the diagnosis of follicular carcinoma. I would actually be hard-pressed to make that diagnosis on any tumor that is not showing overt transcapsular invasion and unequivocal vascular invasion, particularly when it is under 2 cm. in size.

Ady Yosepovich - Thank you for this unusual case – this entity is new to me, now I will be able to recognize it when I see it.

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

Volkan Adsay – Most areas of this tumor made me think of SFT/("HPC). While the atypia may be partly due to peri-infarct symplastic change, I thought there was substantial mitotic activity with atypical forms (high-grade).

Abbas Agaimy – Nice example of "dedifferentiated" SFT, thanks Paul.

Phil Allen – Malignant solitary fibrous tumor of the retroperitoneum removed in 2008 followed by liver metastases in 2012 and stable disease treated with Bevacizumab and Avastin in 2016. All the tumor in the circulated slide looks malignant to me and I would have difficulty supporting dedifferentiation in this case. It could have been histologically malignant from the beginning. On the other hand, I have repeatedly seen tumors that are well differentiated with no poorly differentiated areas in either the first excision or in early recurrences but eventually, late recurrences become less well differentiated. Arkadi Rywlin and Robb argued that unstable clones of undifferentiated stem cells are present in well differentiated tumors. The less well differentiated recurrences arise from these occult stem cells. The fact that ordinary pathologists cannot see these undifferentiated neoplastic stem cells in sections of the initial well differentiated tumors and early recurrences did not trouble them as they proposed a death sentence for the "antiquated concept" and "incorrect" term "dedifferentiated". This is clearly an early example of pathological correctness that in its turn has been corrected by the latest generation of pathologists.

David Ben-Dor – I see the bland monomorphic baseline proliferation, foci of cells with nuclear atypia, and large hyperchromic nuclei with smudged chromatin. I assume the latter are degenerative. Can't and won't argue with the diagnosis of malignant transformation given the behavior. Is it possible to go back and retrieve the blocks for the stat-6 stain? Would it make a difference at that point?

Ira Bleiweiss – Malignant SFT.

Alberto Cavazza – I agree, nice case.

Kum Cooper – Nice case Paul. Thanks. I had both dedifferentiated SFT and liposarcoma in my DD.

Hugo Dominguez-Malagón – Dedifferentiated/malignant SFT, I agree

Göran Elmberger – The "dedifferentiation" shown looks a bit ancient. Completely agree on you comment on terminology. Is undifferentiated any better? I guess high grade transformation is somewhat better as a term.

Franco Fedeli - MSFT dedifferentiated - behavior outside thorax (abdominal region) seems to be more aggressive.

Cyril Fisher – Very interesting case. Whether this should be called malignant or dedifferentiated can be debated. The persistence of CD34 suggests the former. If both the well differentiated and the focally pleomorphic component are fibroblastic (ie, of the same lineage), it can be argued that for this particular tumor dedifferentiation is an inappropriate term. However, as Paul points out, it is now entrenched.

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

Maria Pia Foschini – In this case the malignant features occupy most of the section. In thoracic cases, sometimes, the malignant features are so localized that it is necessary to embed the whole surgical excision to find them.

Masaharu Fukunaga - I agree, malignant solitary fibrous tumor, dedifferentiated. Thank you, Paul.

Ondřej Hes – Very nice case. We have recently encountered malignant SFT of the kidney (sent for second opinion from the USA). I was not entirely happy with STAT6 reactivity. It was positive, but immunoreactivity was not superb. Our patient also had metastases in liver..... Areas with relative bland spindle cells and areas with hyperchromatic atypical cells, occasionally with bizarre morphology were also seen in this case.

Thomas Krausz – Agree with diagnosis, though on the basis of dispersed distribution of the bizarre cells and mitotic activity I was also thinking about the possibility symplastic change.

Thomas Mentzel – Irrespective of if we call the lesion dedifferentiated SFT or malignant SFT with low- and high-grade areas, it's a very interesting case. I recently had an example of dedifferentiated SFT that showed a sharp demarcation of both components, and whereas CD34 was negative in the high-grade component, STAT6 was positive in both components.

Markku Miettinen – Agree on malignant solitary fibrous tumor.

Fredrik Petersson - Based on my section I thought this was a leiomyosarcoma mimicking a uterine-type "symplastic" leiomyoma. Agree with malignancy and IHC findings certainly consistent with malignant SFT (which apparently can look anyway it wants). Thanks.

Brian Rubin – I'm still confused about which cases to call malignant SFT and which to call dedifferentiated SFT. I guess I would have called this malignant SFT because it lacks a heterologous element. It's confusing.

Saul Suster – Agree with the diagnosis of malignant solitary fibrous tumor. In my opinion, the term "dedifferentiated" has been much abused in pathology and is wielded by many as a gimmick or to make the case sound "more interesting".

Ady Yosepovich - Unusual, the morphology is concordant with SFT.

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

Volkan Adsay – The parasites that we saw with this pattern and distribution proved to be strongyloides stercoralis but of course it could be a variety of other types of parasites.

Abbas Agaimy – pretty case of strongyloidosis. Thanks Saul for this excellent slide, I enjoyed it much.

Phil Allen – Colonic hyperinfection with Strongyloides stercoralis. This disease occurs in tribal aborigines in Northern Australia but we do not see it in patients living in the deep South of our Continent.

David Ben-Dor – I did see this once in a stomach biopsy. I don't remember if the patient was from Latin America. The first section just grazed the worm and it was only on deepers that it came forth in all its glory.

Ira Bleiweiss – Beautiful larvae (or not so beautiful, depending on one's point of view).

Alberto Cavazza – Thanks for sharing this spectacular case. Very rare in Italy, I have seen just a few cases.

Kum Cooper – Thank you for the treat Saul. Reminds me of Africa where we saw a handful every year. How did you manage to cut so many sections from the biopsies?

Hugo Dominguez-Malagón – Hyperinfection with Strongyloides, I have seen a case associated to immune deficiency in a patient with kidney transplant.

Göran Elmberger – Thanks for broadening our minds. Surprisingly we had a case circulated as part of EQA program EQUALIS in duodenum recently here in Sweden.

Franco Fedeli - Strongyloides Stercoralis. Thank you for sharing this interesting and very educational case.

Cyril Fisher – Strongyloides, what a pretty slide, thanks Saul.

Jerónimo Forteza Vila - A beautiful and spectacular case.

Maria Pia Foschini – Thank you for sharing this case with us! Sometimes we find unusual infective disease in travelling people and it is always useful to have some experience!

Masaharu Fukunaga - I have never heard of Strongyloides stercoralis. Thank you very much for sharing a rare case.

Ondřej Hes – Fantastic!!!

Thomas Krausz – What an amazing coincidence: one of my colleagues just showed me a morphologically identical case a couple of days ago.

Thomas Mentzel – Many thanks and I´ve never seen this.

Markku Miettinen – Clearly see worms in colonic mucosa; never seen Strongyloides before.

Cesar Moran – Very nice case.

Fredrik Petersson - Helminthosis - Strongyloidiasis. We have a significant population of foreign workers in Singapore that provides interesting pathology, off and on. Strongyloidiasis is endemic in many parts of South East Asia.

Murray Resnick – Very nice case. Impressed that you were able to get 55 serial sections from a small biopsy.

Brian Rubin – My 3 year old son starting playing recently with worms in the garden while I was digging up some plants. I remember having similar experiences discovering the natural world as a small boy. Worms always seem to fascinate me until today. Thanks for sharing the worms Saul – I had not seen this before.

Paul Wakely – NIIIICE!

Ady Yosepovich - Very nice and surprising observation. Saw once a case in a patient that was on long term steroid treatment – that actually was the cause of death.