COMMENTS TO AMR SEMINAR #69

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

Phil Allen – Poorly differentiated, primary, hepatoid right adrenal cortical carcinoma. Before the days of immunohistochemistry. Thanks for the encyclopedic discussion and references.

David Ben-Dor - Totally weird and crazy case, lots of twists and turns with an unexpected ending. This could even be made into a movie! It shows that a diagnostic pathologist must be endowed with a great deal of patience in order not to jump to conclusions based on initial impressions. As I'm in the midst of preparing my cases for the meeting in Poland, my bias was towards epithelioid angiosarcoma- why not? Large very atypical cells, big nucleoli, cracks containing erythrocytes? But on more careful examination- the cells do look like they're forming nests and acini with lumens. But that would lead one to suspect a primary hepatocellular or at least hepatoid tumor. I admit that in scanning the history I picked up the mention of the alcohol abuse and liver nodules so I was surprised to read that the conclusion was primary adrenal carcinoma. Lucky for the patient that the case fell into your hands because it would have definitely stymied a mere mortal practitioner.

Ira Bleiweiss - Agree. Poorly differentiated carcinoma.

Alberto Cavazza – Very interesting and convincing case. I have never seen a carcinoma with hepatoid differentiation in this location.

Thomas Colby - I probably would have called this adrenal cortical carcinoma (assuming there was no extra-adrenal primary) and not have picked up on the hepatoid features.

Kum Cooper - Great instructive case Abbas. Not seen hepatoid carcinoma in the adrenal gland. My experience is confined to the ovary, fallopian tube, pancreas and stomach. Thanks for explaining the role of arginase-1/Hepar-1 in the distinction between HCC and hepatoid carcinoma

Hugo Dominguez-Malagón – Metastatic hepatocellular carcinoma until otherwise proven, to many "non-specific signs", strong keratin positivity, bile ducts shown by CEA, hepatic differentiation, well defined nodule HMB45 negative.

Göran Elmberger – Unique and interesting case. Long-time control liver… Nothing to add.

Giovanni Falconieri - Difficult (and great) case, Abbas. Never seen hepatoid features in adrenal carcinoma. I have memories of carcinoma in adrenal gland deemed primary featuring positivity for cytokeratins indeed. Excellent discussion, by the way.

Franco Fedeli - Great case. Particularly regarding its differential diagnosis. My first impression, without the help of immunohistochemistry, was epithelioid angiosarcoma.

Jerónimo Forteza Vila - I agree with this diagnosis of hepatoid carcinoma. Primary adrenal origin is very unusual but other possibilities have been ruled out at the moment. Considering that hepatoid differentiation suggests an endodermal lineage, the metastatic nature of the tumor from other endodermal epithelia such as NSCLC should be considered under the special endocrine microenvironment of the adrenal.

Maria Pia Foschini - Features consistent with hepatoid carcinoma located in the right adrenal gland. It seems that liver has no sign of tumour, although the present lesions measures 15 cm across. The surgeon should know if the liver was not involved at all. A cheap and effective marker to establish hepatoid differentiation in a tumour would be the use of in situ hybridization for albumin as shown years ago and for unknown reasons never used since (Foschini MP, Baccarini P, Dal Monte PR, Sinard J, Eusebi V, Rosai J. Albumin gene expression in adenocarcinoma with hepatoid differentiation. Virchows Archiv 1998;433(6):537-541).

Masaharu Fukunaga - Thank you very much for the beautiful case and discussion of this type of tumor, Abbas. I have some cases of hepatoid gastric and tubal carcinomas, in which other type of carcinoma were observed.

Ondřej Hes – Dear Abbas, this is a great case. I came across a strange case in 2012 somehow similar to this one. 57-year-old male with generalized tumor in adrenals, liver, lymph nodes and spine. I have material from vertebra. I was not able to resolve the origin (liver vs adrenal). Immunohistochemistry was negative for HSA, S100, Melan A, OSCAR, TTF1. Positive reactions were obtained with glypican 3 and focally for AE1-AE3. Unfortunately IHC was suboptimal thanks to decalcification procedure.

Thomas Krausz – Before reading the excellent discussion my differential also included proximal-type epithelioid sarcoma (in the last few years I had opportunity to see one primarily in the adrenal and also one in the kidney; both with INI1 loss). After reading the immunoprofile, of course, this possibility was excluded. The canalicular CEA positivity is convincing. Whether this is a primary hepatoid carcinoma of the adrenal or a metastatic poorly differentiated hepatocellular carcinoma from an occult primary or even direct invasion to the adrenal from the liver primary is difficult to establish. The provided imaging information is against this. Recently we had an autopsy case of poorly differentiated hepatocellular carcinoma of the liver (histologically very similar to the submitted case) with bulky metastases to the kidney and to the right side of the heart, which mimicked primary renal cell carcinoma with metastases to liver and heart. The immunoprofile (including arginase) was typical for hepatocellular carcinoma.

Janez Lamovec – On H&E this tumor really looks hepatoid, focally rhabdoid. I also thought of epithelioid angiosarcoma before I read the text. I believe that in such cases clinicopathologic correlation is of utmost importance.

Thomas Mentzel – A very difficult case; given the strong expression of HepPar-1 by the neoplastic cells the interpretation of a metastasis cannot be excluded.

Markku Miettinen – Poorly differentiated carcinoma with a solid pattern and rhabdoid features. You would think it is likely primary as the tumor is very large, with no evidence for hepatic or other carcinoma. Agree that it is hepatoid by markers.

Delia Perez Montiel - It is a very interesting case and I agree that it is a diagnosis of exclusion, mainly because the markers of hepatoid differentiation are not so specific in this morphology.

Kyle Perry - I've personally never come across anything like this in the adrenal gland.

Fredrik Petersson - High-grade malignant epithelioid tumor. Vacuoles? lumen formation. Broad range of differential. Carcinoma; adrenocortical, HCC – hepatoid ca, Renal; medullary? urothelial? Non-epithelial - Epithelioid AS, ES-PT, Epitheliod LS?? Requires IHC. Given the results of your IHC, I completely agree: Hepatoid carcinoma. Brief succinct discussion.

Santiago Ramón y Cajal - Hepatoid carcinoma. Agree with the discussion

Juan Rosai – Very erudite discussion of a vanishingly rare entity. I would go along the contributor diagnosis of pleomorphic adrenal cortical carcinoma with hepatoid differentiation, supported in part by the immunoprofile.

Brian Rubin – Histologically, looks like a poorly differentiated carcinoma and given the rare presence of very large neoplastic cells, I thought it might be an adrenocortical carcinoma. The IHC profile supports the diagnosis of hepatoid carcinoma. Great discussion!

Manuel Sobrinho-Simões - We have never seen such a case in the adrenal gland.

Paul Wakely – I agree Abbas that this is an undifferentiated large cell carcinoma, which by exclusion represents adrenal cortical carcinoma due to your extensive work-up ruling out other possibilities. I was not that impressed by it being that hepatoid.

Ady Yosepovich - hepatoid carcinoma – very unusual variant, morphologically I thought it was melanoma. Thank you for this exceptional case

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

Abbas Agaimy – Pretty and very rare example of monophasic SS of pericardium highlighting the limited value of EMA/CK in some cases, pretty FISH image, thanks Gerald for sharing.

Phil Allen – Monophasic synovial sarcoma of the pericardium. I do not think I have seen one of these in the pericardium before but I have seen a few in the pleura. Plentiful mast cells, which are not obvious in this case, are a helpful pointer to the diagnosis when they are present. Biphasic synovial sarcoma is easier to recognize than the monophasic variant, which could account for biphasic tumors appearing to be more common.

David Ben-Dor - Nice herringbone pattern. Would this term make sense to a younger generation of physicians less likely to wear expensive suits?

Ira Bleiweiss - Agree. Wow.

Alberto Cavazza – I agree, an unusual location for this tumor (one of the few soft tissue sarcomas I tend to recognize!).

Thomas Colby - Agree with diagnosis of monophasic synovial sarcoma. Very unusual location.

Kum Cooper - Thanks Gerry. TLE-1 is also a useful screening marker for synovial sarcoma.

Hugo Dominguez-Malagón – Nice case of pericardial monophasic SS, we are preparing an article on visceral SS including two located in the heart, the most useful clues found are: a compact spindle cell tumor, hemangiopericitomatous pattern, positivity for Bcl2, CD56, CD99 and TLE-1

Göran Elmberger – Interesting case. At least in the WHO. Vimentin only. Usually positive for pan CK, CK7, CK8 but not so often CK5. Also EMA, CD99 and TLE1 could be more sensitive markers but with positive FISH I have no doubts.

Giovanni Falconieri - I fully agree with the diagnosis of monophasic synovial sarcoma, never seen primary in pericardium. Great case!

Franco Fedeli - I agree with you. This is a really unusual location for synovial sarcoma. Even though I find the evaluation of the SYT gene rearrangement a reliable approach to this diagnosis, how useful is performing immunohistochemistry for TLE1?

Jerónimo Forteza Vila - Thank you for sharing this amazing case where FISH is of help for the differential diagnosis between monophasic synovial sarcoma and malignant solitary fibrous tumor. In addition, from the pathological point of view I can recall the occurrence of Kaposi Sarcoma whose onset involved pericardium.

Maria Pia Foschini - Spindle cell tumour consistent with monophasic synovial sarcoma, as confirmed by FOSG for SYT. Nevertheless, CD34 was not requested and results of STAT 6 have not been discussed. Certainly, the differential diagnosis with solitary fibrous tumour is difficult.

Masaharu Fukunaga – The location of the tumor is very rare. Thank you very much for the great case.

Thomas Krausz – I have seen primary pleural/pulmonary synovial sarcomas but not pericardial ones before. I agree with the differential diagnostic considerations, and the importance of FISH for the conclusion of synovial sarcoma.

Janez Lamovec – Unusual location of synovial sarcoma.

Thomas Mentzel – Great case, that had been called in the past a fibrosarcoma most likely. Did you stain the lesion for TLE1 also? Although it's not entirely specific it seems to be good marker for synovial sarcoma.

Markku Miettinen – Synovial sarcoma, monophasic. Clinical correlation needed to rule out metastatic origin.

Delia Perez Montiel - Typical morphology in an atypical place. Thank you.

Fredrik Petersson - Malignant spindle cell tumor. Alternating cellular and less cellular (edematous) areas. Mitotic activity is there, but not striking, relative nuclear monotony. DDX: SS, MPNST, Mal-SFT ? No impression of mesothelioma.

Santiago Ramón y Cajal – Agree.

Juan Rosai – Very typical case. I think Gary Witkin and I were the first to describe synovial sarcoma of the mediastinum. It was a classical example of a biphasic tumor, but it was difficult to rule out in those halcyon days of immunohistochemistry the alternative possibility of thymoma.

Brian Rubin – Nice case of synovial sarcoma involving the heart.

Manuel Sobrinho-Simões - Nice, well demonstrated case of monophasic synovial sarcoma

Saul Suster – Agree with monophasic synovial sarcoma. SYT FISH is always nice to have but may be overkill in some cases. A short panel of stains that includes pan-keratin, bcl-2, CD99 and EMA with negative results for other pertinent markers (such as CD34, STAT6, desmin, etc) may suffice in typical examples. Although, I must admit that we seem to be running constantly into aberrant or unexplained IHC results on all sorts of tumors, so in a case with an unusual or unexpected presentation such as this one it is certainly warranted.

Paul Wakely – Beautiful herringbone pattern in areas.

Ady Yosepovich - the HE is classic for synovial sarcoma – thank you for this case;

CASE NO. 3 CONTRIBUTED BY: Thomas Colby, M.D.

Abbas Agaimy – Spectacular case, I missed the fatty emboli until reading the case description, images are impressive. Thanks Tom for superb teaching of non-neoplastic lung pathology. Thanks for description of the osmium infiltration methods.

Phil Allen – Fatal pulmonary fat embolism in a liver and kidney transplant recipient immediately after transplantation of a donor liver with some grossly evident fatty change. Some of our surgeons insist on a pre-transplant frozen section of the donor liver but I have as much trouble as they do in guessing how much donor steatosis is too much for the transplant to proceed, particularly if they have had difficulty finding a donor. We are not allowed to play with osmium here because the fumes cause corneal opacities.

David Ben-Dor - The amount of fat which, as revealed by the special stains, totally clogs the small vessels is inversely proportional to the emptiness seen with H & E. I didn't know about the osmium technique which is useful adjunct for situations where it is necessary to look for fat when all the material was already put in formalin. I remember when I was new on the job and received a call during the evening asking me to come in to do a frozen section on a liver which was to be harvested for transplant. I didn't know what they were talking about until it was explained that the surgeon needed an evaluation of the fat content before transplantation: if on eyeballing it was totally brown he would go ahead; if it was really yellow he wouldn't continue; and if it was something in between he would need the pathologist to confirm if the fat content was below or above 75%- in the former situation the liver was considered suitable. I don't know how scientific all of this is and whether this protocol is rigorously followed all over. Given the rarity of livers offered for transplant I wondered if it wasn't worth it to give the patient a chance even if the liver was overly fatty but I never considered the possibility of massive fat emboli as so graphically demonstrated by this case.

Ira Bleiweiss - A new one for me. Thanks Tom. I think it's very easy to just skip by the lesions.

Alberto Cavazza – A spectacular case you presented in a recent seminar in Italy. I was not aware of this phenomenon before your presentation

Thomas Colby - My case. Although it is clear in the discussion, the brief history did not include the fact that the tissue on the slides is in fact the allograft liver and the patient's native lungs. It is actually quite remarkable how many

liver transplants are performed with livers that have appreciable fat and how rare the complication of pulmonary fat emboli in this setting is.

Kum Cooper - Thanks Tom. What a great case. Fat emboli from a fatty liver. Only read about it. Never seen a case. Reminds me of a case that John Chan shared many years ago with the group.

Hugo Dominguez-Malagón – Sorry I was wrong, I though the hepatic lesion was peliosis and the lung lesion bone marrow embolism.

Göran Elmberger – Wow impressive case. New to me. Open empty alveolar capillaries with erythrocyte displacement in lung HE could probably raise some suspicion but fat stain really makes the diagnosis.

Giovanni Falconieri - Weird and intriguing, Tom. I must admit that I have had to go over the slide several times in order to catch clues, and still I am not sure. Congrats for your remarkable index of suspicion.

Franco Fedeli - Thank you for sharing with us this interesting and teaching case.

Jerónimo Forteza Vila - Beautiful pathological autopsy case. Just a comment to emphasize that cardiac massage can induce artefactual fat emboli in the lungs. But, it is also true that fat liver may involve pulmonary fat embolism.

Maria Pia Foschini - Extraordinary and unique case. Tanks a lot for showing it to all the members.

Masaharu Fukunaga – What a great case! Thank you very much for the detailed information.

Thomas Krausz – Extraordinary case, highly educational both clinically and histologically.

Janez Lamovec – What an extraordinary case! On H&E optically empty vacuoles in capillaries are easily seen.

Thomas Mentzel – Many thanks Thomas for sharing this tragic case.

Markku Miettinen – Agree on fat embolization in lung and liver – but only after seeing your brilliant diagnosis. We never see these.

Fredrik Petersson - I thought this was bone marrow embolism in the lung. Wrong again.

Santiago Ramón y Cajal – Great Case!!

Juan Rosai – I pass**.**

Brian Rubin – Very interesting, sad, and weird case.

Manuel Sobrinho-Simões - We wonder about the relevance of using fat staining in the liver for the confirmation of lipopeliosis. In the lung, besides fat thrombi in capillaries, we have seen also a bone marrow thrombus.

Saul Suster – This was a really subtle pick-up – congratulations! This is the third case of fat embolization of the lung that has been circulated in the club (the two previous cases were contributed in previous seminars by John Chan and myself). But more importantly, thank you for sharing with us the osmium infiltration technique – fat is notoriously difficult to demonstrate by conventional special stains in formalin fixed tissues.

Paul Wakely – Wow! Reminds me of bone marrow emboli to the lung secondary to traumatic fracture of a long bone.

CASE NO. 4 CONTRIBUTED BY: Cyril Fisher, M.D.

Abbas Agaimy – Very rare case of salivary NMC, seems to have small and large cell variant, I got our first case (supraglottic larynx in a young adult) 2 wks ago which looked just like mall cell carcinoma and was called as such by submitting pathologist. Roddy Simpson (a head and neck pathologist) told often that this tumor is present only in

Boston, now we have some example I think in Europe as well. The NUT staining pattern is very distinctive and might be mistaken for artifact if one is unaware of it. Thanks Cyril for sharing this great case.

Phil Allen – NUT midline carcinoma of parotid gland, female age 39. I must have missed these in the past and just called them undifferentiated carcinomas. Thanks for the discussion Cyril. I hope I do not miss the next one.

David Ben-Dor - I'm familiar with the term but never saw a case. I was impressed by the florid acute inflammation even with leukocytoclasis (or leukocytoclastosis?) and equally surprised that this doesn't figure in the diagnostic criteria (interestingly, I looked at a fairly recent article on this entity (French, AJSP 8/12) who reports on 3 cases, in which two show extensive neutrophilic infiltrates). The diagnosis is clinched by the specific NUT stain but I wonder how many labs have access to this marker? French recommends having this done on all poorly differentiated sinonasal carcinomas especially in younger patients. In my examination, albeit not necessarily rigorous, I didn't see any overt squamous differentiation and though overall the tumor does have a vaguely "squamoid" look (interestingly in the French article only 1 of 3 cases showed squamous differentiation) I would consider this tumor to be a generic poorly differentiated or undifferentiated malignancy purely on histological grounds . Like in many other situations the key element here is familiarity with the entity and an appropriate index of suspicion so as not to miss the diagnosis.

Ira Bleiweiss - Hmm, being admittedly too subspecialized, I had not heard of this NUT. There are a lot of jokes coming to mind, but I'll spare the members

Alberto Cavazza – Very interesting case. I tend to think of this entity when I see poorly-differentiated carcinomas in midline locations, particularly in young people, but I missed the series in the parotid gland. In retrospect, the typical small islands of squamous differentiation are there. Interesting the note on CD34 positivity, which I ignored.

Thomas Colby - Agree with diagnosis. I am performing NUT stains more and more frequently now because I think we are just learning the spectrum of this newly-defined carcinoma. I probably would have written this case off as a somewhat peculiar squamous carcinoma in the past.

Kum Cooper - Brilliant diagnosis Cyril. The ones I have seen have been in the midline including the back (scapula). I now see the focal squamous islands. Thanks again for sharing.

Hugo Dominguez-Malagón – I missed that, No abrupt queratinization in my slide. My diagnosis was an Eskimoma (lymphoepithelial undifferentiated carcinoma) but is not supported because EBER is negative.

Göran Elmberger – Nice to see such a rare example. Basically undifferentiated cancer with a focal tendency to squamoid differentiation. This degree of granulocytic infiltration not really well described as far as I read. Usually we stress monomorphic nuclear features (LG?) in translocation associated carcinomas but here really HG nuclei with a fair degree of polymorphism. I guess low threshold for ordering immunos and including entity in differential of poorly differentiated salivary gland tumors is only way to get diagnosis right. Agree diagnosis is potentially of great importance due to emergence of targeted therapy.. (GE)

Giovanni Falconieri - Impossible case, Cyril. Have no experience with NUT midline carcinoma. Thank you for sharing this highly educational example

Franco Fedeli - My personal experience with this tumor suggests that I could include this entity in the group of round blue cell tumor. Actually, this case shows me a different appearance of this lesion with cells with a relatively fair amount of pink cytoplasm.

Jerónimo Forteza Vila - The NUT midline carcinoma of salivary gland is an aggressive form of squamous cell carcinoma defined by the presence of acquired chromosomal rearrangements involving NUT and an anaplastic phenotypes leading to aggressive behavior and poor prognosis. Usually NUT leads to the generation of NUT fusion genes involving BRD4 and BRD3 and other uncharacterized genes. Mechanistically, BRD-NUT fusion proteins appear to act by blocking differentiation, possibly by sequestering histone acetyltransferase activity. Accordingly, histone deacetylase inhibitors or BET inhibitors, the latter of which inhibit binding of BRD-NUT proteins to chromatin, induce terminal differentiation of NMC cells. These insights provide a rationale for targeted therapy of NMC, which is almost uniformly refractory to conventional chemotherapy and radiotherapy.

Maria Pia Foschini - Interesting case of poorly differentiated squamous cell carcinoma, with focal better differentiated areas. Metastasis should be taken into consideration in the diagnostic process. Positivity for NUT is quite unusual in salivary gland tumours. This case further underlines that the NUT antibody should be applied to all poorly differentiated carcinomas of the head and neck region, to better define this, that appears to be a unique entity.

Masaharu Fukunaga – A nice case. Cyril. I have NUT-like case arising in thymus, which is negative for NUT. The patient died of disease three month after his admission.

Thomas Krausz – Diagnostically very difficult case, especially in view of the heavy inflammatory background. In any case, NUT midline carcinoma is always a diagnostic challenge for me. Once one thinks about this possibility, it is highly satisfying when the molecular comes back as positive.

Janez Lamovec – I wonder how many of previously diagnosed poorly differentiated squamous cell carcinomas in different locations were of this type of cancer. I see no end to similar molecular and genetic splitting of common or less common cancers in the future.

Thomas Mentzel – Thanks for this case in an unusual location, however, probably these neoplasms are more common than previously believed. We have seen recently a case in the skin of a South African patient as well.

Markku Miettinen – Carcinoma with squamoid features c/w nut midline carcinoma.

Delia Perez Montiel - I thought in a poorly differentiated squamous cell carcinoma.

Fredrik Petersson - Undiff ca? ALCL, pyogenic variant??? Molecular nails it. On a second look, I can appreciate the relative nuclear monotony. Could not see any minute ("metaplastic") foci of extremely well differentiated squamous foci on my section.

Santiago Ramón y Cajal - Thank you very much for sending the case!

Juan Rosai – I'll buy it as a NUT carcinoma because of the genetic findings. A feature in keeping with this diagnosis is the admixture of small undifferentiated tumor cells and foci of squamous differentiation. It still bothers me to name a tumor on the basis of non-morphologic findings.

Brian Rubin – Nice case of NUT midline carcinoma. I haven't seen a lot of cases but the two or three cases I've seen were very similar.

Manuel Sobrinho-Simões - NUT in parotid gland (quite rare).

Saul Suster – Great case Cyril. We have just ordered the antibody in our lab and will start using it routinely in poorly-differentiated carcinomas both in the thoracic cavity and in the head and neck. Because of the particularly aggressive behavior of the tumor and the dismal prognosis it is of particular importance to make this diagnosis.

Paul Wakely – Beautiful case Cyril. Appears morphologically identical to SNUC. Was not aware that such an intense neutrophilic infiltrate could accompany this neoplasm.

Ady Yosepovich - thank you for this teaching case.

CASE NO. 5 CONTRIBUTED BY: Andrew Folpe, M.D.

Abbas Agaimy – Having been interrupted by a routine case and trying to continue looking at the slides again, I have had to look again at the slide label to be sure I am looking at the AMR cases and not routine splenectomy??? very interesting case indeed, I have seen a couple of case as abdominal (peritoneal, gastric wall and perihepatic) but never extra-abdominal, thanks Andrew for this fine contribution.

Phil Allen – Left sided thoracic splenosis post gunshot wound to the spleen and diaphragm several years previously. Thanks for the contribution Andrew. I was not aware that splenosis could occur in the thorax.

David Ben-Dor – Yup, it does look like spleen. I wondered where the catch was and was relieved that sometimes what quacks like a duck is one (even if in an unexpected location- say a henhouse).

Ira Bleiweiss - Crazy case defying the notion of location, location, location.

Alberto Cavazza – Very nice case. Recently I have seen an almost identical case: after the diagnosis the patient was further investigated and he reported a trauma 40 years previously.

Thomas Colby - Agree with diagnosis. Without any history, I thought this was spleen and was having trouble finding the subtle lesions that I was obviously missing.

Kum Cooper - I thought I had the wrong slide Andrew. LOL. Nope not pedestrian at all! Thanks.

Hugo Dominguez-Malagón – Thoracic splenosis, nice case. I have seen abdominal but never before thoracic location.

Göran Elmberger – On the contrary great case! Perfect histology for spleen! We have restrictive gun laws and strong speed enforcement so rarely see this here but perhaps in future will be more common also in Sweden.

Giovanni Falconieri - Quite an educational case! Never seen this before but I can imagine how easily this can be overlooked or misinterpreted especially if the history is not adequately addressed. Thank you for sharing this.

Franco Fedeli - I have never seen a similar lesion. Thank you for sharing with us this teaching case.

Jerónimo Forteza Vila - It is well-known that thoracic splenosis can occur from autotransplantation of splenic tissue into the left side of the chest, usually after diaphragmatic and splenic rupture after penetrating abdominal trauma. However, we cannot discard that diaphragmatic defects allowing the transmission of air and even ascites from the peritoneal to the pleural cavity can operate as shown at thoracoscopy.

Maria Pia Foschini - Thoracic splenosis subsequent to gun-shot! Interesting case, I have never seen a case like this. Traumas, such as gun-shot, can create late reactions, among which heterotopic mesenteric ossification is also comprised.

Masaharu Fukunaga – I have never seen thoracic splenosis. Thank you, Andrew.

Ondřej Hes – I have seen more than 2-3 cases during my early years in autopsy service (we had more than 1000 autopsies a year at that time). Fortunately/unfortunately, number of autopsies rapidly decreased here with new laws introduced a few years ago.

Thomas Krausz – I heard about the condition, but never seen one before. Thank you very much for submitting it.

Janez Lamovec – To me this is the most interesting case, far from being a pedestrian one. Thank you for submitting it.

Thomas Mentzel – Andrew, you are forgiven! Many thanks I`ve never seen a case of this rare lesion.

Markku Miettinen – Splenic tissue, splenosis with marginal-zone hyperplaisia of white pulp.

Delia Perez Montiel - Very nice case, I have never seen one in this location, thank you.

Fredrik Petersson - Splenosis. Got that one ☺. Dig into the history. YES! Reference: Thoracic splenosis more than 40 years after thoracoabdominal trauma. O-Yurvati AH, Thompson JB, Woods TN. J Am Osteopath Assoc. 2013 Nov;113(11):853-6

Santiago Ramón y Cajal - Esplenosis. I would be worried about the lymphoid infiltrate in a normal spleen!

Juan Rosai – Great case of splenosis. Does this phenomenon qualify as a metastasis? Think about it before saying NO WAY!

Brian Rubin – Interesting case of thoracic splenosis, something I've never seen before.

Manuel Sobrinho-Simões - Thoracic splenosis (very nice "pedestrian" case)

Saul Suster – I saw a couple of cases like this at autopsy while a resident in Israel. Posttraumatic thoracic splenosis is extremely unusual; more often intraabdominal splenosis is the one more commonly seen.

Ady Yosepovich - Very nice case, thank you.

CASE NO. 6 CONTRIBUTED BY: Ondřej Hes, M.D., Ph.D.

Abbas Agaimy – Beautiful example of PUC, vesicular counterpart of pleomorphic lobular carcinoma. given the overall appearance I would suggest to stain for neuroendocrine markers as well. Thanks Ondra.

Phil Allen – Plasmacytoid urothelial carcinoma of bladder base associated with Gleason 6 prostatic acinar adenocarcinoma. Yet another tumor I do not remember having seen before. Thanks for the contribution.

David Ben-Dor – This is another case that caused me some consternation. My first impression before reading the handout was a high grade lymphoma, maybe even anaplastic as I found a few cells which reminded me of the "hallmark" cells seen in that condition. I was surprised by the diagnosis and even double checked the slide label. In fact, I had a case of plasmacytoid carcinoma of the bladder which I even presented at our Tokyo meeting in 2014. The case was also included in the review put together by Mahul Amin and published in the AJSP of March 2009 (Nigwekar et al, 33(3) 417-424). In my case the nuclei were round and more delicate than in this case where they have coarse features, and there was always some cytoplasm even if only a small amount. In my case there were admixed spindle cells and the tumor cells were separated by edematous or myxoid stroma. Of course I'm not denying the diagnosis if the immunostains were appropriate and especially if there was a component of conventional urothelial carcinoma (in my case it was present in the initial biopsy but was not seen in the resection).

Ira Bleiweiss - Agree, but VERY plasmacytoid.

Alberto Cavazza – Nice case and discussion. I have to admit that to me the distinction between plasmacytoid and rhabdoid is not so clear. In any case this is an aggressive tumor

Thomas Colby - Agree with diagnosis. Lovely histology. Some of the tumor cells are more plasmacytoid than others.

Kum Cooper - Thank you Ondra. My DD included PUC and neuroendocrine carcinoma (large cell). Did you do SYN/chromo? I notice the CD56 was focally positive.

Hugo Dominguez-Malagón – Plasmacytoid carcinoma, nice case.

Göran Elmberger – For sure HG ca. Perhaps plasmacytoid.. No better suggestion. Mimicker.. Zukerberg! Almost like our famous FB inventor.

Giovanni Falconieri - Remarkably difficult, Ondra. Have little experience with PUC, so I may not supplement decent comments. Thank you for this contribution and the discussion.

Franco Fedeli - Interesting case. My curiosity about this lesion is to know if it fits the group of tumors with loss of expression of INI-1.

Jerónimo Forteza Vila - The plasmocytoid cells pose mainly a differential diagnosis of lymphoma and metastasic lobular carcinoma of the breast. Immunohistochemistry for cytokeratin 7 is essential for the diagnosis.
Thank you for sharing this incredible case, where this morphological variety is significant of a worst prognostic value.

Maria Pia Foschini - Poorly differentiated non-cohesive carcinoma. The neoplastic cells have a plasmacytoid appearance. Interesting discussion with the differential diagnosis with plasmacytoma.

Masaharu Fukunaga – A beautiful case of plasmacytoid urothelial carcinoma. It is very rare in Japan.

Thomas Krausz – Agree with diagnosis, though karyorrhexis in this case makes interpretation on H&E difficult. So discohesive – I am wondering whether this tumor type is deficient in e-cadherin?

Janez Lamovec – High grade carcinoma with dissociated cell growth, plasmacytoid to rhabdoid with intact superficial cell layer. The urothelial component must have been overgrown by tumor.

Thomas Mentzel – A nice case of a poorly differentiated urothelial carcinoma.

Markku Miettinen – Very poorly differentiated carcinoma. Could also call it "lymphoma-like", not very plasmacytoid in this case, perhaps still fitting under this name.

Delia Perez Montiel - Plasmocytoid urothelial carcinoma, very nice example.

Kyle Perry - Nice case, the lack of an associated in situ or conventional urothelial component impresses on how closely this carcinoma variant can mimic a true plasma cell neoplasm.

Fredrik Petersson - Aggressive urothelial carcinoma; rhabdoid/plasmacytoid. DDX aggressive hematolymphoid malignancies. INI-1 status IHC ? Morphology a bit like Abbas' SMART-B deficient carcinomas.

Santiago Ramón y Cajal – Great case!

Juan Rosai – Good case of high-grade urothelial carcinoma with plasmacytoid features (including Dutcher bodies).

Brian Rubin – I guessed lymphoma/anaplastic myeloma. Of course, carcinoma makes more sense based on the anatomic site.

Manuel Sobrinho-Simões - Carcinoma (plasmacytoid).

Saul Suster – This is a difficult diagnosis! The differential includes melanoma and embryonal rhabdomyosarcoma. Special stains are certainly helpful in this setting. The chromatin pattern in this slide resembles the spirema-type nuclei of spermatocytic seminoma. Very difficult to diagnose without the stains and an in-situ component.

Paul Wakely – This slide certainly appears very lymphomatous Ondřej.

Ady Yosepovich - Very nice example. I am acquainted with invasive lobular – breast like urothelial carcinoma.

CASE NO. 7 CONTRIBUTED BY: Jason Hornick, M.D., Ph.D.

Abbas Agaimy – Nice case of a very rare entity, diagnosable on HE if one read Jason´s AJSP paper carefully, I have one case a few yrs ago still trying to get some data about crizotinib therapy of that patient. Thanks Jason.

Phil Allen – Epithelioid inflammatory myofibroblastic sarcoma, mesentery invading small bowel, male aged 31. I am pretty sure I have not seen one of these before. I hope I would have found the references if left in my own devices.

David Ben-Dor - I recently saw a case of IMT in of all places the jaw of a young patient. Per my recollection in our case the inflammation was less abundant. My first impression of this case was that of a mostly spindle cell tumor; the rounded cells to me look more histiocytoid or even plasmacytoid. I didn't know that there is an "epithelioid" IMT variant- I guess everything comes in flavors.

Ira Bleiweiss - Agree.

Alberto Cavazza – I agree. An important diagnosis, also for the therapeutic opportunities

Thomas Colby - Agree with diagnosis. My suspicion is that in the past this might have been called inflammatory fibrosarcoma by Jeanne Meis. Obviously those in the soft tissue group would know.

Kum Cooper - Thank you Jason. We had a case earlier this year in a 21 year old that had much more neutrophils. Patient did not do well. Thank you for this case and the paper describing this entity.

Hugo Dominguez-Malagón – Epithelioid inflammatory myofibroblastic sarcoma, nice morphology.

Göran Elmberger – Beautiful beast. Amphophilic cytoplasm certainly in line with myofibroblastic phenotype. Another translocation associated sarcoma with HG nuclei albeit perhaps not so polymorphic. Only typical mitotic spindles.

Giovanni Falconieri - Beautiful case. Scattered cells with clear nuclei and prominent nucleoli, "virocytes" or "ganglion-like", may be recognized. The latter remind me of a conventional, intra-abdominal inflammatory myofibroblastic tumor seen almost 25 years ago which fooled everybody around here, being interpreted as Hodgkin lymphoma (and confirmed as such by a reputable Hemepath guru!). In that particular case Chris Fletcher, who was still at St Thomas in London, reappraised the case and rendered the correct interpretation. Thank you for this submission

Franco Fedeli - Very charming case.

Jerónimo Forteza Vila - I agree with "epithelioid inflammatory myofibroblastic sarcoma", which conveys both the malignant behavior of the tumor and it is in close relationship with inflammatory myofibroblastic tumors.
Approximately 50% of conventional inflammatory myofibroblastic tumors harbor anaplastic lymphoma kinase (ALK) gene rearrangement and most of them show diffuse cytoplasmic ALK overexpression. However, rare inflammatory myofibroblastic tumors with a distinct nuclear membrane or perinuclear pattern of ALK staining and epithelioid or round cell morphology have been reported. Because these cases pursue an aggressive clinical course, I suggest paying attention to the nuclear membrane/perinuclear immunostaining pattern for ALK. Although advances in systemic therapy of soft-tissue sarcomas have been hampered by their biologic heterogeneity, several targetable molecules have been recently validated. One example is ROS1. Interestingly, it shares about 49% sequence homology with ALK primary structure, and ALK kinase inhibitors have shown in vitro inhibitory activity against ROS1 kinase. After Crizotinib approval by FDA for the management of ALK-rearranged lung cancer, other ROS1-positive tumors may be good candidates for Crizotinib therapy. Finally, because immune suppression is also associated to the pathogenesis of these aggressive soft-tissue sarcomas, it would be helpful to assess the immunophenotype of the tumor for better understanding the contribution of an immune disfunction to the progression of this tumor.

Maria Pia Foschini - I agree with the diagnosis of epithelioid inflammatory myofibroblastic sarcoma.

Masaharu Fukunaga – Epithelioid inflammatory myofibroblastic sarcoma. Epithelioid feature seem to be less prominent for me. Thank you very much for the nice case and informative comments.

Thomas Krausz – I know this variant of IMT only from literature. What a superb example. Thank you Jason very much, for submitting it.

Janez Lamovec – Malignant myofibroblastic tumor. Very nicely presented nuclear membrane reaction for ALK.

Thomas Mentzel – Wonderful case of an epithelioid IMT; does it represent a morphological form of progression of IMT?

Markku Miettinen – Agree on epithelioid myofibroblastic sarcoma (malignant IMFT). Mitoses >10/10 HPFs.

Delia Perez Montiel - Very difficult case for me, I considered other differential diagnoses such as dendritic cell sarcoma.

Kyle Perry - Nice case and thanks for posting the IHC.

Fredrik Petersson - I was considering a follicular dendritic cell sarcoma (?IHC, EBV?). A mixture of lymphoid cells and large atypical cells, of which a good number have a spindle cell appearance (spindle cell variant of EIMS? ☺), on my section. ALK-immunoexpression convincing. Thanks for good and educational case!

Santiago Ramón y Cajal - thank you for the case. Nice picture of ALK.

Juan Rosai – Ten years ago I would have called it MFH.

Brian Rubin – Beautiful case. I've only ever seen one other case. The pattern of ALK staining by IHC is very striking.

Manuel Sobrinho-Simões - Epithelioid inflammatory sarcoma – very nice case

Saul Suster – This is a very unusual case that can be quite difficult to interpret. Being an "old timer", I recognize this as what used to be called an "inflammatory MFH" (an entity that has now completely disappeared from the literature). Conceptually I'm still having trouble understanding where this tumor falls in the menu of soft tissue lesions. The ALK positivity would seem to suggest that it is somehow related to inflammatory myofibroblastic tumor; however, ALK+ does not strictly define IMT given that they are not all positive. On the other hand, the present case is clearly a malignant neoplasm (not a pseudo-tumor) and the only point of resemblance with IMT is the presence of inflammatory infiltrate (not a very highly specific feature) and the ALK positivity. The vibes I'm getting is that this may not necessarily be related to IMT but rather represent a distinctive and unrelated type of soft tissue sarcoma that happens to be associated with this specific fusion gene translocation.

Ady Yosepovich - great teaching case, thank you for this example.

CASE NO. 8 CONTRIBUTED BY: Janez Lamovec, M.D.

Abbas Agaimy – Very nice lesion Janez, I got the myelolipoma but missed the CLL component before reading the case description.

Phil Allen – Right sided retroperitoneal myelolipoma with subclinical infiltrates of B-cell lymphoma of chronic lymphatic leukemic type. I would have been satisfied to diagnose a right sided retroperitoneal myelolipoma outside the presacral region and would not even have thought about the B-cell lymphoma colonization.

David Ben-Dor - I thought that I was looking at marrow except that there was no bone. The differential includes reactive nodules but on closer examination of this slide the nodules aren't as well defined as they look on lower power. I wonder if the hematopoietic tissue of myelolipomas is always synergized with the native marrow?

Ira Bleiweiss - Agree. Wow.

Alberto Cavazza – Very unusual and nice case. These foci of CLL, sometimes clinically incidental, can be found in many different specimens.

Thomas Colby - Agree with diagnosis. I particularly enjoyed the presence of the CLL. It turns out we have a visitor from Slovenia at the moment (Gregor Vlacic) and he knew the case well.

Kum Cooper - Thank you Janez for this educational case, I was not aware of lymphoma arising in myelolipoma.

Hugo Dominguez-Malagón – Myelolipoma with an "in situ" small lymphocyte lymphoma of no clinical significance, no leukemia developed.

Göran Elmberger – Two for one always impress me. My teacher in cytology Sixten Franzen often surprised us in FNA service picking up the second malignancy - most often being a hematolymphoid neoplasm.

Giovanni Falconieri - Nice case, Janez. I have never seen SLL associated with myelolipoma. Thank you for this contribution and the thorough case discussion

Franco Fedeli - Great case. This shows how much is common to find a CLL associated with several types of lesions.

Jerónimo Forteza Vila - Adrenal myelolipomas (AMLs) are rare benign neoplasms with varied clinical presentations that consist of mature fat interspersed with hematopoietic elements resembling bone marrow. However, the rarity of these tumors precludes any randomized study into their management. In this particular case, small lymphoid with immunophenotypic features of small lymphocytic lymphoma was detected. Whether bone marrow-derived cancer stem cells colonize the myelolipomas to generate a B-cell lymphoma or myelolipoma contains certain cancer stem cells able to transdifferentiate into the B-cell lymphoma are unknown. Fat cells in this tumor are originated from mesenchymal stem cells of adrenal stromal fat and become activated by hypoxia and mechanical stimuli at the tumor microenvironment. On the one hand, because circulating hematopoietic progenitors are frequently recruited in the inflammatory microenvironment generated by activated fat cells, the possibility that bone marrow-derived cancer stem cells colonize the myelolipomas to generate a B-cell lymphoma should be considered.

Maria Pia Foschini - Very nice myelolipoma of the retroperitoneum: I would probably have missed the B cell lymphoma.

Masaharu Fukunaga – Thank you, Janez, for the beautiful case and comments.

Ondřej Hes – Very nice case. I have just one technologic question: How did you separate infiltration by CLL-type from "natural" bone marrow elements within myelolipoma? Or clonality was just done on lymphoid tissue from myelolipoma without any micro/macrodissection? Sorry for stupid question ☺.

Thomas Krausz – Highly satisfying for a pathologist to make an additional diagnosis, CLL in this case, which is more important than the one the surgery was done for.

Thomas Mentzel – A nice case of myelolipoma, the diagnostic problem is to appreciate the small aggregates of small but atypical lymphoid cells, many thanks.

Markku Miettinen – Myelolipoma, would be hard to diagnose CLL in it – if you have CLL, your lymphoid infiltrates likely also have CLL.

Delia Perez Montiel - Myelolipoma with small B cell, Congratulations, you must have a high index of suspicion to diagnose it.

Fredrik Petersson - Extramedullary hematopoiesis and fat. Extra-adrenal myelolipoma. Never encountered before. Educational discussion.

Santiago Ramón y Cajal - Agree.

Juan Rosai – Cute combination of two hematolymphoid processes.

Brian Rubin – That's very cool. You can see the lymphoma infiltrate. I doubt I would have picked this up. Great diagnosis.

Manuel Sobrinho-Simões - Very nice case; we fully agree with the diagnosis of myelolipoma with infiltrates of small B-Cell Lymphoma of CLL type

Saul Suster – Great case – never seen this combination before. Very subtle and easy to miss!

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

CASE NO. 9 CONTRIBUTED BY: Hugo Domínguez Malagón, M.D.

Abbas Agaimy – Pretty & unusual example of EWSR1/FLI1- positive Ewing with prominent rosettes, As focal rosettes may be seen in conventional Ewings, i believe it is not a problem to see a predominance of such features in rare tumors although the biology of this particular case seems to be somewhat different from classical cases. I like the descriptive term Neuroblastoma-like Ewing. Thanks.

Phil Allen – EWS 1 positive sarcoma with an alveolar or retiform pattern. I agree that EWS 1 gene rearrangements are not diagnostically specific. The histological appearances of this case are so characteristic that it ought to be a specific entity. I do not remember having seen one like this before. The CD34 is negative but I wonder if any other endothelial markers are positive.

David Ben-Dor - The rosettes are very nice. I say "if the genes fit then diagnose it". Eventually I think that tumor diagnosis will condense around the genetic findings with morphology subsidiary especially since geneticists will want to know what mutation to treat.

Ira Bleiweiss - Agree. Very much like neuroblastoma.

Alberto Cavazza – I like the idea of Ewing, but this case is simply too difficult for me.

Thomas Colby - I like PNET with some pseudo rosettes, but in cases like this I feel lucky just to get to PNET much less all of the further subtleties.

Kum Cooper - This is a great instructive case Hugo. Thank you. I prefer pseudo rosette-forming EWS.

Göran Elmberger – Peculiar morphology. Helpful molecular studies. Challenging case and I seem to be one of few non-soft tissue specialists in the group.

Giovanni Falconieri - Impossible case and great contribution, Hugo. Have no experience with this.

Franco Fedeli - In my opinion the presence of structures resembling true Homer-Wright rosettes indicates the exact diagnosis, even in absence of ancillary techniques, however it is very important performing properly investigations in order to rule out entities in differential diagnosis, for example alveolar rhabdomyosarcoma.

Jerónimo Forteza Vila - This case is amazing. We all know that the presence of EWSR was nominated as key for Ewing sarcoma diagnosis. But nowadays is important to know that this genetic alteration (EWSR+) is becoming increasingly frequent in other soft tissue tumors. So we have changed the histopathology, as "gold standard", by the genetic pattern to be more accurate in the diagnosis. Perhaps we should consider a new "gold standard" that considers not only the histology or the genetics, but both parameters and also the treatment's response. It is important to always remember the complexity of these tumors.

Maria Pia Foschini - This is a very intriguing case. I agree with the discussion proposed. Molecular data should not have been considered the gold standard for diagnosis, without a morphological support. Many molecular alterations are shared by tumours of different origin and behaviour. One example is the EWTR6 translocation, shared by mammary, salivary gland tumours as well as soft tissue sarcomas.

Masaharu Fukunaga – Adamantinoma-like Ewing sarcoma, a beautiful case with rosettes. A papillary feature seems to be rare in conventional Ewing sarcoma. Thank you very much for the comments and detailed analyses. I reported a case of Ewing-like adamantinoma without molecular studies many years ago.

Ondřej Hes – Terrible case. I can contribute to your philosophical question: we are facing the same problems in kidney tumors. "Stable" features, like LOH 3p in "Grawitz" can be rarely found in other tumors as well as "specific" chromosomal numerical aberrations. Seems we have, with increased numbers of large scale analyses, to take results coming from genetic labs with caution in similar way, like we use IHC.

Thomas Krausz – I would probably also explore RT-PCR to pin down the partner, which would help at least in part to answer your question. On the basis of histology and the provided immuno/FISH result I would favor the PNET end of the spectrum of the Ewing family of tumors.

Janez Lamovec – It seems almost impossible, at least to me, to answer to your philosophical questions in regard to the true nature of such tumors. However, it is quite acceptable to consider your tumor as a member of the large family of Ewing sarcoma type tumors. We presented a case of adamantinoma-like Ewing sarcoma at Bratislava meeting that

was positive for CD99 and, in contrast to your case, very strongly positive for different types of cytokeratins; FISH reaction showed EWS gene rearrangement. The latter has never been observed in Ewing-like adamantinoma.

Thomas Mentzel – Indeed, an unusual papillary and pseudopapillary growth in a MPNET. In regard to the raised "philosophical question" we have both, a genotype shared by different and otherwise not related clinicopathological entities (i.e. clear cell sarcoma and angiomatoid fibrous histiocytoma) or different morphological variants of a single entity defined (also) by the genotype, and I think these examples will increase within the next years (the biological importance may be sometimes unclear).

Markku Miettinen – Consistent with Ewing sarcoma/Ewing family tumor, with PNET-like features. Fusion studies would still be useful considering EWSR1 gene rearrangements in other tumor types, although would not doubt Ewing here.

Kyle Perry - With the EWSR1 gene rearrangement, I would consider this in the Ewing sarcoma/PNET family (with an unusual neuroblastoma like morphology?). Your discussion regarding the relationship of morphology vs genotype is highly relevant. With the discovery of additional fusion genes associated with two or three distinct entities (e.g. PAX3-FOX01-Avleolar rhabdomyosarcoma or biphenotypic sinonasal sarcoma), I feel these issues will continue to arise.

Fredrik Petersson - Malignant small round blue cell tumor, discohesive, pseudo-rosettes. PNET ?

Santiago Ramón y Cajal - I think that the diagnosis of Ewing sarcoma is the first one. The translocation diagnosed by FISH with a break part probe of the gene EWS is not specific of Ewing sarcoma. EWS is involved in many others translocations.

Juan Rosai – Ewing sarcoma /PNET. The thoughtful discussion of this case supports my impression about the difficulties one can encounter when mixing morphology, genetic and molecular findings (see discussion of Case 4).

Brian Rubin – Really unusual case. The S-100 makes me wonder about myoepithelial carcinoma (my new favorite diagnosis) but if it has a FLI-1 fusion, as suspected from the IHC then I would definitely call it Ewing sarcoma.

Manuel Sobrinho-Simões - We would go for the designation of PNET with pseudo-rosettes. We would like to hear the opinion of the panel about when does the presence of EWSR alterations "gains" power for the diagnosis of malignancy?

Saul Suster – I think both from histology and the EWSR-1 study I would regard this as a PNET (better differentiated variant of Ewing sarcoma).

Paul Wakely – I think you have convincingly proven this to be a histologic subtype of Ewing sarcoma Hugo.

Ady Yosepovich - excellent presentation, thank you for this case.

CASE NO. 10 CONTRIBUTED BY: Michal Michal, M.D.

Abbas Agaimy – Pitfall and rare feature in granulosa cell tumor, I misinterpreted these cells initially as luteinized. Thanks Michal for teaching me.

Phil Allen – Adult granulosa cell tumor of the ovary with true hepatic cell differentiation. Does the Mallory's hyaline indicate a history of tippling?

David Ben-Dor – I saw the granulosa cell tumor but not the hepatoid part.

Ira Bleiweiss - Never seen this before.

Alberto Cavazza – I heard about this spectacular tumor, but I have never seen it before. Thanks for sharing

Thomas Colby - Agree with diagnosis. Have not seen this phenomenon before. This is a lovely example.

Kum Cooper - Thank you Michal for this education. I was not aware of this phenomenon in AGCT.

Hugo Dominguez-Malagón – Extraordinary phenomenon, I thought they were Leydig cells.

Göran Elmberger – Wonderful. Is that greenish pigment bile? (GE)

Giovanni Falconieri - Difficult case, Michal. I am not sure that I have recognized the diagnostic clue, congrats to your high index of suspicion and eye sensitivity. Great contribution and thank you.

Franco Fedeli - Interesting case. Very rare differentiation in this type of tumor.

Jerónimo Forteza Vila - This interesting case also shows the specificity of the Hep Par-1 antibody as a marker of true hepatic differentiation, through its marking of the mitochondria. As should be expected, the hepatic differentiation is related with the increase of mitochondria numbers.

Maria Pia Foschini - Very nice example of granulosa cell tumour with hepatic differentiation. It would be nice to study it by ISH for albumin!

Masaharu Fukunaga – This is the first time I see granulosa cell tumor with true hepatic differentiation. Thank you very much, Michal.

Thomas Krausz – Highly educational case. Before reading the diagnosis/references I was considering luteinized stromal cells or even Leydig cells (no Reinke crystalloids though). I am just thinking how "adult" granulosa cell can differentiate on a heterologous hepatocytic way? I assume they "borrowed" the idea from Sertoli/Leydig cell tumors which can exhibit heterologous differentiation.

Janez Lamovec – Very tricky lesions. I was unaware of true hepatic differentiation in this type of tumor, so I thought of luteinized cells in granulosa cell tumor. Thank you for presenting it.

Thomas Mentzel – Given the prominent spindle cell morphology and the lack of Call-Exner bodies, I had no idea that this is a granulosa tumor.

Markku Miettinen – Granulosa cell tumor. Yes, it has hepatocyte-like component with your studies supporting hepatic differentiation.

Delia Perez Montiel - Granulosa cell tumor, I thought it only had decidual change.

Fredrik Petersson - Blew me away Michal. Cells looks like GCT, but the hepatoid, I did not get (and did not know). A big Wow!

Santiago Ramón y Cajal - nice case

Juan Rosai – Granulosa cell tumor, adult type, with foci of hepatoid differentiation. It looks like there is no end to the combinations of tumors in the gynecologic field.

Brian Rubin – That's a really amazing case.

Manuel Sobrinho-Simões - We have not seen before such a nice case of Granulosa cell tumour of the ovary with true hepatic differentiation

Saul Suster – Wow! The "hepatic" differentiation is extremely subtle and does look like stromal luteinization. It does not really resemble normal liver (i.e., no true liver plates are being formed). Could this "hepatic" differentiation actually be another example of spurious immunohistochemical results due to cross reactivity or simple switching-on of some proteins in a neoplastic cell population – after all, we really don't have any specific hepatocyte cell markers but surrogate markers that happen to stain hepatocytes. Did you try glypican-3 on these cells?

Paul Wakely – This case brings to mind many questions. Among them are: would it be legitimate to call this a teratoma? why does the hepatic tissue only occur in cell clusters rather than forming real hepatic plates and ducts? is the concept of *neometaplasia* as mentioned by Scully in that reference real?

CASE NO. 11 CONTRIBUTED BY: Michal Michal, M.D. (Case nr. M27261/13)

Abbas Agaimy – Paratesticular (Müllerian-type!) cystadenoma with ovarian stroma (synonym: MEST), uncommon lesion, thanks Michal.

Phil Allen – Cystadenoma of the testis with ovarian stroma (mixed epithelial and stromal tumor of the testis). I could not see any of the rete testis but there are few adjacent testicular tubules lined mainly by Sertoli cells.

David Ben-Dor - I wonder what the psychological repercussions are of telling a man that he has an ovarian tumor attached to his testis especially in the Donald Trump era. The pages devoted to ovarian epithelial-like tumors of the testis in the relevant AFIP fascicle (series IV #18 pp. 311- 319) don't specifically mention the presence or absence of ovarian stroma in their discussion. In this case the ovarian nature of the stroma isn't all that apparent and I wonder whether this may have been overlooked in other previously described cases. ER stain would be helpful. The suggestion that these tumors are members of the MEST family appearing in the paratestis is intriguing.

Ira Bleiweiss - Agree. Ovarian stroma seems to line cystic structures not uncommonly down in the abdomen and pelvis, so maybe not so surprising.

Alberto Cavazza – Similar to my comment on the previous case: very educational for me, because I read the paper but I have never seen a similar case before.

Thomas Colby - Agree with diagnosis. I suspect these lesions have been simply called cystadenomas in the past until we tuned in to the ovarian stroma.

Kum Cooper - I like that Michal: MEST of the testis!

Hugo Dominguez-Malagón – Cystadenoma of the paratestis, new entity to me.

Göran Elmberger – Great case and paper!

Giovanni Falconieri - Another phenomenal case. I wonder how easily the subtle "ovarian type" of stroma may be missed and just rubricated as a banal serous cyst of the cord. Thank you for this educational submission

Franco Fedeli - I have never seen a tumor like this. It makes me think about the cystic mucinous neoplasms of the pancreas with ovarian like stroma.

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

Maria Pia Foschini - Very interesting, thank you for sharing it with us.

Masaharu Fukunaga – Here, again, very rare and interesting tumor; cystadenoma of paratestis with ovarian stroma.

Thomas Krausz – This is new to me, however I agree with the message in the publication and the description of the lesion.

Janez Lamovec – Another rarity. I recognized ovarian type stroma and cystadenoma but was not aware of the entity.

Thomas Mentzel – Many thanks Michal.

Markku Miettinen – Agree on serous cystadenoma in paratestis. Some of these could be von Hippel-Lindau-associated.

Delia Perez Montiel - Fantastic case, I only have seen this tumor outside of gynecological area in posterior mediastinum. How was PAX8? and hormone receptors?

Fredrik Petersson - Mullerian type epithelium and ovarian-type stroma = Mixed epithelial and stromal tumor.I haven't regretted spending time in Plzen.

Santiago Ramón y Cajal - Great case.

Juan Rosai – Are both components of this lesion neoplastic?

Brian Rubin – I'm speechless or whatever the equivalent term is when typing. That's very interesting.

Manuel Sobrinho-Simões – Nice case.

Saul Suster – Very nice case! Very easy to miss the ovarian-type stroma – great observation!

Ady Yosepovich - Thank you for this illustrative case.

CASE NO. 12 CONTRIBUTED BY: Markku Miettinen, M.D.

Abbas Agaimy – Great case of recurrent chondroid lipoma, never seen one, thanks Markku for sharing.

Phil Allen – Recurrent chondroid lipoma, right shoulder muscle. At last a tumor that I recognize, but I have not previously seen as a recurrence. The reference to Maestro Franz Enzinger reminds me that my vocabulary is not adequate to describe those responsible for the "disestablishment" of the AFIP.

David Ben-Dor - Fixating on the smaller cells with single vacuoles might lead one to consider an endothelial tumor but the larger cells with multiple vacuoles and the scattered mature fat cells rule that out.

Ira Bleiweiss - Agree.

Alberto Cavazza – I have seen a few cases of this rare and distinctive tumor, but never a recurrent example.

Thomas Colby - Agree with diagnosis. Very instructive case for me. I have not seen this before. The surrounding skeletal muscle is well marbled as well.

Kum Cooper - Thank you Markku, I have only seen this tumor twice before.

Hugo Dominguez-Malagón – Chondroid lipoma, beautiful case.

Göran Elmberger – I like the title of original paper. Certainly a great deal of chondrocyte atypia.

Giovanni Falconieri - Nice case, Marku. I have seen another case many years ago circulating in the AMR and submitted by Phil Allen. A highly educational contribution, thank you.

Franco Fedeli - Thank you for sharing this peculiar case.

Jerónimo Forteza Vila - Thanks for sharing such an unusual case.

Maria Pia Foschini - I agree with the diagnosis. Chondroid lipoma is a rare lesion.

Masaharu Fukunaga – A great case of chondroid lipoma in the shoulder. Thank you, Tom.

Thomas Krausz – Beautiful example.

Janez Lamovec – Most characteristic example of chondroid lipoma. The adipocytic differentiation in epithelioid tumor cells is present to different degree in numerous cells.

Thomas Mentzel – A great example of chondroid lipoma! All the cases that I have seen did not recur, and this represents probably a rare event.

Delia Perez Montiel - Thank you for this nice case.

Kyle Perry - Thanks so much for submitting this case. I have been looking for one of these for years.

Fredrik Petersson - Beautiful case. Just read about. Many thanks Markku for allowing me to see a case IRL.

Santiago Ramón y Cajal - Chondroid lipoma, thank you !!

Juan Rosai – It would have fooled me into consider it a soft tissue chondrosarcoma, an impression reinforced by the recurrence.

Brian Rubin – Something I actually recognized and I agree with the suggested diagnosis. That's a beautiful and extremely rare case, even for someone who sees a lot of soft tissue tumors. Thanks Markku!

Manuel Sobrinho-Simões - Nice case

Saul Suster – Very rare tumor….and, recurrent!

Ady Yosepovich - Very nice example, thank you.

CASE NO. 13 CONTRIBUTED BY: Cesar Moran, M.D.

Abbas Agaimy – I thought of spindle cell (sclerosing!) rhabdomyosarcoma, was this true testicular or paratesticular? if true testicular, was there any spermatocytic seminoma (although age does not fit) or GCT? thanks Cesar for this unusual case and looking for other comments.

Phil Allen – What about a malignant solitary fibrous tumor, after synovial sarcoma has been worked out of the picture?

David Ben-Dor - Synovial sarcoma? Sarcomatoid something else? Where are the immunos? genetics?

Ira Bleiweiss - Sarcoma, looking a bit like leiomyosarcoma perhaps. Welcome to the club Cesar, but is this a quiz case?

Alberto Cavazza – I think this is a spindle cell tumor, not particularly aggressive-looking. Solitary fibrous tumor or schwannoma are my guesses.

Thomas Colby - Malignant spindle cell neoplasm. I would start with a small battery of immunostains to see what is positive with my initial concern being to assess the possibility of monophasic synovial sarcoma.

Kum Cooper - SFT vs SS.

Hugo Dominguez-Malagón – Looks like a solitary fibrous tumor.

Göran Elmberger – Spindle cell tumor suspicious for malignancy. Sorry need IHC before further speculation.

Giovanni Falconieri - Thank you Cesar for contributing this bonus quiz case! Sorry, have no clues whatsoever other than malignant spindle "something".

Franco Fedeli - Morphology of this lesion puts in my mind two entities in differential diagnosis: synovial sarcoma and MPNST.

Jerónimo Forteza Vila - Sometimes only with the morphology it is difficult to find a reliable diagnosis. Perhaps in this case the use of immunohistochemistry and electron microscopy could help us.

Maria Pia Foschini - My proposed diagnoses are solitary fibrous tumour versus Sertoli ell tumour.

Masaharu Fukunaga – Welcome back, Cesar. It might be SFT, atypical perineurioma, synovial sarcoma.

Ondřej Hes – I would like to know basic IHC: inhibin, OCT3/4, SALL 4, S100, beta-catenin, etc.....

Thomas Krausz – I would explore the possibility of SFT and synovial sarcoma first.

Janez Lamovec – ?Malignant SFT, ?Synovial sarcoma

Thomas Mentzel – Monophasic fibrous synovial sarcoma?

Markku Miettinen – Looks like cellular fibrothecoma-like Sertoli/stromal tumor but needs immunostains. Perhaps even has a granulosa cell component. Differential diagnosis depends on whether intra- or paratesticular. In the former case, testicular stromal/ Sertoli cell tumor is a good choice; could be (low-grade) malignant by mitotic rate and cellularity. Paratesticular possibilities include rhabdomyosarcoma with spindle cell features (does not look likely). Does not look like synovial sarcoma. Dedifferentiated liposarcoma is very unlikely at this age.

Cesar Moran – My case: This case was sent to me with the diagnosis of rhabdomyosarcoma, which I was having a problem in arriving at that particular diagnosis. I did desmin, SMA, caldesmon and MyoD1 and all were negative. Then, I did more IHC including keratin, EMA, TLE, FLI1, S-100 protein, MelanA, Inhibin, Calretinin, Keratin 5/6, keratin "Oscar", CD34, CD31,and CD99; all these stains were also negative. The only positive stain was Vimentin. At this point I do not have any specific diagnosis and essentially my diagnostic line for this case was "descriptive." The age of the patient makes me think that this is a primary testicular tumor and I did not consider metastatic disease. In addition, the patient does not have any other pertinent clinical history. Could this be a Sertoli cell tumor? In some areas it looked to me like what used to be called in the past in the ovary "arrhenoblastoma." I am not sure of the correct diagnosis and the IHC was not very helpful in this case.

Delia Perez Montiel - Solitary fibrous tumor?

Kyle Perry - YST with sarcomatoid features? Poorly differentiated sex cord stromal tumor… Would also exclude synovial sarcoma.

Fredrik Petersson - Low-grade cellular spindle cell tumour, reticular, some collagen, low mitotic activity. Difficult without immunos.

Santiago Ramón y Cajal - I would rule out synovial sarcoma and then neurofibrosarcoma, malignant solitary fibrous tumor...

Juan Rosai – Spindle cell sarcoma, rule out angiosarcoma with immuno.

Brian Rubin – I'll go with synovial sarcoma based on histological appearance and age. The less cellular areas would be unusual for MPNST, which is another possibility. Of course, it could be a weird stromal tumor of the testis but I don't recognize it as such.

Manuel Sobrinho-Simões - We would like to see the macroscopy of the specimen, in order to be sure about the location of the lesion. Considering a gonadal origin, we would favour a myoid gonadal stromal tumour (fibrotecoma group). In the DD we considered several hypotheses: solitary fibrous tumour, peripheral nerve sheath tumour and myofibroblastic tumour.

Saul Suster: Welcome back to the club, Cesar! This is a strange case. I don't think this is solitary fibrous tumor or synovial sarcoma. It looks to me more like a low-grade sex-cord stromal tumor that is primary in the testis.

Paul Wakely – Cesar, my first thought would be SFT (solitary fibrous tumor), followed by synovial sarcoma.

Ady Yosepovich - malignant spindle cell tumor – monophasic synovial sarcoma? malignant solitary fibrous tumor? germ cell – yolk sac?

CASE NO. 14 CONTRIBUTED BY: Vania Nosé, M.D., Ph.D.

Abbas Agaimy – A case of hereditary paraganglioma syndrome with bilateral neck paragangliomas, I agree with diagnosis, beautiful SDHB stain, Thanks Vania.

Phil Allen – Paraganglioma with therapeutic embolic spheres in a patient with hereditary multicentric paraganglioma-pheochromocytoma syndrome due to a mutation of the SDH gene. The family history would be of interest. Thanks for submitting this rare case.

David Ben-Dor - This is an involved topic that I'm unfamiliar with though I have previously heard about SDH deficiency in GIST and in renal carcinomas from conferences. Is it now the state of the art to test for these mutations in all cases of paraganglioma or pheochromocytoma? Or was there a specific reason to do so in this case? Are there any particular histological indications for the presence of this mutation? I see on the slide large round red-pink discs in vascular lumina- is this an artifact? Can't seem to place it.

Ira Bleiweiss - Agree.

Alberto Cavazza – Very nice case and educational discussion. Recently I have seen a case of SDH-related pheochromocytoma associated with gastric GIST.

Thomas Colby - Agree with diagnosis. The lesion appears to have been embolized preoperatively.

Kum Cooper - Thank you Vania for this lovely example and the wonderful write up explaining the SDH in PGs.

Hugo Dominguez-Malagón – Nice case of paraganglioma associated to SDH gene mutation, illustrative discussion, thank you.

Göran Elmberger – Nice case and good update. Embolization material tipped me off.

Giovanni Falconieri - Impossible case, although clues to paraganglioma may be caught on a morphologic basis. Thank you for this valuable submission

Franco Fedeli - Thank you for sharing with us such a rare case. Your comment has been fully comprehensive.

Jerónimo Forteza Vila - In this interesting case it is essential to carry out cytogenetic studies to determine the status of SDHB. We need to know its importance in familiar cases.

Maria Pia Foschini - Paraganglioma. Thank you for the interesting and detailed comments.

Masaharu Fukunaga – Thank you very much, Vania for the beautiful slide and very informative comments.

Ondřej Hes – This is great case for me. We have several SDH deficient RCC but I´ve never ever seen paraganglioma-pheochromocytoma from this setting. Thank you!

Thomas Krausz – Highly educational case. Excellent discussion.

Janez Lamovec – Bilateral paraganglioma. Instructive in-depth discussion.

Thomas Mentzel – Many thanks for the nice case and the wonderful discussion.

Markku Miettinen – Agree on paraganglioma, with embolization material. In our experience SDH-mutant tumors are not histologically distinctive so that immunostain is always needed to evaluate this, unless genetic or family data are already available.

Delia Perez Montiel - Very nice discussion.

Fredrik Petersson - Looks paraganglioma to me. Bilateral, should investigate SHD-B . Nice case.

Santiago Ramón y Cajal – Ok, agree.

Juan Rosai – Another great tumor combination. This one makes more sense histogenetically than the others.

Brian Rubin – Cool case with nice discussion of SDH-deficient paragangliomas. Why some SDH-deficient patients get paragangliomas and others get GIST or other neoplasms is still an interesting mystery.

Manuel Sobrinho-Simões - Nice case

Saul Suster – Very interesting case. Good to know that paraganglioma can also be seen in SDH-deficiency.

CASE NO. 15 CONTRIBUTED BY: Kyle Perry, M.D.

Abbas Agaimy – Rare example of biphenotypic sinonasal sarcoma, fully agree, the most paucicellular lesions might be easily overlooked as other sinonasal polyps or hamartomas. Thanks

Phil Allen – Biphenotypic sinonasal low grade sarcoma, right nasal cavity. The spindle cell component is over shadowed by the entrapped glands and could easily be missed. I fear that I would have written this off as an unusual, harmless nasal polyp.

David Ben-Dor - I must admit that upon a first superficial glance I was impressed by the glands lined by respiratory epithelium and thought of a respiratory hamartoma. In this case the spindle cell aspect is very bland. In discussing this entity Bruce Wenig describes the stroma as being "highly cellular" and in the photos he shows in his atlas (second edition, p. 178) it is more impressive and scary than in this case. I wondered where "biphenotypic" came from but apparently the first person who described it thought that it had neural and myogenic features (as per the 2012 reference). I personally never came across this entity previously.

Ira Bleiweiss - Agree.

Alberto Cavazza – Very educational example of this peculiar low-grade tumor.

Thomas Colby - Agree with diagnosis. A new lesion to me; probably one I should have known about.

Kum Cooper - Thanks Kyle for this great example. The other differential which is not often mentioned is sinonasal (cellular) schwannoma (which would be diffusely S-100 positive).

Hugo Dominguez-Malagón – Biphenotypic sinonasal sarcoma. A new one for me.

Göran Elmberger – Thanks. I appreciate one case in my collection. Unique for SN location?? Why??

Giovanni Falconieri - Another extraordinary case! Never seen this before, thank you Kyle for this submission.

Franco Fedeli - I have never seen this entity. I was wondering if a lesion with this morphological and immunohistochemical features could exist in another location.

Jerónimo Forteza Vila - A very interesting case due to the translocation with gene PAX-3. Nowadays this is a new concept that can be found in recent research literature in these types of tumors.

Maria Pia Foschini - Very interesting case. The first one I see.

Masaharu Fukunaga – Initially it seems to be low grade spindle cell tumor. Thank you very much for the excellent description of this tumor.

Thomas Krausz – Agree with diagnosis. It shows some morphologic similarity to adenosarcoma of the GYN tract and phyllodes tumor of the breast.

Janez Lamovec – I saw your case presented for another slide seminar group some time ago and recognized it and you were the first to make me aware of this entity.

Thomas Mentzel – A nice example of a recently described entity. I have only a simple question, do the spindled tumour cells stain for both S-100 and myogenic markers (seen by double staining) or do we have two cellular components as in a hybrid tumour?

Markku Miettinen – Good for the nasal biphenopypic translocation sarcoma, low grade. They seem to be usually indolent.

Delia Perez Montiel - A new entity for me. Thank you.

Fredrik Petersson - Agree, biphenotypic sinonasal sarcoma (low-grade). On low power, a bit adenosarcoma-like. Waiting for the first case with dediff/HGT.

Santiago Ramón y Cajal - Thank you for sharing the case!!

Juan Rosai – Slide missing (too bad, it sounded like a great case).

Brian Rubin – Nice example of biphenotypic sinonasal sarcoma. These are really distinctive. I keep wondering what I called them in the past - Schwannoma?

Manuel Sobrinho-Simões - Nice case.

Saul Suster – Terrific case! Thank you for sharing it! This lesion looks so bland that barring knowledge of its existence one could be tempted to call it benign! The bizarre IHC profile would be the only saving grace on working up a case like this. The PAX3 translocation is interesting and another example of "molecular promiscuity" in neoplasia.

Paul Wakely – Thank you for submitting such a nice example of this neoplasm. That staghorn vascular pattern, as you know, is too non-specific being seen also in sinonasal glomangiopericytoma as well as sinonasal SFT.

Ady Yosepovich - Very bland morphology could have missed this easily, thank you for this case

CASE NO. 16 CONTRIBUTED BY: Kyle Perry, M.D.

Abbas Agaimy – Very unusual case of myeloid sarcoma with aberrant immunophenotype, can be confusing as endothelial (epithelioid angiosarcoma), there seems to be another large cell population expressing VIII and others, possibly megakaryocyte-like lineage??? I think to think of this possibility you need the clinical history. Thanks for teaching us on this.

Phil Allen – Myeloid sarcoma, left side of scalp developing in 2015 oh 2016 after a bone marrow transplant in 2014 for acute myeloid leukaemia. It looks just like a pleomorphic undifferentiated sarcoma with monstrous cells. Without the history, I would never have thought of a myeloid malignancy. How did this patient survive the pancreatic cancer?

David Ben-Dor - Maybe this is a poor excuse but the crush artifact induced by the surgeon who took the biopsy obscures the features of the cells. The history does make life easier.

Ira Bleiweiss - Wow. Great case. So easy to confuse with other things, particularly carcinoma. I recently had a case in a breast core biopsy in a patient without clinical history. The breast core was the diagnostic tissue that led to the hematologic workup and confirmation. Just one of those things one has to think about when the case doesn't look right.

Alberto Cavazza – A very tricking tumor, with an immunophenotype which can be misleading (particularly if you do not have the clinical informations, as you said)

Thomas Colby - Agree with diagnosis. As emphasized in the discussion, if I did not know the history I am not sure I would have gotten to the correct diagnosis in this one.

Kum Cooper - Thank you Kyle for this extraordinary case. Great educational experience!

Hugo Dominguez-Malagón – Myeloid sarcoma, the time occurring has impact on prognosis, it is worse when leukemia or myeloproliferative syndrome precede.

Göran Elmberger – As stated one needs to know the history. Histology and IHC clearly full of pitfalls.

Giovanni Falconieri - Great contribution, Kyle. Agree with you that despite not impossible, myeloid sarcoma in unusual places can be quite challenging and epithelioid angiosarcoma (of which I thought initially) is definitely on top! Thank you for circulating this educational case.

Franco Fedeli - Tricky case! Particularly its immunophenotype could lead to error in absence of adequate clinical information. I have never tested ERG in acute leukemia.

Jerónimo Forteza Vila - This is a difficult case to diagnose just by the morphology. We need to include in the diagnosis the evaluation of myeloperoxidase by immunohistochemistry and the FISH study of RUNX1-RUNX1T1 t(8;21) (q21.3;q22) and BCR/ABL t(9;22) (q34;q11.2) translocations. These markers may help diagnose undifferentiated sarcomas without systemic involvement.

Maria Pia Foschini - I agree with the diagnosis of myeloid sarcoma. Thank you for the discussion pointing on the interpretation of the immunohistohemical results, especially the endothelial markers that could point toward a wrong diagnosis.

Masaharu Fukunaga – A wonderful case. It is very difficult to make a diagnosis without patient history. The immunoprofile may indicate epithelioid angiosarcoma. Thank you very much for sharing the case, Kyle.

Thomas Krausz – Very nice example. I agree, it is often a diagnostic challenge. There are scattered "rhabdoid" cells – I am just wondering whether INI1 or BRG1 were retained or not?

Janez Lamovec – This is a very pleomorphic malignant tumor and difficult to diagnose on H&E only; even the megakaryocytes are not that easily differentiated from other pleomorphic cells. In myeloid sarcomas that we see here, the pleomorphism was not so prominent and eosinophils were more numerous. However, without clinical information and immuno, this is a real diagnostic challenge.

Thomas Mentzel – A difficult case, given the cytomorphology and the expression of endothelial markers, the neoplasm can be easily mistaken for a poorly differentiated epithelioid/pleomorphic angiosarcoma (now rarely seen in this location).

Markku Miettinen – Rare example of extramedullary myeloid tumor/sarcoma with both blastic and megakaryocytic components. Certainly can be confused with a variety of sarcomas

Delia Perez Montiel - Myeloid sarcoma can be very problematic when is not in mind, this is a very good example of this.

Fredrik Petersson - Anaplastic, light microscopically undifferentiated, malignant pleomorphic tumor. IHC!!?? Wow. Thanks for this case. Immunohistological pitfall big time!

Santiago Ramón y Cajal - Nice and difficult case. Thank you

Juan Rosai – A great simulator, mainly because one does not think of it.

Brian Rubin – Great case and tricky diagnosis.

Manuel Sobrinho-Simões - Difficult case; could be confounded with anaplastic carcinoma (pancreatic origin).

Saul Suster – This is a truly difficult case and I would have never even thought of granulocytic (myeloid) sarcoma based on the histology. I have never seen this degree of nuclear pleomorphism in myeloid sarcoma. This looks more like anaplastic large cell lymphoma or pleomorphic sarcoma on H&E. The funny results on IHC are also worrisome – can we really trust the results of the myeloid-associated markers given the other spurious results in this case? I guess the only solid information we really have here for supporting the diagnosis is the history.

Paul Wakely – Beautiful example of a real diagnostic pitfall if one is unaware of the history of AML.

Ady Yosepovich - Thank you for this extraordinary case.

CASE NO. 17 CONTRIBUTED BY: Fredrik Petersson, M.D.

Abbas Agaimy – Nice example of EMC with multifocal myoepithelial overgrowth, thanks Fred, I really have enjoyed your review on HGT.

Phil Allen – Epithelial myoepithelial carcinoma with multifocal clear cell myoepithelial overgrowth, left submandibular gland. Yet another instructive case which I have not seen before. Thanks for the discussion.

David Ben-Dor - Even if not "earth shattering" (journalists use the terms "man bites dog" and "dog bites man" to categorize newsworthiness) it's a nice example of a tumor which if not very common can show up on anyone's slide tray and which it pays to be familiar with. Focally there are crowded glands without an obvious myoepithelial proliferation but elsewhere the appearance is classic. There are polypoid foci lined by 2 layers of bland cells with hypocellular fibrous and focally fibromyxoid stroma - I wonder what that's about. There is also some chronic inflammation at the periphery- TALP? Frederik's thorough and well composed presentation made me revisit the case that I previously submitted and which he referred to which brought up the slippery aspects of determining invasion in salivary gland tumors. Unfortunately, the clinicians see everything as black and white and based on the diagnosis I gave on that case (which not everyone agreed to) the possibility of radiation was considered even though whatever invasion was minimal.

Ira Bleiweiss - Agree.

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

Thomas Colby - Agree with diagnosis. I probably would have called this epithelial myoepithelial carcinoma and not have recognized the myoepithelial overgrowth.

Kum Cooper - Thanks Fred. Agree with your interpretation. Nice write up.

Hugo Dominguez-Malagón – EMC with myoepithelial overgrowth, I agree.

Göran Elmberger – Nice case and good update. Thanks Fred.

Giovanni Falconieri - A great case and in-depth discussion, Fredrik. I agree with the diagnosis. Thank you for your contribution.

Franco Fedeli - I have found this morphological appearance, in particular the areas with myoepithelial overgrowth, really challenging. I am used to recognizing this lesion on the basis of its peculiar biphasic tubular growth pattern.

Jerónimo Forteza Vila - A beautiful, spectacular and unusual case. It is difficult to recognize as a carcinoma since its myoepithelial morphology is similar to the mesenchymal-epithelial transition.

Maria Pia Foschini - I agree with the proposed diagnosis of epithelial myoepithelial carcinoma, invasive. This type of tumour is especially difficult to diagnose on incisional pre-operative biopsy.

Masaharu Fukunaga – It is very difficult to make a convincing diagnosis for me. Thank you very much the excellent comments and discussion, Fredrik.

Thomas Krausz – Great example with superb discussion. I am wondering whether one day in the future head & neck, breast, pulmonary etc. pathologists will agree to use the same terminology for this type of tumors rather than epithelial-myoepithelial or adenomyoepithelial depending what subspecialty one is practicing.

Janez Lamovec – Epithelial–myoepithelial carcinoma, very characteristic example of this tumor and a thorough discussion.

Thomas Mentzel – A great case, and I´m asking if we have comparable neoplasms in the skin, in other words a epithelial-myoepithelial carcinoma of the sweat glands.

Markku Miettinen – Agree on "biphasic" salivary gland carcinoma with a prominent myoepithelial component.

Kyle Perry - Great case.

Santiago Ramón y Cajal - Agree.

Juan Rosai – Myoepithelial cells on the run! They deserve to be called the cells of the year.

Brian Rubin – Very educational discussion and interesting case.

Manuel Sobrinho-Simões - Nice case regarding the prominent, multifocal, myoepithelial component

Ady Yosepovich - Very interesting case, thank you.

CASE NO. 18 CONTRIBUTED BY: Murray Resnick, M.D.

Abbas Agaimy – Pretty case of primary gastric Ewing, thanks.

Phil Allen – Primary high grade malignant tumor of the stomach with an EWSR1 rearrangement. I cannot see how this tumor in the stomach wall of a 63-year-old woman can be the same clinico-pathological entity as the bone and soft tissue tumors of the young. Newly evolved tests seem to be much more infectious when pathologists' diagnostic immune systems have not had sufficient time to develop enthusiasm suppressor cells.

David Ben-Dor - Prototypical blue tumor and an eye opener. My first guess was Burkitt lymphoma. I don't think that in this context I would have even think of Ewing sarcoma. Hopefully via trial and error immunohistochemistry one would eventually figure out the correct diagnosis (or at least avoid a wrong one) despite the fact that many of these markers show overlapping positivity. Regarding cross positivity of the new ES marker NKX2.2 for Merkel cell carcinoma: I once had a case of the latter which was TdT positive! Is this any relation to the relatively recent prostate marker NKX3.1?

Ira Bleiweiss - Another Wow case!

Alberto Cavazza – Thanks for the educational case, I ignored the new antibody you quoted.

Thomas Colby - Agree with diagnosis. Particularly lovely histology for what we fondly call small round blue cell tumors.

Kum Cooper - Thank you Murray for this great example. We saw a case in the small bowel earlier this year.

Hugo Dominguez-Malagón – Gastric PNET, I agree.

Göran Elmberger – Highly unusual but as far as I can judge typical case (after ancillary stains…). Thanks for sharing.

Giovanni Falconieri - Very, very difficult! Ewing? Stomach? I would never recognize it. Thank you for this educational contribution

Franco Fedeli - I do not have any experience with this marker NKX2.2

Jerónimo Forteza Vila - Is very interesting the reference to NKX2.2 that is made in this case. NKX2.2 gene is identified as a target of EWS-FLI-1 (fusion protein specific to Ewing sarcoma) and is upregulated in this disease. Not only this, but also has a very sensitivity and high specificity for Ewing sarcomas diagnosis. Could be that the "gold standard" for the diagnosis of Erwin sarcomas is not only the evaluation of the morphology or CD99 expression or EWS-FLI-1 fusion protein, but the set of this panel that currently is offered. In each case, these markers must take into account.

Maria Pia Foschini - Ewing sarcoma of the stomach. This is very unusual both for the site (stomach) and the old age of the patient. Very interesting the discussion about the new marker NKX2.

Masaharu Fukunaga – Welcome, Dr. Resnick. I agree with gastric Ewing sarcoma, a beautiful case. How about immunostaining of desmin? How do you differentiate it from intraabdominal desmoplastic round cell tumor? Thank you very much for the case and the information of NKX2.2.

Thomas Krausz – Yes, it is a diagnostic challenge with a convincing conclusion. I haven't used NKX2.2 yet, but I will.

Janez Lamovec – What a rare tumor! The story of NKX2.2 is a nice illustration of too often claimed "specificity" of this or that immune marker.

Thomas Mentzel – A wonderful example of a MPNET arising in an unusual location.

Markku Miettinen – Agree on Ewing sarcoma of stomach.

Delia Perez Montiel - I agree, my first diagnosis was neuroendocrine carcinoma.

Fredrik Petersson - Malignant small round cell tumor with abundant fibrous stroma. Initially, I thought of DSRCT. Molecular nails it.

Santiago Ramón y Cajal - Agree.

Juan Rosai – Ewing Sarcoma/PNET of stomach (the man from Istambul)!

Brian Rubin – Wow! I've never seen Ewing sarcoma as a primary tumor of the stomach and I thought the case was going to be a lymphoma. It has an unusually high level of mitotic activity for a Ewing sarcoma. However, the IHC and molecular studies certainly leave no doubt as to the diagnosis. Gorgeous NKX2.2 staining too!

Manuel Sobrinho-Simões - Nice case in a rare location.

Saul Suster – Never seen or heard of primary Ewing sarcoma of the stomach! My initial though was a desmoplastic small round cell tumor of the omentum secondarily invading the serosa of the stomach. Thank you for the nice discussion on the new antibody NKX2.2 – look forward to the papers describing it in all sorts of other unsuspected lesions……

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

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

Abbas Agaimy – Difficult to solve case, seems to have a myoepithelial-like phenotype. I too would think of OFMT as most likely, possibly metastatic, this might explain lack of bony shell!!!.

Phil Allen – Undiagnosed, histologically bland, multifocal, bilateral, endobronchial epithelioid tumor of the lung in a male aged 78. I do not think this is an ossifying fibromyxoid tumor. I fear that Saul and I are both missing the diagnosis because the histological picture is so distinctive. Perhaps Tom Colby has seen one of these before. The phyllodes growth pattern is reminiscent of a benign metastasizing leiomyoma in the lung.

David Ben-Dor - The possibility of OFMT did pop into my mind not because I'm so smart or have much experience with this entity but due to the fact that I did see a case about a year ago which I'm preparing for the upcoming meeting so at the moment I'm "minded" about it. The cells of this tumor in of themselves are hard to categorize and it helps mightily if there is bone which is not always the case. More recently this entity was found to have a gene rearrangement -PHF1-which it shares with endometrial stromal sarcoma and which might be diagnostically useful in cases without bone (Graham et al, AJSP 2013; 37: 1751-1755). Given that the patient is male the latter would not be feasible (though in this generation the definition of gender is becoming a bit elastic). Histologically the tumor has a "leaf-like" growth pattern which reminded me of phyllodes tumor but again in a man this would be a non-starter. This slide at the beginning made me think of a case presented by one of the club members of a woman who presented with multiple pulmonary spindle cell nodules with a remote history of granulosa cell tumor of the ovary which was only revealed after much ado. Besides the gender there are no coffee bean nuclei in this tumor.

Ira Bleiweiss - Low grade for sure. I'm not sure of the diagnosis.

Alberto Cavazza – I do not know what this is. Because it is so unusual, and because it may be bilateral, my first guess is a metastasis from an occult low-grade sarcoma, maybe ossifying fibromyxoid sarcoma as you suggest (I like your idea). I would accept this tumor as a primary low-grade sarcoma (maybe ossifying fibromyxoid sarcoma, as I said) only after a metastasis has been carefully excluded. I am very curious to know the follow-up and the opinion of the other experts

Thomas Colby - Low-grade, likely mesenchymal or melanocytic neoplasm, with interstitial growth. I agree that this is not a hamartoma. This looks like a metastatic low-grade neoplasm with interstitial growth and the immunophenotype might raise the possibility of a peculiar melanocytic lesion or peripheral nerve tumor that may very well be occult.

Kum Cooper - Thanks Saul for sharing this case. I have nothing intelligent to add. This is what the Italians call an "*impossible*" case!

Hugo Dominguez-Malagón – I do not remember seeing anything like this, phyllodes-like, could be myoepithelial cells?

Göran Elmberger – I have no personal experience with OFMT but literature review suggests INI mosaic stain and PHF-1 rearrangements as diagnostic tools. Bilateral nodules and growth pattern in lung is suggestive of metastases and this could off course still be due to occult OFMT. However, only from morphological perspective I do not feel convinced this is a manifestation of OFMT so probably also other low-grade sarcomas or "benign metastasizing" tumors should be searched for. IHC could also indicate PNST or melanoma… More antibodies…

Giovanni Falconieri - Challenging case, Saul. I would also give top consideration to a metastatic mesenchymal tumor although I would likely apply a more comprehensive cytokeratin cocktail if not done yet.

Franco Fedeli - Could be useful to perform MUC4 in order to exclude a weird form of epithelioid fibrosarcoma/low grade fibromyxoid sarcoma?

Jerónimo Forteza Vila - I had never seen before a similar case in lung. I favor -but with all caution- a lung primitive tumor, although the ossifying fibromyxoid tumor is rare in lung. We must be aware that the radiological pattern is not

the typical associated with metastasis. The tumor shows low grade proliferation, according to the positivity of MIB-1 (10% of nuclear which is rare in a metastasis). Thank you for sharing this interesting case.

Maria Pia Foschini - I do not know what this lesion is. I would favor a low grade sarcoma. Some cells look like oncocytes.

Masaharu Fukunaga – It is a challenging and interested case. My impression without history was PEComa, but this tumor is negative for melanoma cocktail. Ossifying fibromyxoid tumor, non-ossifying type is a good idea. I prefer soft tissue origin and multiple lung metastases.

Ondřej Hes – Dear Saul, of course, never seen such a case....Just, knowing it is something weird, I would try CD117.....there are some features with a vague touch of GIST and another tumor, which I always miss on first turn is PECOMa.....so, HMB45. However, I believe, both markers will be negative..... and the tumor will turn to be something else ☺

Thomas Krausz – Not sure either, but I would consider the possibility of metastatic malignant glomus tumor in view of the sharp cell borders (provided that the cells are "enveloped" by basal lamina, collagen IV/laminin) and expression of SMA.

Janez Lamovec – Saul, you might be right but I don't know how to call this tumor. Here we thought of meningioma but EMA is negative, even of metastasizing prostatic stromal sarcoma. Finally, morphologic description with added NOS would also be my option.

Thomas Mentzel – It looks distinct but I don´t know what it could be. For me the diagnosis of OFMT is rather unlikely.

Markku Miettinen – Likely metastatic sarcoma, considering low-grade fibromyxoid sarcoma (LGFMS). It can have a very epithelioid pattern in metastases. MUC4 immunostain and FUS-gene rearrangement or gene fusion studies could be useful. I have seen a case of LGFMS with 11 thoracotomies for bilateral metastases over 25 year-period before a retroperitoneal primary tumor was found.

Delia Perez Montiel - Maybe an endometrial stromal sarcoma with epitheliod cells?

Kyle Perry - OFMT was one of the first things to come to mind (could be interesting to fish for PHF1). The perivascular whirling is odd (not sure if I've ever noticed that in an OFMT). Morphology doesn't look great for a sclerosing epithelioid fibrosarcoma.

Fredrik Petersson - Monotonous low-grade mesendchymal neoplasm, possibly multifocal. Mets from unknown primary need to be considered/excluded. Bx from another pulmonary lesion would be helpful. Although not typical for EBV-SMT, would consider; ?immunocompromised. A bit glomoid?? IHC and morphology for sure raise the possibility of OFMT, which may be very minimally myxoid and a good proportion of cases do not form bone. I am (also) very interested in the members' views.

Santiago Ramón y Cajal - I do not know either. After ruling out Pecomas, SFT…I believe that your diagnosis can be right.

Juan Rosai – Low grade fibromyxoid tumor, rule out metastasis.

Brian Rubin – Hmmmm. I've never seen OFMT metastasize to lung or seen a lung case. Could it be a myoepithelial neoplasm? Did you do any cytokeratin IHC? I only see a negative EMA. I wonder about myoepithelial tumor, possibly low-grade myoepithelial carcinoma.

Manuel Sobrinho-Simões - We were not able to go further than you on this "Low-grade epithelioid neoplasm"

Saul Suster – This was my case; I still don't know what it is. I followed up on all of your suggestions for additional stains – we have now done cytokeratin AE1/AE3, SMA, HMB45, CD117 and MUC4 – all of these were negative. We do not currently have the PHF-1 probe in our lab. No history of tumor elsewhere has been forthcoming so far, but I agree with those who felt the tumor is more likely metastatic due to the multifocality. If I hear any additional history I will be happy to share it with you. In the meanwhile, if you see a case like this, please let me know. To be continued……

Paul Wakely – This tumor reminds me of adenofibromas of the GYN tract.

CASE NO. 20 CONTRIBUTED BY: Ady Yosepovich, M.D.

Abbas Agaimy – I too would call this cystic hypersecretary lesion with flat or flat-papillary low-grade DCIS. I find the uniform atypia throughout and the tufting not going with hyperplasia.

Phil Allen – Micro-papillary duct carcinoma in situ, left breast. There is not much tumor in my slides but the photomicrographs are convincing. I agree that this patient should be treated as for a ductal carcinoma in situ.

David Ben-Dor - I think that in the micropapillary proliferative areas it's justifiable to consider this atypical and the question is whether it's necessarily DCIS or if one can get away with atypical hyperplasia. It's very low grade and if the only treatment in both cases would be preventative hormonal (since the lumpectomy was already done) I don't know what difference it would make (except that clinicians and patients like everything to be black and white even if they don't understand what you're talking about). There are a number of dilated spaces lined by flattened cuboidal cells which no matter how hard I try I can't qualify them as atypical. Then there are foci in which the cells become columnar but not necessarily atypical, and also places where there are a few layers of atypical cells not forming micropapillae. So maybe this case fits into the flat atypia/columnar epithelium spectrum.

Ira Bleiweiss - Based on the slide I would not go beyond cystic hypersecretory hyperplasia. I don't see the right pattern or enough cytologic atypia for DCIS. On the other hand the photos you sent look a bit worse from a cytologic point of view. I still think the micropapillae have an underlying florid duct hyperplasia pattern of proliferation. I don't see the usual almost "naked nuclei" type cells with finely vacuolated or bubbly cytoplasm lining the cystic areas in a single layer. A tough case, but I'd leave it as atypical.

Alberto Cavazza – A difficult case for me, but like you I think this is a cystic hypersecretory lesion with foci of micropapillary in situ ductal carcinoma. I am not an expert, so I asked for the opinion of Dr. Moira Ragazzi, one of my colleagues with an interest in breast pathology, and she agreed with this interpretation

Thomas Colby - I would agree with low-grade DCIS with prominent hypersecretory features. Given the extensive changes, I would rather error on the side of over-calling atypical hyperplasia in this case. I think lumpectomy with negative margins is the right way to go with this lesion.

Kum Cooper - Thank you Ady. I agree with cystic hypersecretory micropapillary DCIS.

Hugo Dominguez-Malagón – Cystic hypersecretory DCIS.

Göran Elmberger – I agree. DCIS high nuclear grade micropapillary and clinging type.

Giovanni Falconieri - Excellent case, Ady! Love it and your discussion as well. I fully agree with your assessment; I would just add Rosen's juvenile papillomatosis to the differential in light of the remarkable "swiss cheese" low power appearance (and grossly evident as your description implies). By the way, sometimes JP may harbor foci of ductal epithelial proliferation attaining DCIS

Franco Fedeli - I agree with you.

Jerónimo Forteza Vila - I agree with the diagnosis of a cystic hypersecretory lesion with small areas of micropapillary DCIS.

Maria Pia Foschini - Typical case of cystic hypersecretory carcinoma \ micropapillary carcinoma as seen in the present case.

Masaharu Fukunaga – I am not breast pathologist however; I would call it intraductal carcinoma.
This is the first time I see this hypersecretory breast lesion. Thank you very much, Ady.

Ondřej Hes – I would also vote for micropapillary DCIS.

Thomas Krausz – Very little micropapillary proliferation is present on my slide. Combined with the additional pictures I also favor micropapillary DCIS. However before concluding, I would do immunostain for cytokeratin 5/14 in order to determine whether the micropapillarity is purely luminal/clonal or mixed.

Janez Lamovec – I would call this lesion a cystic hypersecretory hyperplasia with foci of cystic hypersecretory carcinoma. I believe that hyperchromatic and atypical nuclei are just too many in too many ducts to call this only hyperplasia or atypical hyperplasia.

Thomas Mentzel – I think the given diagnosis of a multicystic breast lesion with small foci of micro papillary DCIS is very good.

Markku Miettinen – Cystadenoma of breast with atypical features, favor borderline atypical ductal hyperplasia over low-grade DCIS.

Delia Perez Montiel - Micropapillary DCIS.

Fredrik Petersson - Secretory carcinoma in-situ ? Mammaglobin? ETV6-rearrangement?

Santiago Ramón y Cajal - Agree with cystic hyper secretory lesion. The atypical epithelial proliferation for us is consistent with micropapillary DCIS.

Brian Rubin – I'm the wrong guy to comment on this since I don't look at epithelial breast lesions any more but your description is accurate.

Manuel Sobrinho-Simões - Our breast pathologist was not convinced about the malignancy of the lesion and would suggest IHC (CK5) for the DD.

Saul Suster – I agree there are foci of micropapillary DCIS.

Paul Wakely – I haven't done breast pathology in some time, but it looks like cystic hypersecretory carcinoma.

CASE NO. 21 CONTRIBUTED BY: Ady Yosepovich, M.D.

Abbas Agaimy – Possibly encapsulated solid papillary, small ducts likely reactive or misplaced or residual after prior core??? I do not think there is invasive growth. Thank Ady for sharing these tough but beautiful cases. ER pattern is quite strange.

Phil Allen – Intracystic breast carcinoma with seeding of the tumor along the core biopsy needle tract. I would stick with the Tru-Cut biopsy diagnosis of carcinoma.

David Ben-Dor - I certainly feel your pain on this. Concerning the intracystic lesion: histologically there is a monomorphic proliferation which looks like carcinoma in situ arising in a papilloma. According to the p63 and calponin stains there are no myoepithelial cells anywhere which is consistent with an atypical proliferative lesion/ carcinoma (in situ) but the CK5/6 stain looks strongly positive. I'm not sure what the significance of this is: maybe there are myoepithelial cells so this could be usual hyperplasia or else this is a proliferation of basal type epithelial cells such as seen in triple neg. carcinoma, but this doesn't make any sense. The ER shows spotty not diffuse positivity also expected in hyperplasia. So is this a florid hyperplasia? – the monomorphic cells do seem a bit delicate for malignancy. Then there are the small acini scattered outside the cystic lesion. These are again positive for CK5/6 and negative for other myoepithelial markers. I'm not sure what the significance of the former could be except for showing that these acini are composed of the same cell type which is proliferating in the cystic lesion. These small acini are limited to granulation tissue which is presumably secondary to the needle biopsy. I don't see any of them invading outside the granulation tissue into normal parenchyma which would clinch the diagnosis of malignancy. Inside the granulation tissue there are also a few necrotic fat cells and cholesterol clefts associated with the small ducts. The small acini don't show the unequivocal atypia that you would want to see before diagnosing malignancy in an equivocal circumstance. Page 670,

Fig 1 of "Diagnostic Pathology of the Breast" ed. Hicks and Lester (Elsevier, 2016) shows an image with the caption "epithelial displacement in core needle biopsy site" very similar if not identical to this case, though the depicted displaced epithelium is acinar and we don't know what the previously biopsied lesion looked like. However, the authors sound categorical about interpreting epithelium in damaged tissue following a biopsy as resulting from displacement. This may be grasping for straws but it would be interesting to try a basement membrane stain.

Ira Bleiweiss - Intraductal carcinoma (solid, grade II), involving intraductal papilloma. I don't think this is invasive. In the context of such lesions, I prefer to see tumor cells directly invading adipose tissue and/or breast tissue clearly beyond the confines of the lesion. I regard most other areas as the lesion sclerosing upon itself, regardless of p63 staining or lack thereof. I agree with you that the epithelial nests on your photos (not on my slide) are iatrogenic displacement due to the core biopsy (typically happens with papillary lesions). The cells appear to be in granulation tissue. In terms of DCIS versus florid duct hyperplasia in the papilloma, I try to take the proliferation out of the papilloma and ask myself what I would call it in a regular duct. If the answer is DCIS, that's what I diagnose, and that's what I think in this case.

Alberto Cavazza – The papillary lesion is quite marginally represented in the slide I received. Considering also the immunostains I tend to favour a papilloma with florid hyperplasia, and like you I think the small tubular structures are misplaced due to the previous biopsy.

Thomas Colby - I vote for papilloma or at most atypical papilloma. Our breast pathologist agrees with that.

Kum Cooper - Papillary carcinoma with epithelial displacement.

Hugo Dominguez-Malagón – Intracystic papilloma, atypical, I go benign.

Göran Elmberger – Intraductal carcinoma with biopsy site implantation artifacts. Could be solid papillary carcinoma that usually does not reveal peripheral basal cell staining. Thus implants could not be expected to reveal basal rim. Scar tissue rather typical.

Giovanni Falconieri - Very difficult, Ady. Again, I may not be of great help yet I agree with your assessment and stay over the conservative side as long as convincing areas of unquestionable IDC are recognized.

Franco Fedeli - My attention was captured by the small gland proliferation and in this regard a peculiar microglandular adenosis has been my first impression.

Jerónimo Forteza Vila - Perhaps we do not have other option to handle the case, only allow it to evolve with a very narrow follow up and repeat the biopsy. From my point of view it seems to be a papilloma with florid ductal hyperplasia, not a malignant neoplasia.

Maria Pia Foschini - Solid papillary and frank papillations present in the tumour. Nuclei are clear, some grooving is present. No myoepithelial cells are visible. It resembles the breast tumour resembling the tall cell variant of papillary thyroid carcinoma, described by Eusebi V. et al. Am J Surg Pathol 2003;27(8):1114-8.

Masaharu Fukunaga – I would call it intracystic papillary carcinoma.

Thomas Krausz – I favor intraductal papillary carcinoma, solid variant. Some of these may show a degree of neuroendocrine differentiation. I agree that the background epithelial nests are benign and represent "displacement".

Janez Lamovec – I would call this lesion a papilloma (I wonder whether p63 reaction is O.K. comparing it with CK5/6) and consider epithelial nests in the scar as displacement phenomenon.

Thomas Mentzel – The intraductal lesion looks like an atypical papillary neoplasm but the nature of the small epithelial islands is obscure.

Markku Miettinen – Favor fibrocystic disease with atypical intraductal (myoepithelial?) proliferation. The slide did not contain distinctly bad-looking areas.

Delia Perez Montiel - I favor benign, Intacystic atypical papilloma.

Fredrik Petersson - Could this be a papilloma with "myoepithelial overgrowth". This is supported by CK5/5 positivity and the patchy ER expression, but not the negative p63 stain. Can myoepithelial cell loose the p63 expression ? I concur with the misplacement of the epithelial nests. Ira, what's your take ?

Santiago Ramón y Cajal - We are not convinced that the epithelial component is malignant, looks like myoepithelial cells.

Juan Rosai – Cystic hypersecretory in situ ductal carcinoma (according to Rosen).

Brian Rubin – I'll leave this one for others to comment on. I'm not qualified to say something intelligent about it.

Manuel Sobrinho-Simões - Our breast pathologist thought the papillary lesion is benign and the nests represent epithelial displacement.

Saul Suster – I favor this is solid papillary carcinoma, non-invasive.

Paul Wakely – Could those nest represent some form of microglandular adenosis?

QUIZ CASE NO. 1 CONTRIBUTED BY: Thomas Colby, M.D.

Abbas Agaimy – I believe this is most likely atypical myocobacteriosis (MAI???) in HIV setting. I could not see or suspect any foci of Kaposi. Thanks Tom.

Phil Allen – Looks like necrotising pneumocystis pneumonia with cyst formation complicated by a pneurothorax in an HIV positive patient. What have I missed?

David Ben-Dor - there is a lot of frothy material and with close examination I can make out many small greyish dots. In principle you can't document pneumocystis cyst walls without silver stain but you can make out the protozoa. Interesting to learn eventually what the special stains show. I think there are a few dilated bronchi but I can't make out alveolar parenchyma.

Alberto Cavazza – You presented this spectacular case at a recent meeting in Italy. Just to prove that I was not sleeping: invasive pneumocystis with cavity formations and secondary pneumothorax! I remember you said there was also an atypical lymphoid infiltrate, which is present but quite focal in my slide.

Kum Cooper - Pneumocystis and MAI.

Hugo Dominguez-Malagón – Pneumocystis carinii pneumonia with xantogranulomatous reaction.

Göran Elmberger – One suspects infectious disease and there is sub mesothelial but also intraalveolar granular eosinophilic deposits where one could imagine microorganisms like toxo. Special stains should be performed as well as microbiological work-up. Other causes might be aerosolidized pentamidine deposition or other iatrogenic cause.

Giovanni Falconieri - Difficult Tom, have no clue. I just recognize PCP in subpleural lung, but I am sure that I am missing the point

Franco Fedeli - Presence of groups of histiocytes, plasma cells and lymphocytes make me think about atypical mycobacteriosis, especially in a HIV patient.

Masaharu Fukunaga – Granulomatous infectious lung disease with HIV infection, I can not specify it.

Janez Lamovec – ?Pneumocystosis.

Markku Miettinen – Inflammatory, likely infectious process with granulomatous features. Would need special stains for pneumocystis, fungi, and AFB.

Kyle Perry – PJP.

Delia Perez Montiel - Pneumocystis carinii pneumonia.

Fredrik Petersson - Pneumocystis with pneumothorax, why not ? Apparently not that unusual in HIV patients.

Santiago Ramón y Cajal - We are missing other microorganisms!

Brian Rubin – Looks inflammatory and histiocytic so I'd guess it must be some sort of infection, possibly pneumocystis since the patient is HIV-positive.

Manuel Sobrinho-Simões - No evidence of cancer. We would consider infection by *Pneumocystis (*and *Mycobacteria?)*

Paul Wakely – Certainly looks like it could be pneumocystis along with some histiocytic proliferative lesion, but I'm sure you have some wild & wonderful diagnosis for us.

Thomas Colby - My case. The reason I shared this case is to show an unusual example of **invasive Pneumocystis** which is associated with tissue destruction and pneumothorax. One can see the invasive Pneumocystis in the interstitium and in the pleura and alveolar walls. There is some involvement of vessels. This case, however, was more complicated than simply being an unusual Pneumocystis case. There are a large number of histiocytic somewhat granulomatous infiltrates that I think are probably a reaction to the Pneumocystis. In addition, some of the sections show plasmacytic infiltrates and this patient turned out to have a bi-clonal process with clusters of kappa-positive plasma cells in some regions and lambda-positive plasma cells in others and finally there was a third region where there was a proliferation of large lymphoid cells that were B cells that were positive for EBER and out hematopathology people thought this was a polymorphous EBV-associated lymphoproliferation occurring in the setting of AIDS.

QUIZ CASE NO. 2 CONTRIBUTED BY: Saul Suster, M.D.

Abbas Agaimy – Beautiful something with impressive amianthoid fibers. Based on site, I would think of unusual looking SFT as well given the unusual site for palisaded myofibroblastoma. betacatenin??? STAT6?

Phil Allen – Could this be an orbital solitary fibrous tumor with amianthoid fibers?

Alberto Cavazza – I think this is a low-grade spindle cell tumor, and much more than this I cannot say. A mammary-type myofibroblastoma is my first guess. A peculiar solitary fibrous tumor may be an alternative, but I am waiting for your diagnosis.

Thomas Colby - Amianthoidicus fibricus maximus. I am guessing palisaded myofibroblastoma in an unusual location but the cytology of the spindle cells bothers me a little bit (but cytology of spindle cells has always bothered me and that is one of the many reasons I am not a soft tissue pathologist).

Kum Cooper - DD: Sclerosing PECOMA, myofibroblastoma (extra-mammary), meningothelial.

Hugo Dominguez-Malagón – Solitary fibrous tumor with amianthoid fibers.

Göran Elmberger – Hyalinizing spindle cell tumor with giant rosettes/LG fibromyxoid sarcoma with giant rosettes.

Giovanni Falconieri - Spindle cell (myofibroblastic) tumor with amianthoid fibers? Low grade stromal tumor? Don't know!

Franco Fedeli - My differential diagnosis includes SFT and synovial sarcoma.

Masaharu Fukunaga – Cellular angiofibroma, solitary fibrous tumor?

Janez Lamovec – ?Solitary fibrous tumor with amianthoid fibers.

Thomas Mentzel – Solitary fibrous tumor.

Markku Miettinen – Favor solitary fibrous tumor with amianthoid fibers, probably benign. In the old days these were often called "fibrous histiocytoma" of the orbit.

Delia Perez Montiel - Solitary fibrous tumor.

Kyle Perry - Meningioma of orbit? SFT?

Fredrik Petersson - Spindle cells neoplasm with sclerosis, almost collagenous pseudorosettes. Appears not very infiltrative. Myoepithelial? Sclerosing RMS ? (not very many mitotic figures though..) , funny SFT ??

Santiago Ramón y Cajal - For me it looks like a myofibroblastic tumor.

Juan Rosai – Solitary fibrous tumor. Impressive deposition in the orbit of hyaline collagen, reminiscent of the "amianthoid fibers" (only a morphologic resemblance) seen in the hemorrhagic spindle cell tumor with amianthoid fibers.

Brian Rubin – Looks like a solitary fibrous tumor. Was it positive for CD34 and/or STAT6?

Manuel Sobrinho-Simões - We would suggest solitary fibrous tumour, collagenous variant (if IHC fits). Some people considered synovial sarcoma in the DD.

Paul Wakely – Palisaded myofibroblastoma?

Saul Suster – My case: this is a peculiar **solitary fibrous tumor with abundant "amianthoid" fibers**. An identical tumor has been previously reported in the literature under the designation of "amianthioma" (Connolly CE. Crystalline collagen production by an unusual soft tissue tumor ("amianthioma"). Histopathology 5:11-20, 1981). The collagenous structures are identical to those described in intranodal hemorrhagic spindle cell tumor with amianthoid fibers/palisaded myofibroblastoma but, as previously noted in several papers, these structures are not exclusive to such tumors and can be observed in a variety of other soft tissue neoplasms. The cases in which I have encountered them most often has been in solitary fibrous tumor, and this is a nice example of such phenomenon. We described this feature in SFT many years ago with Cesar Moran in a review of solitary fibrous tumors of the pleura from the AFIP (Moran CA, Suster S, Koss MN. The spectrum of histologic growth patterns in benign and malignant fibrous tumors of the pleura. Semin Diagn Pathol 9:169-180, 1992). The present case showed strong positivity of the tumor cells for CD34, bcl-2 and STAT6. Stains for keratin, S100, EMA, SMA, desmin and calponin were negative. Parenthetically, the term "amianthoma" is derived from the ultrastructural appearance of the fibers, which are composed of abnormal collagen that resembles amyloid ("amianthos").