COMMENTS TO AMR SEMINAR #67

CASE NO. 1 – CONTRIBUTED BY ABBAS AGAIMY

Phil Allen - This case appears to be mislabelled. My slide 1 is a thyroid lesion rather than a uterus. It's actually quiz case 1.

David Ben-Dor - when I opened the envelope and noticed the seminar number my first reaction was "wow, has so much time already passed?" My first seminar was in the early '30s. That's a lot of water, comments, and glass slides under the bridge. Was anyone aware that fumarate deficiency was associated with tumors? I would like to congratulate Dr Agaimy for his always cutting edge contributions to the seminars and presentations I've heard at the international meetings. Take this as a compliment: after a point (usually early on) I have trouble following them! As for this case: what will they think of next? Hats off for the pick-up and the work up. To my reptile brain- when I first saw the slide my reaction was "what a strange smooth muscle tumor". On reviewing it again I was struck by what I would describe as hyalinization of the cytoplasm, which reminded me of the ground glass appearance of HBV infected hepatocytes. I assume that this is referable to what you described as "eosinophilic cytoplasmic globules" though I wonder if these aren't related to the rhabdoid inclusions or plasmacytoid cells; I'm not sure I could tell them apart. I wouldn't be surprised if I had missed cases like this in the past though the appearance is quite distinctive.

Ira Bleiweiss - I may be crazy but it seems that in my set case # 1 was switched with quiz case #1. If so, the real case #1 really looks like leiomyosarcoma but, as you say, with staghorn vessels.

Alberto Cavazza – Beautiful example of an entity I read about but I have never seen before (or more probably I missed): in retrospect, the features seem quite characteristic. Thanks for the very nice and useful summary of the literature.

Thomas Colby - Agree with diagnosis. Very nice discussion and very instructive for me. I had been thinking about odd smooth muscle tumors, PECOMAs, etc.

Kum Cooper - Thank you for this educational case Abbas. I showed the case to my colleague Dr Reyes who identified it immediately (author of the Mod Path paper); although the MGH group including Glen McCluggage have refuted the specificity of the eosinophilic globules and peri-nucleolar changes.

Hugo Dominguez Malagon – Wrong slide, it belongs to Quiz case 1.

Goran Elmberger – Very interesting and new to me. Nice morphological fit with descriptions. Sometimes I wonder how many hereditary syndrome associated tumors we miss in daily practice. Now we start having the tools to decipher cases with odd features with the help of molecular genetics.

Giovanni Falconieri - No slide (just received a duplicate slide of the quiz case#1)

Franco Fedeli - Very interesting case. Looking for in literature, according to this article (Int J Cancer: 119, 283-287, 2006) at least in a small percentage of cases FH defects seem to play a role in early onset uterine leiomyosarcoma too.

Jeronimo Forteza - An example of how histological diagnosis can use to infer a molecular alteration that defines the disease.

Maria Pia Foschini - Fumarate Hydratase (FH) deficient uterine smooth muscle neoplasm, highly suspicious for HLRCC. This is a very rare and interesting case. The neoplastic cells have rhabdoid features, that should be differentiated from skeletal muscle differentiation that can occur in uterine leiomyomas (Hum Pathol. 1999 Mar;30(3):356-9.). In addition to the immunohistochemical stains suggested, in situ fluorescence hybridization showing LOH at 1q43 might help to reach the correct diagnosis. (Am J Surg Pathol 2013; 37: 74-80).
Masaharu Fukunaga - Thank you very much for sharing the case and detailed discussion of this type of lesion. This is the first time I see this type of tumor and clinical features. What a wonderful case! Abbas.

Ondrej Hes - Seems in my set of slides, there are 2 identical cases, both came from thyroid gland.

Thomas Krausz – No slide received (Case#1 slide is a duplication slide of Quiz#1)

Janez Lamovec - I have never seen uterine leiomyoma in association with HLRCC syndrome and now you and Markku presented one case each. On first glance, they don't seem too particular but when examined more carefully, they are different from usual leiomyomas. Thank you for this case, Abbas.

Thomas Mentzel - Many thanks for this wonderful case and for mention our study on cutaneous smooth muscle tumours showing loss of FH in HLRCC cases. We now found also an overexpression of 2SC in these cases, or in other words the FH and 2SC stainings are very helpful identifying HLRCC patients presenting initially with multiple cutaneous smooth muscle tumours.

Liz Montgomery – Oops - somehow it is the thyroid from Quiz case 1!!!! Wonderful that Markku also shared one!

Fredrik Petersson - Subtle, but fairly characteristic set of morphological features - If you where to look for it! Initially I noted focal (“PEComa-like”) cytoplasmic clearing in cells that merged with cell adjacent to a vessel, but the overall features did not fit. Given the absence of clinical characteristic findings/features, could this be a spontaneous, non-germ-line associated FH-deficient leiomyoma?

Santiago Ramón y Cajal - It is a very interesting case. Thank you very much for sharing it with us.

Brian Rubin - Thanks for the interesting case and discussion. I’ll be on the lookout for more cases. It’s fascinating how Krebs cycle enzymes like fumarate hydratase and succinate dehydrogenase are turning up as tumor suppressors whose loss is associated with tumor syndromes and sporadic cancers such as paraganglioma and gastrointestinal stromal tumor in the case of loss of succinate dehydrogenase.

James Strauchen - Wow! What are the chances of having two in the same AMR slide seminar (see case 13).

Paul Wakely - I must have the wrong slide since mine is a section of thyroid tissue.

CASE NO. 2 – CONTRIBUTED BY GERALD BERRY

Abbas Agaimy - Pretty example of plexiform fibromyxoma of the stomach, thanks Gerald.

Phil Allen - Plexiform fibromyxoma of the stomach. A wonderful case. As far as I know, it is the first one I have seen. Thanks for the contribution.

David Ben-Dor - quite a remarkable case. It's not surprising that another example of this entity was already contributed to the seminar and that I have no recollection of it. I don't think in that in my entire career I've seen 150 cases of GIST so it stands to reason statistically that I haven't had a case such as this. The appearance looks memorable enough so that I hope it rings a bell should I come across one. What if you get a tiny fragment of this on a gastroscopic biopsy- call it “granulation tissue”?

Ira Bleiweiss - Agree. Interesting and certainly a good descriptive name.

Alberto Cavazza - I agree, a quite characteristic (but very rare and always nice to see) entity.

Thomas Colby – Agree with diagnosis. Beautiful case.

Kum Cooper - Thanks Gerry for this example. I also showed a case in Japan last year. I recall Markku giving credit to an earlier group who coined the term plexiform fibromyxoma.
**Hugo Dominguez Malagon** - Nice case of plexiform angiomyxoma of the stomach, would be nice to know the cell of origin. I could not find the macro.

**Goran Elmberger** - Distinct morphology. Good fit with unusual tumor with distinct morphology. Precursor cell? Occult molecular marker? (GE)

**Giovanni Falconieri** - Very difficult, I did not know this entity. I was impressed by the remarkable angiomatoid pattern.

**Franco Fedeli** - About this nice case, as reported in literature (Int J Clin Exp Pathol: 7(2), 823-827, 2014) the focal expression of desmin may suggest that this tumor is not a purely myofibroblastic lesion but it could present neoplastic cells with smooth muscle differentiation too; In addiction this immunohistochemical finding may link this tumor to angiomyofibroblastoma of the vulva.

**Jeronimo Forteza** - It would be interesting if molecular studies could unify these morphological variants with the differences observed using GIST.

**Maria Pia Foschini** - This is a relatively recently described tumour, that should be known especially when dealing with diagnosis of gastric tumours on small endoscopic biopsies. Plexiform fibromyoma of the stomach can simulate malignancy at presentation, as described by Lee et al. (International Journal of Surgical Pathology 2014; 22(3):286-290).

**Masaharu Fukunaga** - Thank you very much for the beautiful case of plexiform fibromyxoma. I had reported the same tumor as gastric fibromyxoma many years ago.

**Thomas Krausz** - Beautiful example. Strikingly infiltrative (even an endometrial stromal sarcoma would envy the infiltrative pattern), perhaps best to classify as intermediate category rather than benign.

**Janez Lamovec** - Although the appearance of nodules vary from myxoid to fibroblastic and collagenized, the capillary network is similar in all of them. In Markku's series no desmin positivity was demonstrated in tumor cells, you found its focal positivity which, of course, may be found in myofibroblasts.

**Thomas Mentzel** - A nice example of a rare entity, and given the vascular pattern, I think that the term "plexiform angiomatoid myofibroblastic tumour" is very useful.

**Markku Miettinen** - Agree, a nice plexiform fibromyxoma. It should be noted that the plexiform architecture is seen only in intramural tumor components. Now we have atypical and even malignant-looking variants (no data on malignant behavior yet obtained). If anyone has malignant or atypical variants, I invite all for collaboration.

**Liz Montgomery** - This plexiform fibromyxoma is so pretty. Thank goodness these look nothing like SDH deficient GIST!!!!

**Frederik Petersson** - Beauty! Terminology-wise, why was the “angio or angiomatoid” dropped?

**Santiago Ramón y Cajal** - Thank you for sharing this case with us.

**Brian Rubin** - Beautiful case and very interesting clinical history! These are super rare so glad to have another example for my teaching file.

**James Strauchen** – Plexiform fibromyxoma. New one to me!

**Ady Yosepovich** - very nice case – thank you for sharing.
CASE NO. 3 – CONTRIBUTED BY IRA BLEIWEISS

Abbas Agaimy - Pitfall of serous carcinoma of the fallopian tube presenting in axillary lymph nodes. Many such unusual cases might have been misinterpreted as metastatic breast carcinoma. Presence of psammoma bodies is a useful clue to diagnosis. I am not aware if microcalcifications as seen in primary breast cancer do rarely occur in axillary metastasis?

Phil Allen - Metastatic papillary serous carcinoma with psammoma bodies in right axillary lymph node from primary in the left fallopian tube. I would never have considered a tubal primary.

David Ben-Dor - again this flies in the face of all expectations but if the epithelial component showed up a needle biopsy of an omental cake would my first thought be "let's rule out a breast primary"? The psammoma bodies could be a tip off with the WT-1 being confirmatory but still it requires some persistence and stamina on the part of the pathologist to convince the clinicians to perform abdominal investigation especially since the primary was itself limited- how big was it? Was it obvious on imaging or palpable? I suppose that this sort of thing can happen- a gynecologist who used to work at my hospital but who had trained at Maimonides Hospital in Brooklyn told me about a woman who kept on shedding psammoma bodies in her pap smears and on work up eventually was found to have a gynecological primary (I forget the exact details) with the pathologist performing a leading role in getting at the truth. I assume that the clinical workup included MRI.

Alberto Cavazza - Very educational case: in the absence of clinical data, it could be easily a trap. PAX8 may be another antibody useful in this setting.

Thomas Colby - Agree with diagnosis. I think I have seen a couple of papillary serous carcinomas present this way.

Kum Cooper - I agree Ira, the psammoma bodies catch your eye. In addition the sinuous papillae (and focal micropapillae) are useful too, although most of it is solid. p53 would also have been diffusely positive. Another curious question is her BRCA status?

Hugo Dominguez Malagon - High grade serous papillary carcinoma, was it located in the fimbria, has the patient BRCA1 or BRCA2?

Goran Elmberger - Nice case. I start to regard every tumor as a cancer of unknown primary till proven otherwise. Can be useful mindset since we meet many surprises. Mesothelioma is also one of those tumors I have seen making it to diagnosis in an axillary lymph node.

Giovanni Falconieri - Great case, Ira. Nick artifacts due to focal calcifications are sure a clue to the correct recognition of focal psammoma bodies. I had the same experience years ago with serous carcinoma of ovary metastatic to bone, not a common metastatic site of ovarian cancer compared with primary in breast, lung or kidney.

Franco Fedeli - According to my experience PAX8 immunostain could be a useful tool to recognize the ovarian origin of a metastatic lesion.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - This is a quite unusual and challenging case. Axillary metastases from unknown primaries are not rarely encountered in Breast Units. Most frequently they are considered metastases from occult breast cancers. Indeed the papillary features with psammoma bodies are quite unusual in breast cancer, but estrogen receptor positivity in cancer cells could be misleading. Patients with axillary metastases from unknown primary should undergo extensive screening in order to find a possible distant source of origin. Serous carcinoma of the Fallopian tubes is rare, but axillary and breast metastases are on record (Int Journal of Gynecological Pathology 2010;30:53-57; Am J Surg Pathol 2004;28:1646-1651).

Masaharu Fukunaga - A beautiful case of metastatic serous carcinoma of fallopian tube origin. High grade serous carcinoma sometimes has metastatic disease in the lymph node in the axilla or mediastinum.
Ondrej Hes – Just a short question: would PAX 8 staining be helpful? I use it as part of the panel for lymph node intraabdominal/retroperitoneal metastases in females (clinically uncertain origin). To be honest, tubal carcinoma wouldn’t be my number one diagnosis 😊 in axillary lymph node.

Thomas Krausz - Agree with diagnosis. One wonders how this metastasis managed to get to the contralateral axillary lymph node. The clinical history helps, but it is still a diagnostic challenge.

Janez Lamovec - I agree that psammomatous calcifications in breast carcinoma metastases are rare and even in breast papillary carcinoma rich in psammoma bodies and without in situ lesion one should think of metastatic carcinoma, usually of female genital tract origin. We have seen papillary carcinoma metastatic to the breast with unknown primary that was later found in the ovary; it showed abundant psammoma bodies. Moreover, it’s been recently recommended that whenever an invasive papillary carcinoma is found in the breast, in view of the fact that the latter is rare, a metastasis from the lung or ovary should be considered (Histopathology 2015; 66: 761-770).

Thomas Mentzel - A good to think on diagnosis and it can be a real pitfall.

Markku Miettinen - Focal papillary architecture and psammoma bodies are clues but difficult to see because expectations, especially for an ER+ metastasis, are so skewed toward a breast primary.

Liz Montgomery - This is amazing. I have never seen a tubal met to the upper body!

Fredrik Petersson - A case that shows that one has to be prepared for everything. The clinical course unusual. No mets elsewhere??

Santiago Ramón y Cajal - A very illustrative case and a clear example of the importance of looking biopsies without prejudices.

Brian Rubin - Interesting case. I definitely don't think of gynecologic cancers as presenting with an axillary metastasis. I always tell my fellow and the residents to "stay on their toes" and this is a perfect example of something unexpected that required investigation and a solid approach to figure it out.

James Strauchen - Nicely worked up!

Saul Suster – What a surprise! A nice example of why we need to always stay on our toes.

Paul Wakely - Thank you Ira. I sort of ignored the psammoma bodies, and was thinking metastatic breast CA all the way till I read your discussion.

Ady Yosepovich - thank you for this case – it is pretty unusual to see localized tumors with distant metastasis to unusual sites – I always thought that it is a feature of aggressive biological behavior, it is probably not the case in this patient.

CASE NO. 4 – CONTRIBUTED BY THOMAS COLBY

Abbas Agaimy - Yet another fine contribution by Tom, pleuroparenchymal fibroelastosis. What is the source of smooth muscle nodules seen frequently in such cases? Thanks for nice discussion of the topic.

Phil Allen - Apparently idiopathic bilateral pleuroparenchymal fibroelastosis in explanted lungs. On looking at the slide "blind," I thought the numerous dilated thin walled vessels, presumably lymphatics, indicated a primary vascular proliferation but that would not explain the elastic tissue. Thanks for this instructive case, Tom.

David Ben-Dor - I picked up the elastotic change but didn't realize that it defined an entity. I'm used to seeing this as an "incidental" finding at autopsy in the upper pole of upper lobes of the lung - while I was a resident a wise old pathologist taught me the term "Medlar's cap" for this (is this term familiar to anyone?) - but here I assume that the changes were more widespread and had clinical significance. It was very nice to include the article in the handout.
**Ira Bleiweiss** - Verrrrry elastic lung, stretchhhhhable one might say. Thanks for the article, Tom.

**Alberto Cavazza** - To increase the pain, I can just say that pleuroparenchymal fibroelastosis can be combined with other patterns (particularly UIP and NSIP). Based on a recent paper (Chest 2014;146:1248-1255), it seems that pleuroparenchymal fibroelastosis combined with UIP is an aggressive disease, with a progression more similar to the former than to the latter (but the reported cases are few).

**Kum Cooper** - Thanks Tom for this walk on the wild side. I got as far a fibroelastosis!! So leaving aside the ass, the donkey and Amitani’s disease....the question is: “Is it safe to go back to the water?”

**Hugo Dominguez Malagon** - Excellent example of pleuropulmonary fibroelastosis and nice discussion - I learned a lot.

**Goran Elmberger** - Classical case, rare entity. Is there something ongoing in accessory salivary type glands – Sjögren like?

**Giovanni Falconieri** - Thank you Tom for including this new entity, and the supplemented paper thereof. I am sure that I have never recognized this should I ever come across it.

**Franco Fedeli** - Pleuroparenchymal fibroelastosis. Great teaching case. Thank you for your paper.

**Jeronimo Forteza** - A very interesting case. I wasn't aware of this entity.

**Maria Pia Foschini** - Thank you for showing us this recently recognized lesion. I have never seen similar cases and I have some questions. Can it be colonized by bacteria, specifically can TBC be superimposed or cause the disease? Small menigothelial-like nodules are present, are these part of the lesion?

**Masaharu Fukunaga** - Pleuroparenchymal fibroelastosis (PPFE) is very new for me. Thank you very much the case, detailed discussion and the paper, Tom.

**Thomas Krausz** - I was not familiar with this entity and I am sure I did see subpleural fibroelastotic scarring, perhaps on a smaller scale, in association with pneumothorax before.

**Janez Lamovec** - New to me. Most instructive slide and enclosed article. Thank you.

**Thomas Mentzel** - Many thanks also for including the literature.

**Liz Montgomery** – Medical lung pathology makes it hard to breathe.

**Santiago Ramón y Cajal** - Thank you, Thomas, for this excellent case and the accompanying literature.

**Frederik Petersson** - Never heard about this. Adds to the mystery, on many levels, for me, with interstitial lung diseases. Very educated discussion.

**Brian Rubin** - Not something I’ve ever heard of before. Looks like a ”scar” to me but I’m a soft tissue pathologist. I don’t think a lot about interstitial lung disease but I remember being terrified by it as a resident. It’s an intimidating area for the non-specialist.

**James Strauchen** - . Great case of pleuroparenchymal fibroelastosis!

**Saul Suster** – Thank you Tom for contributing an example of this new “entity” included in the latest proposal for the classification of interstitial lung diseases. While elastosis is obviously a degenerative process that can occur in any tissue, and is certainly not that rare in the lung in older patients, I'm not sure the role it plays in the functional damage and progression of interstitial fibrosis has been very well delineated yet. Most of the time it seems to be an incidental finding in areas of subpleural scarring.
Paul Wakely - Wow! - you learn something new every day. First time I see or heard of this PPFE, and makes me glad I don’t see non-neoplastic lung cases in either humans or donkeys since I make a jackass out of myself just with the regular tumor specimens I have to examine.

Ady Yosepovich - thank you for this very nice presentation of this new entity - I have no knowledge in the field of interstitial lung disease yet I had great pleasure reading your case.

CASE NO. 5 – CONTRIBUTED BY IVAN DAMJANOV

Abbas Agaimy - Huge ovarian metastasis from cervical SCC. A real pitfall given that similar tumors do rarely occur in the ovary. Not having the full clinical image would make such a diagnosis rather difficult. Thanks Ivan for good teaching.

Phil Allen - Anaplastic metastatic carcinoma in the left ovary from a primary squamous cell carcinoma of the cervix in a 34-year-old, morbidly obese, pregnant woman. There is only the faintest suggestion of squamous differentiation in the H&E stained section. The squamous differentiation only became apparent to me after reading the answer.

David Ben-Dor - The Istanbul man is making an appearance in Kansas City! The alveolar pattern is striking. After realizing that this was an ovarian mass my first thought was hypercalcemic small cell carcinoma but of course the serum calcium rules that out. Then comes slogging through the immuno panels (which if you're in a large department is doable). Somewhere along the line the thought of a squamous tumor comes to mind (maybe after other more common or intuitively obvious options are ruled out). This case brings up the same point as Ira's (case 3 in this seminar) and also reminds me of a case I submitted to an earlier seminar of an inguinal nodule in a young man which turned out to be seminoma metastatic from the testicle in a man with a history of undescended testis (which of course I didn't know about!). In all fairness looking again at the slide and even while aware of the final diagnosis there is nothing cytological which reminds me of squamous differentiation. In acantholytic type of squamous carcinoma the cells are more cohesive and at least in part are forming structures recognizable as epithelium (or even take on a vascular appearance) with focal formation of channels which could lead one to think of adenocarcinoma or even angiosarcoma but here everything is falling apart (as in the "tumbling bricks" seen in pemphigus) and if epithelial then they're very primitive almost anaplastic. Earlier on in my AMR career I submitted a case of urothelial (then known as transitional cell to show how far back we go) carcinoma which to me mimicked an angiosarcoma due to the same phenomenon and I noticed that Tom Kraus recently published an article on angiosarcoma-like bladder carcinomas.

Ira Bleiweiss - I thought about germ cell tumors. I never would have thought of squamous cell carcinoma.

Alberto Cavazza - I agree with the diagnosis, but I missed it (even if in retrospect there are less acantholitic areas in which the possibility of squamous cell carcinoma could arise). Very instructive case, thanks for sharing. A propos of acantholytic squamous cell carcinoma, I enclose a couple of images (see below) of a liver metastasis from a lung tumor that I was ready to call metastatic adenocarcinoma, and I did the immuno (diffuse positivity for p63, negativity for TTF1) just because I knew that the lung tumor was a squamous cell carcinoma!
Thomas Colby - Agree with diagnosis and probably would have struggled with the precise diagnosis just as Ivan did. I hope I would have thought of cervix as a possible primary.

Kum Cooper - Ivan call it what you will, “man from Istanbul”, humility .... this is an excellent educational experience. Going back to the slide it is clearly a squamoid pattern!!!

Hugo Dominguez Malagon - Sorry I missed that, I saw the polygonal cells but was impressed by the discohesiveness, septa and multinucleated cells.

Goran Elmberger - Tough case. Again. All tumors should be regarded as cancer of unknown primary till otherwise proven. Blind first review. If this case showed up labeled as biopsy of oral cavity I guess most of us would sign it out as acantholytic SCC without further ado.

Giovanni Falconieri - Nice case, Ivan. Agree with your assessment; the alveolar pattern is quite remarkable indeed, although the pavement-like arrangement of tumor cells are recognizable here and there. Another lesson from "the man of Istanbul!"

Franco Fedeli - In my opinion this case shows us how useful is the determination of p16 expression when your task is solving the differential diagnosis from a metastatic cervical squamous cell carcinoma, especially in order to establish the right tumor stage.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - In these days, in which uterine cervix screening has led to a markedly decreased incidence of squamous cell carcinoma (SCC) of the uterine cervix, finding a ovarian metastasis as first appearance if quite rare. This case interestingly is an acantholytic variant of SCC, that is frequently seen in the skin and in other organs (as the breast) but is apparently rare in the uterine cervix (Pathology International 2010;60:245-246). The prognosis of acantholytic SCC is quite debated. The present case seems to confirm the highly aggressive nature of acantholytic SCC, compared to the usual SCC. Nevertheless, a recent review paper (Dermatol Surg. 2011 Mar;37(3):353-6) does not confirm this hypothesis.

Masaharu Fukunaga – Very challenging case, Ivan, my impression is large cell neuroendocrine carcinoma, primary or metastatic. I had no idea of primary cervical squamous cell carcinoma.

Ondrej Hes - I have seen cases of squamous ca originating in the cervix, growing via the isthmus into the uterine cavity and via both tubes reaching the surface of the ovaries. However our tumor was obviously well-differentiated squamous carcinoma. Just the spreading was strange. This one is more complicated and squamous origin wouldn´t be my first impression.

Thomas Krausz - Before reading the discussion, I also had a broad differential diagnosis. Looking at the slide again, indeed there are less dissociated islands with acceptable squamous morphology. I assume mucin stains were negative.

Janes Lamovec - We have seen similar acantholytic type of SCC in the vulva, breast and skin.

Thomas Mentzel - What a terrible story.

Markku Miettinen - Excellent example of how a good immuno work-up can resolve a diagnosis. Additionally SMARCA4/BRG1+ (no loss) could also help to rule against hypercalcemic small cell carcinoma. The tumor does have small areas indicative of squamous cell carcinoma. I also wondered about an adenocarcinoma component because of vacuolization and signet ring cells.

Liz Montgomery - What a terrible looking tumor. I would have assumed the lesion was primary in the ovary but I guess knowing the story the cells do have that hard cytoplasm one sees in squamous cell carcinoma. This case is a good lesson for me.
Frederik Petersson - Terrible pitfall! Very convincing work-up. In addition, my slide contained several tumor cells with large intracytoplasmic vacuoles ("pseudo-signet ring cells" that I frequently see in poorly differentiated SCCs – but then in conjunction with more convincing squamous features). Even when going back at the slide I only make up vague "squamous" features. Massive dyscohesion/acantholysis. A large cell variant of small cell hypercalcemic carcinoma (Fukunaga Pathol Int 1997) was my first impression. This was the man from Istanbul - in disguise.

Santiago Ramón y Cajal - Agree, cervical squamous cell carcinoma, metastatic. It has been very enlightening and educational. Thank you very much.

Brian Rubin - Similar to case 3 in that it required an open-minded approach to figure out the correct diagnosis. I could easily see this signed out as a poorly differentiated ovarian primary.

James Strauchen – Acantholytic squamous cell carcinoma of the cervix metastatic to the ovary. Nice case!

Saul Suster - Another spectacular "pitfall" for diagnosis! Thanks for sharing.

Paul Wakely - I got as far as poorly-differentiated carcinoma, but would have never considered a cervical squamous carcinoma. As you said, Ivan, another wonderful lesson in diagnostic humility.

Ady Yosepovich - fantastic case, thank you. Acantholotic SCC is always a surprise and a pitfall

CASE NO. 6 – CONTRIBUTED BY GIOVANNI FALCONIERI

Abbas Agaimy - Beautiful example of the rare granular cell epulis at an even rarer and unusual site, the tongue; thanks Falco.

Phil Allen - Congenital granular cell tumour of the newborn, lateral aspect of the tongue. We had one of these on the alveolar ridge about five years ago at Flinders Medical Centre. The negative S-100 stain was the give-away.

David Ben-Dor - To me the lesional cells have a finely granular- ground glass appearance while in granular cell tumor the granularity is more coarse and obvious. I would think that these cells are related to histiocytes and even at the onset thought of a storage disease but apparently there is no support for that. I took this case as an excuse to perform a cursory update on the nki-c3 antibody- it rose to fame as a melanoma marker and while is known to stain lysozomes it does so also in non-histiocytic cells in which these are secondarily acquired as a degenerative phenomenon (for anyone interested- the reference with credit to google is Sachdev et al, Am J Clin Pathol 2006;126:554-563).

Ira Bleiweiss - Beautiful case of granular cell tumor. I've seen many of course in the breast, as I'm sure most of us have.

Alberto Cavazza - Really a good teaching case (surely for me, not only for residents!) and a very useful summary of the literature.

Thomas Colby - Agree with diagnosis. Lovely case.

Kum Cooper - Thank you Falco. I have only seen one case before in Africa. And the only point I recall was the S-100 negative. Thank you for sharing this interesting case.

Hugo Dominguez Malagon - Congenital granular cell epulis. I believe that "granular cell" is a phenotype and is found in many unrelated tumors like schwannoma, adamantinoma, leiomyoma etc. The cell of origin is difficult to recognize in the congenital type.

Goran Elmberger - Illustrative case of unusual tumor and location.
Franco Fedli - Congenital granular cell epulis. Thank you for sharing this teaching case with us, especially considering its unusual location.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - Congenital granular cell epulis of newborn (CGCE). Granular cell tumor seen in adults is superimposable to the CGCE, but differs on the immunohistochemical profile, as it is positive for S-100 and CD68 antibodies. Interestingly, Alemayehu et al. (Journal of Pediatric Surgery 2015, in press), reported cases of granular cell tumor of the oral cavity, affecting children whose mean age was about 8 years, showing intermediate immunohistochemical features between granular cell tumors of the adults and CGCE. In addition granular cell tumor in children had invasive pattern of growth. Nevertheless, in spite of this invasive growth, surgical resection was followed by good prognosis.

Masaharu Fukunaga – This is also very new to me, granular cell epulis. Thank you, Falco.

Thomas Krausz - Very nice example; I haven’t seen one for a long time.

Janez Lamovec - In addition to granular cells, the perivascular lymphoid infiltration is quite prominent; this would be unusual in granular cell tumor.

Thomas Mentzel – What is the relationship to “non-neural polypoid granular cell tumour” that has been described in the oral cavity as well? (AJSP 1991; 15: 48; Oral Surg Oral Med Oral Pathol 2007; 103: 382)?

Markku Miettinen - Nice case. A prominent vascular pattern is a clue, besides the location and young age.

Liz Montgomery - This granular cell epulis is fantastic and, as you suggest, I will share it with the trainees.

Frederik Petersson - Excellent case, classical in all but its “ectopic site”.

Santiago Ramón y Cajal – agree.

Brian Rubin - Stunning case in an unusual location.

James Strauchen - Classic case of congenital granular cell epulis.

Ady Yosepovich - thank you for the presentation of this rare entity.

CASE NO. 7 – CONTRIBUTED BY CYRIL FISHER

Abbas Agaimy - Nice case of myoepithelial carcinoma of neck soft tissue showing rhabdoid morphology. The diagnosis was confirmed by FISH (EWSR1) and in line with the rhabdoid morphology SMARCB1 was lost in the tumor cells. This case represents a nice example of what can be called “composite genetic hit” neoplasms with specific secondary genetic aberrations (INI1 loss). The genetic basis of the INI1 loss in the group of EWSR1-altered sarcomas (like myoepithelial carcinomas, extraskeletal myxoid chondrosarcomas etc) remains to be further explored. Thanks Cyril for wonderful case!

Phil Allen - Poorly differentiated rhabdoid tumor involving right sympathetic chain. The reference mentioned in the circulated case details was not included in the electronic paperwork I received. On the basis of the one slide, this could pass as a primary malignant tumor of the sympathetic trunk. I use the word “rhabdoid” only as a non-specific descriptive term. In addition, I have great difficulty understanding how a myoepithelial carcinoma can arise in soft tissue sites where there is no naturally occurring epithelium or myoepithelium. Could there be an alternate explanation for the immunohistochemical results in this, and other cases?

David Ben-Dor - the eosinophilic globules giving rise to the rhabdoid appearance are nicely developed in this case. Reference is also made to “plasmacytoid” cells: is this a spectrum of changes (coincidentally the same features are described in case #1 submitted by Abbas Agaimy) or maybe different aspects of the same phenomenon? Plasmacytoid cells are a recognized variant of myoepithelial tumors. This lesion was said to arise in the neck but
where exactly? I remember an FNA sent from a "cervical lymph node" which I interpreted as tumor but which at the end turned out to be a Warthin tumor exophytically arising from a parotid gland: if this was from the upper neck then maybe the case could be made for a salivary gland tumor which disconnected from the parent organ (though I note that no salivary gland parenchyma was found - in my case the connection was easily seen on the surgical resection specimen).

Ira Bleiweiss - Rhabdoid carcinoma or signet ring cell CA, I would have thought metastatic.

Alberto Cavazza - Myoepithelial carcinoma vs malignant rhabdoid tumor was my differential diagnosis in H-E, but to tell between the two was beyond my possibilities. Thanks, also for the complete version of your comments.

Thomas Colby - Agree with diagnosis. I was in the rhabdoid tumor camp but was dissuaded from that by the discussion and immunohistochemical findings.

Kum Cooper - Thank you Cyril for this educational experience. I would have stopped at INI-1 deficient and called it proximal ES. Thank you for the reminder that a subset of myoepithelial tumors are EWSR-1 rearranged and INI-1 deficient.

Hugo Dominguez Malagon - Agree, myoepithelial carcinoma of soft tissue, in my slide there is focally condro-myxoid stroma.

Goran Elmberger - Certainly widens the concept of myoepithelial neoplasms but having seen a few soft tissue primaries along that line I have no better explanation. Rhabdoid morphology ≠ rhabdoid tumor!

Giovanni Falconieri - Quite difficult case, as far as my comment can matter I recognized the distinct epithelioid qualities of tumor cells and their arrangement in discrete fascicles. Looking at the slide "blind" I thought of melanoma, an interpretive pitfall favored by S100 positivity.

Franco Fedeli - Personally I appreciated very much this case and I guess that the growing recognition of EWSR-1 rearrangement in myoepithelial tumors is increasing the number of overlapping features being between myoepithelial tumors and extraskeletal myxoid chondrosarcoma.

Jeronimo Forteza - The extent to which rhabdoid differentiation is marked is surprising. So too is the strong acidophilic nature of the cytoplasm in which acidophilic bodies are released on occasion. One would expect this rhabdoid morphology to be of greater importance in the diagnostic criteria?

Maria Pia Foschini - Myoepithelial carcinoma of soft tissue with rhabdoid morphology. Rhabdoid features can be encountered in a great variety of tumors having different histogenesis. In general rhabdoid features correspond to a more aggressive behavior, when compared with the same tumors showing more conventional morphologies. I wonder if this could be true also in cases of soft tissue myoepithelial carcinomas.

Masaharu Fukunaga - H&E morphology seems to be ganglioneuroblastoma. It is myoepithelial carcinoma, INI negative. Thank Cyril for this case.

Thomas Krausz - Keratin-negative soft tissue myoepithelial tumors always cause me diagnostic dilemma. Cyril, thank you for the excellent discussion.

Janez Lamovec - My first thought when examining this tumor was metastatic MM that often exhibits rhabdoid morphology. However, with all this immune results, the myoepithelial carcinoma is the right diagnosis. In pre-immuno era, the MM would be the first option, I believe.

Thomas Mentzel - A beautiful example of malignant myoepithelial tumour with prominent plasmacytoid features.

Liz Montgomery - Cyril, this is a stunning case of myoepithelial carcinoma. I enjoyed looking at it a lot. I am impressed by the favorable outcome to date.
Frederik Petersson - Interesting case. Rhabdoid malignant something. I find the topic - and terminology - of soft tissue myoepithelial neoplasms challenging and, to be honest, confusing.

Santiago Ramón y Cajal - Thank you, Cyril. After the immunohistochemical and molecular study, the diagnosis seems quite convincing.

Brian Rubin - Nice case. I seem to be making the diagnosis of myoepithelial carcinoma with increasing frequency. These are definitely more common than previously believed.

James Strauchen - Nicely worked up!

Saul Suster – Thank you Cyril for this nice case! The topic of tumors with “rhabdoid”, “plasmacytoid” and “myoid” differentiation is still confusing. The current definition of soft tissue mixed tumor/myoepithelioma of soft tissue/parachordoma as representing all one and the same entity is also rather simplistic and I suspect we may be lumping disparate and distinctive entities under the same umbrella. Because of their rarity, these tumors have been difficult to study and define. The immunophenotype in this case certainly is more confusing than definitive (given total absence of cytokeratin staining!).

CASE NO. 8 – CONTRIBUTED BY ONDRA HES

Abbas Agaimy - Very nice lesion that I have never seen before, thanks Ondra for sharing this rare case.

Phil Allen – Spermatocytic seminoma associated with undifferentiated sarcoma, right testis. Thanks very much for this most instructive case. I was not aware of the prognostic significance of sarcomatous differentiation in spermatocytic seminoma.

David Ben-Dor - My first impulse on seeing sheets of poorly differentiated cells and given the fact that testicular tumors in older men are often or most often lymphomas was to consider lymphoma. Immunos for lymphoid related antigens would easily rule that out but I would have had a dilemma with the seminoma related markers; I didn't realize that they were negative in spermatocytic seminomas. Would CD117 work? Maybe you need to rely on experience and common sense for this one. The sarcomatous element looks quite bland to me. Did the patient have metastases? Clinical course?

Ira Bleiweiss - Agree, great case.

Alberto Cavazza - Thanks for this very nice example of such an exceptional entity, and for the exhaustive comments.

Thomas Colby - Agree with diagnosis. Instructive for me. I got as far as spermatocytic seminoma but was not aware of (or more likely did not remember) that they could be associated with sarcomas.

Kum Cooper - Thank you Ondra. Yes it did remind me of my case submitted in the early nineties.

Hugo Dominguez Malagon - Spermatocytic seminoma with sarcomatous component, nice case.

Goran Elmberger - Thanks for bringing up this important variant of spermatocytic seminoma. Sarcomatous part present on every slide or hiding well?

Giovanni Falconieri - Great case, Ondra. I have seen a few cases of spermatocytic seminoma but never with sarcomatous component.

Franco Fedeli - Great case. It's very surprising that, also in presence of anaplastic component, the excellent prognosis of this lesion doesn't seem to change. However, very different is the outcome of the tumors with sarcomatous transformation, according to a paper published from Lombardi M, Valli M, Brasigotti M, Rosai J Int J Surg Pathol. 2011 Feb;19:5-10 Spermatocytic seminoma: review of the literature and description of a new case of the anaplastic variant.
**Jeronimo Forteza** - It would be a metaplastic and malignant phenomenon at the same time.

**Maria Pia Foschini** - Spermatocytic seminoma (SS) is a quite rare variant of germ cell tumor, having usually good prognosis even if anaplastic features are present (Lombardi et al. Int J Surg Pathol. 2011 Feb;19(1):5-10). This unlucky patient presented sarcomatous component associated to a classic SS. Immunohistochemical profile seems to be similar in the two components, thus suggesting a common origin. It would be interesting to know if the sarcomatous component bears the same cytogenetic features (gain of chromosome 9 and disomic status of chromosome 12p) of the SS component.

**Masaharu Fukunaga** – Thank you for sharing the interesting and rare case of spermatocytic seminoma and sarcoma Ondra.

**Thomas Krausz** - I had opportunity to see a case of spermatocytic seminoma with rhabdomyosarcomatous differentiation before. It has behaved aggressively.

**Janez Lamovec** - Spermatocytic seminoma is a rare tumor, if associated with sarcoma it is exceptionally rare. How do you consider this occurrence – a collision tumor, a dedifferentiated tumor, or else?

**Thomas Mentzel** - Was the staining for CD117 negative as well?

**Markku Miettinen** - Could not find definitive sarcoma in the slide, but tumor looks aggressive with prominent angioinvasion.

**Liz Montgomery** - Goodness. This case is over my head. It all just looks like poorly differentiated malignant neoplasm to me and I think I saw the background spermatocytic seminoma and the lymphoid backdrop. This case is very instructive for me.

**Fredrik Petersson** - Excellent case. My slide was a bit faded. The sarcomatous component does not show obvious high-grade features. Would have been interested to learn about the proliferation (Ki-67?) Reminds me about this case: Low-grade sarcoma in classical seminoma - the first case reported. Petersson F, Michal M, Grossmann P, Franco M, Zámecník M, Hes O. Int J Clin Exp Pathol. 2009 Nov 1;3(2):203-9.

**Santiago Ramón y Cajal** - Nice spermatocytic seminoma. In my slide I do not see the spindle cell sarcomatous component.

**Brian Rubin** - Definitely looks like high grade “progression” of spermatocytic seminoma to unclassified spindle cell sarcoma. Very interesting.

**James Strauchen** – Spermatocytic seminoma with sarcoma. Thank you for this classic case!

**Paul Wakely** - I must have missed the sarcomatous component in my slide.

**Ady Yosepovich** – thank you for this unusual case.

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**CASE NO. 9 – CONTRIBUTED BY JASON HORNICK**

**Abbas Agaimy** – Pretty example of hybrid LGFMS/SEF and superb discussion, thanks Jason.

**Phil Allen** - Hybrid sclerosing epithelioid fibrosarcoma/low-grade fibromyxoid sarcoma. A most convincing case.

**David Ben-Dor** - thanks for the case. For me this is rather an arcane aspect of pathology. This matter was also nicely discussed by Kum in Tokyo. I’m not sure I understood: is the MUC4 positive equally in both epithelioid sclerosing fibrosarcoma and low grade fibromyxoid sarcoma so that the two would be separable only by genetics (apart from histology)? In my slide there are well formed cords composed of the clear epithelioid cells which seem to be well spaced but there are also areas where these seem to become crowded, the nuclei are closer together, and
there is a vague spindly look- is this supposed to represent the fibromyxoid sarcoma element or maybe a "bridging" population?

Ira Bleiweiss - Wow, there's a reason I leave the soft tissue tumors to the soft tissue gurus.

Alberto Cavazza - I have nothing clever to say about this very nice case with exhaustive comments.

Thomas Colby - Agree with diagnosis and agree that there are two components present. I was trying to lump them all as part of the sclerosing epithelioid fibrosarcoma.

Kum Cooper - Nice Jason. Hybrid LGFMS/SEF. Keep the B/W flag flying!

Hugo Dominguez Malagon - Hybrid sclerosing fibrosarcoma/LGFMS, there are few hyalinized areas perhaps representing giant rosettes.

Goran Elmberger - Very interesting and elucidating case. Two classical morphologies and one unifying genetic mechanism in same patient.

Giovanni Falconieri - Another impossible case. Hybrid SEF? Cannot comment due to lack of knowledge, feel quite frustrated about this.

Franco Fedeli - Hybrid sclerosing epithelioid fibrosarcoma/LGFMS, Very interesting case. In my practice I saw cases with a more pronounced sclerosing background than in this tumor.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - Hybrid sclerosing epithelioid fibrosarcoma\low grade fibromyxoid sarcoma. This is an interesting and rare case of sarcoma showing positivity for an epithelial apomucin, MUC4. Recently, Chebib et al. (Int J Surg Pathol. 2015 Apr;23(2):144-8) described a case of sclerosing sarcoma, showing focal features of glandular differentiation. These features underline the concept that sarcomas can present sometimes features of true epithelial differentiation. Finally, I do not understand why a tumor giving rise to 50% of local recurrences and distant metastases (even if over a prolonged time interval) is called “low grade”!

Masaharu Fukunaga - Epithelioid sclerosing fibrosarcoma with low grade fibromyxoid sarcoma (hybrid sclerosing epithelioid fibrosarcoma/low grade fibromyxoid sarcoma). A beautiful case, thank you very much.

Thomas Krausz - Superb case; the best example of hybrid I have ever seen. Thank you very much Jason.

Janez Lamovec - We have seen a couple of sclerosing epithelioid fibrosarcoma but never a hybrid case like this one. Thank you.

Thomas Mentzel - A wonderful example of a hybrid tumour, many thanks.

Markku Miettinen - Low-grade fibromyxoid sarcoma with a sclerosing epithelioid fibrosarcoma component. In this case the latter is clearly a morphologic pattern of the fibromyxoid sarcoma. Could this possibly indicate more aggressive behavior, but does not look high-grade by mitotic rate.

Liz Montgomery - This is a really pretty case of SEF/LGFMS combo! Thanks so much for sharing this beauty! It is really nice to share with residents since there is a two-fer on the slide.

Fredrik Petersson - Wow. I have been waiting long to see such a case. Thanks.

Santiago Ramón y Cajal - Agree. Thank you very much for such illustrative case.

Brian Rubin - Nice case and good discussion.
James Strauchen - Sclerosing epithelioid fibrosarcoma/low-grade fibromyxoid sarcoma. Nice case!

Saul Suster - Never seen this combination before, but looks convincing (the sclerosing component is definitely strikingly different from the LGFMS component!). The more we study these tumors the more we are coming to understand that they are all likely very closely related, like LGFMS and the fibroblastic sarcoma with giant rosettes which were at some point thought to be two separate and unrelated entities.

Ady Yosepovich - thank you for this highly unusual case.

CASE NO.10 – CONTRIBUTED BY JANEZ LAMOVEC

Abbas Agaimy - Melanoma metastatic to the breast and showing unusual spindled and occasionally bland histology, such cases can easily be mistaken for sarcoma or even mimic lymphomas, if one is not aware of this feature or of the clinical history. Metastatic melanoma can adopt a highly variable (dedifferentiated) phenotypic appearance, we recently collected a series of metastatic MM fully lacking melanoma markers and mimicking a variety of other malignancies (paper in press in AJSP). Thanks Janez

Phil Allen - Metastatic desmoplastic malignant melanoma, left breast, five years after excision of the primary on the face. This seems to be similar to the tumors described by Conley, Lattes and Orr in Cancer 1971; 28:914-936.

David Ben-Dor - thanks for this eye-opener. The spindle cell tumor is for me on the bland side and there is a lot of inflammation. In 2010 in Mexico City I presented a case of recurrent desmoplastic melanoma which completely eluded me on multiple reprises. That tumor also showed a "bland" spindle cell proliferation overshadowed by lymphocytes so I thought that I was looking at reparative and inflammatory changes due to the multiple surgeries she underwent (each episode reinforcing the misconception). After hearing that the patient had gone to another hospital where the diagnosis of "melanoma" was made I reviewed the sections and S100 made the situation obvious. Does sox-10 do a better job of staining desmoplastic melanoma cells? The inflammation obscures the tumor and makes reaching the correct diagnosis that much more difficult. This amazing case illustrates the point that the desmoplastic portion of a melanoma can metastasize in the absence of the epithelioid component. I saw a case of metastatic melanoma in the breast which came without any clinical history; the cells were epithelioid and it was very tempting to sign it out as some sort of high grade carcinoma but some subterranean impulse made me do immunos which revealed the true nature of the beast. The surgeon later apologized for not including the history. I am impressed by the long survival of this patient despite multiple tumor recurrences which for melanoma would appear to be unusual. The patient I described also did relatively well despite my malfeasances. The question is whether desmoplastic melanomas, despite the difficulty in recognizing them and their being prone to recur, are fortunately biologically more compatible with survival than the usual type.

Ira Bleiweiss - Completely impossible diagnosis without the history ---- Once Again!

Alberto Cavazza - Another beautiful example showing the kind of mimicker a melanoma can be.

Thomas Colby - Agree with diagnosis. Was stumped by this one and fooled again by the great mimicker. In retrospect the spindled fascicles of neoplastic cells would fit quite well with desmoplastic melanoma and I have seen other desmoplastic melanomas with this sort of inflammatory/fibrotic type reaction.

Kum Cooper - Falco will love this case. My "blind" diagnosis was metaplastic carcinoma!!!

Hugo Dominguez-Malagon - Malignant melanoma metastatic to the breast, very difficult to pick up without the clinical history.

Goran Elmberger - As you state without knowledge of history... Also IHC can be difficult in poorly differentiated spindle cell melanomas making situation even worse.
Giovanni Falconieri - It seems that melanoma metastatic to breast is not so uncommon, I have seen about 3-4 such cases in the last 5 years. Your case corroborates further our preliminary impression that metastases to the breast of melanoma does not portend a bad prognosis at suggested in the past. At least 2 of the patients of our series with available follow up are definite long survivors (>10 years) with no evidence of disease.

Franco Fedeli - Very good case. Actually, I think that just the expression of S-100 doesn't exclude the possibility of an interdigitating reticulum cell tumor/sarcoma. However, in order to solve this differential diagnosis may be useful to have SOX10.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - Metastatic melanoma to the breast. I agree with Janez’s comment that dealing with breast malignancies we should always keep in mind that metastases can occur. To this purpose, the nice review written by Andrew Lee (J Clin Pathol 2007;60:333-341) underlines the importance of the clinical history. I would also like to suggest that similar attention should be paid dealing with lymph-node examination. We recently saw a breast cancer case, showing isolated tumor cells in the related axillary sentinel node. The ITC were cytokeratin negative and S-100 positive. The patient also had an unrecognized melanoma of the skin.

Masaharu Fukunaga - Melanoma! I would have never imagined it. It looked like inflammatory myofibroblastic tumor or IgG4-related lesion. Thank you, Janez.

Ondrej Hes - I am always afraid of melanoma.....I missed two (or rather, I know about 2), both terrible cases mimicking carcinoma in soft palate and mouth. So, always considering melanoma 😊 in doubtful case.

Thomas Krausz - Highly educational case. Without the clinical history, a spindle cell tumor such as this, in the breast, would be a major diagnostic challenge. The relatively high percentage of the cellular spindle component compared to the desmoplastic one, both in the primary (as judged from the picture) and in the metastasis perhaps explains the aggressive course.

Thomas Mentzel - An almost impossible case on H&E and without the clinical history.

Markku Miettinen - Very difficult to recognize as melanoma; keeping S100 always in the panel would help. Histology somewhat resembles desmoplastic melanoma with prominent collagenous matrix and lymphoid reaction.

Liz Montgomery - This is a nice case that shows how sneaky melanomas can be! Of course the lymphoid cuff and lots of plasma cells are a nice clue!.

Frederik Petersson - Initially very confusing; spindle cells with different morphologies – one clearly neoplastic. Crucial piece of clinical information. Interesting to note the lymphoplasmocytic, partially nodular component. Would be expected also in the primary Spindle cell ?Desmoplastic MM.

Santiago Ramón y Cajal – A complicated and difficult case, without prior history, would have been almost impossible to diagnose. Initially, I even raised, once discarded the sarcomatoid carcinomas, a dendritic cell sarcoma.

Brian Rubin - Excellent teaching case. I see many spindly metastatic melanomas in my consultation practice but my usual problem is that there isn’t any primary to compare it to. I’m struck by how many cases like this I see where there is no known primary. I get the distinct feeling that the pathologists who send me these cases don’t believe my diagnosis. I’m considering looking for canonical melanoma-type mutations like BRAF V600E to support these diagnoses.

James Strauchen - Metastatic melanoma. Supports the adage that melanoma can look like anything!

Saul Suster – Impossible case to diagnose in the absence of a history. First, the tumor cells show significant nuclear pleomorphism, unlike conventional desmoplastic melanomas in which the cells more often resemble benign fibroblasts. Metaplastic carcinoma would come to mind first in this clinical setting!

Paul Wakely - Fooled me completely Janez. I was thinking ‘inflammatory myofibroblastic tumor’ for this lesion until I read your handout summary.
**Ady Yosepovich** - thank you for this extraordinary case – In the era of breast core needle biopsies, I don’t want to be the one to get a CNB from this lesion with no clinical history.....

**CASE NO.11 – CONTRIBUTED BY MICHAL MICHAL**

**Abbas Agaimy** - Thank you for sharing this unique and interesting case, Michal. At first glance, I though the stroma is somewhat inherent to the tumor suggesting a biphasic pattern as seen in Müllerian adenosarcomas etc. The spatial relationship between the epithelial and stromal component in this case seems unique. The endometrioid component is clear-cut and squamoid differentiation prominent, so the case is unique in several aspects including site.

**Phil Allen** - Endometrioid adenocarcinoma of the uterus with minimally atypical, copious myxoid stroma. To me, the myxoid stroma is not quite the same as myxoid nodular fascitis or the nodular fascitis-like stroma of some papillary thyroid carcinomas or the occasional metaplastic breast carcinoma, which can almost exactly mimic nodular fascitis except that the spindle cells are keratin positive. On the other hand, I agree that it is not a malignant mixed Mullerian tumor. I will be very interested to hear what other club members think. I do not think I have seen a tumor quite like this before.

**David Ben-Dor** - this epithelial tumor is very squamous looking. The myxoid stroma is impressive but while on its own it is on the bland side it otherwise seems to merge with the epithelium. By Occam’s razor I would think of mixed Mullerian but I can’t deny the logic of Michal’s diagnosis.

**Ira Bleiweiss** - I found the endometrial carcinoma very subtle, at least on my slide, mostly I have squamous metaplasia. I wasn’t so convinced the stroma was benign and was concerned for MMMT

**Alberto Cavazza** - I agree, the stroma looks myofibroblastic/reactive to me.

**Thomas Colby** - Agree with diagnosis. I was trying to make this into a peculiar MMMT but I like the idea of fasciitis-like stroma.

**Kum Cooper** - This diagnosis seems very plausible Michal; since the MMMTs usually have high grade carcinoma and sarcoma. Thank you I have not seen this entity before neither uterus nor thyroid.

**Hugo Dominguez Malagon** - The stroma has a peculiar appearance, it shows myxoid nodules pushing the glandular structures like in fibroadenoma and some odontogenic tumors. Could it represent a biphasic neoplasm of the family of mixed Mullerian tumors? There are adeno fibromas, carcinosarcomas etc. The name could be carcino-fibroma.

**Goran Elmberger** - Seems like a plausible but rare explanation.. (GE)

**Giovanni Falconieri** - Quite remarkable loose, spindle cell stroma which suggests at a glance a biphasic neoplasm. Squamous morulae are also prominent. Great case, Michal, as always!

**Franco Fedeli** - CASE 11) Thank you for sharing this case. To me it’s possible to observe this stromal reaction in a wide set of tumors, first of all I remember the papillary thyroid carcinoma with exuberant nodular fasciitis-like stroma.

**Jeronimo Forteza** - Important for the differential diagnosis with a sarcoma.

**Maria Pia Foschini** - Endometrioid adenocarcinoma of the uterus, with fasciitis-like stroma. This is a fascinating and rare case. I do not understand if there can be a relation with low grade Mullerian carcinosarcoma affecting the uterus. (Michal published a case in Ann Diagn Pathol. 2005 Dec;9(6):335-9).

**Masaharu Fukunaga** - I agree endometrioid adenocarcinoma with fasciitis like stroma. I have never seen it before.
There are no atypia and no mitotic figures.

**Thomas Krausz** - Carcinoma with fasciitis-like stroma is a great idea, provided the spindle cells are keratin/p63 negative.

**Thomas Mentzel** - I think that cases in which the fasciitis-like stroma is predominant are very difficult.

**Markku Miettinen** - Has a weird "adamantinoid" appearance with squamous differentiation and tooth matrix-like stroma. Very unique as a uterine tumor. Even wondered if this was the right slide (but it was numbered AMR67 Case 11).

**Liz Montgomery** - This is really fascinating with this strange stroma.

**Frederik Petersson** - I cannot relieve myself from the possibility of the stromal component being neoplastic, albeit low-grade. Clonality analysis – HUMARA?

**Santiago Ramón y Cajal** - Very interesting case, Michal. The stromal component type fasciitis is benign and even a cartilaginous component is seen in my slide.

**Brian Rubin** - Very interesting case. I’m really out of my element here but I think there are a couple of possibilities besides the suggested diagnosis of endometrioid adenocarcinoma with fasciitis-like stroma. Some of the more myxoid lobules look neoplastic to me, not just reactive so it may be some sort of MMT, but the stroma looks much lower grade than usual. I also wondered if the lesion could be metastatic. Since metastatic lesions frequently cause desmoplastic stroma is it possible that the adenocarcinoma metastasized from somewhere else? That would be in keeping with cases 3 and 5, which would be ironic if true.

**James Strauchen** - I was not aware of this variant of endometrioid carcinoma with fasciitis-like stroma. Thank you!

**Saul Suster** – Not familiar with this phenomenon in endometrial carcinoma – but I don’t see much GYN pathology to begin with!

**Ady Yosepovich** - thank you for this unusual case.

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**CASE NO.12 – CONTRIBUTED BY MICHAL MICHAL**

**Abbas Agaimy** - Yet another case from Michal’s peculiar collection of strange cases. Wouldn’t this tumor be a oncocytic variant papillary carcinoma with lymphoid stroma? thinking of your large series of similar metaplastic lesions presented at the USCAP 2014 on same topic and having observed the distinctive bilayered "Warthinoid" epithelium, I agree that such a variant exist in the thyroid, albeit of unsure genetic basis. It would be interesting to look for similar cases unassociated with Hashimoto´s thyroiditis.

**Phil Allen** - Benign Warthin’s tumor of the thyroid. I initially thought it was a Warthin’s-like variant of papillary carcinoma but it really looks like a true Whartin’s tumour.

**David Ben-Dor** - Michal has very original and interesting "takes" on lesions that could be banalized by mere mortal pathologists. In this lesion there are papillary structures lined by eosinophilic cells that I would have thought were Hurthle cells. Was this the component interpreted as Warthin tumor and were these cells negative for thyroid markers? Is Warthin tumor appearing in the thyroid formed by thyroid cells or by the same cells which compose the tumor in the salivary gland? Is there a connection between the Warthin tumor and the branchial cleft portion?

**Ira Bleiweiss** - Agree. Weird.

**Alberto Cavazza** - I thought of a peculiar benign cystic lesion with squamous and Warthin-like areas occurring in the background of Hashimoto’s thyroiditis, but I was not aware of this entity: thanks!
Thomas Colby - Agree with diagnosis. I probably would have simply called this Warthin’s tumor with some metaplastic changes.

Kum Cooper – Yes, the two layered eosinophilic columnar cells are the giveaway. Again thank you for this educational case. Not seen this before. Thank you Michal.

Hugo Domionguez Malagon - Hashimoto thyroiditis with Warthin tumor, differential diagnosis with Warthin-like papillary carcinoma of the thyroid described years ago by LiVolsy.

Goran Elmberger - Interesting case. My first association was sclerosing mucoepidermoid carcinoma but closer look is more in line with Warthin with squamous metaplasia. Translocation negative?

Giovanni Falconieri - Another “man of Istanbul”. Reminds me of a Warthin-like papillary carcinoma submitted many years ago to this seminar. The papillary configuration of this particular case is remarkable.

Franco Fedeli - Educational case, especially considering the differential diagnosis with an oncocytic variant of PTC. However, the immunohistochemical profile (p63+, TTF1-, thyroglobulin-) sustain this diagnosis.

Jeronimo Forteza - The relationship with solid cell nests is interesting.

Maria Pia Foschini - This case is very interesting. The morphology is focally similar to a Warthin tumor of the parotid, and the p63 positivity, if located to the basal cell layer can confirm it. As all of you know, Warthin-like papillary carcinoma of the thyroid are described and in the present case should be considered in the differential diagnosis. In the present case, TTF1 is reported negative, and the double cell layer is underlined by the presence of p63 positive cells. Nevertheless, the nuclear contour and grooving are quite similar to those of papillary carcinoma. I wonder if the case had been diagnosed by fine needle aspiration before surgery.

Masaharu Fukunaga - A benign Warthin’s tumor in the thyroid, I have never been seen it.

Thomas Krausz – Agree with diagnosis. Intriguing at this anatomic location.

Janez Lamovec - This lesion is, of course, very different from what is known under the name Warthin-like papillary carcinoma of the thyroid that is essentially an oncocytic variant of papillary carcinoma with lymphoid stroma. This type of lesion submitted by you must be extremely rare.

Thomas Mentzel - What an unusual finding!

Liz Montgomery - Very beautiful Warthin tumor in the thyroid. Thanks so much.

Markku Miettinen - Yes, there is a strange Warthin-tumor like area in the background of lymphocytic thyroiditis. Also squamous metaplasia.

Fredrik Petersson - Agree. Despite nuclear grooves, other features of PTC not present – also architecture not worrying. Interesting histogenesis. Michal, the “recent” publication was from 2006. Time flies.

Santiago Ramón y Cajal - According to your diagnosis, Michal. It looks like a Warthin’s tumor. However, I would call it Warthin-like tumor.

Brian Rubin - I leave this diagnosis to the thyroid experts but it does remind me of a Warthin’s tumor. I’m glad that you think of 2006 as “recent”. That’s really a European perspective, which I appreciate. In the USA that paper would be categorized as “old”.

James Strauchen - Interesting lesion! I was not aware of the relation of branchial cleft cysts, Warthin’s, and SCN’s.

Saul Suster – Very rare lesion! It does indeed show some resemblance on scanning magnification to a Whartin tumor of salivary gland. Although some of the papillae are lined by tall columnar granular cells, the more solid portions are clearly squamous and show very well-defined cell membranes and pavement-like architecture. The
squamous nature of these cells is supported by the p63 positivity. Don’t know how to interpret this lesion. Although it resembles a Whartin tumor it is not really a perfect fit for it (no double cell layer in the papillae, absence of lymphoid follicles in the stroma, foci of squamous metaplasia/differentiation). It looks more like a thyroid cyst with oncocyic and metaplastic changes arising from the cyst lining.

Parenthetically, “Warthin-like PTC” does not enter in the differential here due to the absence of the nuclear features of PTC. The latter was initially presented in a platform at USCAP in 1994 as “Warthin-like tumor of the thyroid gland”, and in the same platform session there was another platform describing the oncocyic variant of PTC. It dawned only later that the two platforms were actually presenting the same thing. “Warthin-like PTC” is nothing other than the oncocyic variant of papillary thyroid carcinoma with prominent lymphoid stroma, a feature that was well-illustrated in the original platform and paper on oncocyic PTC. Dr. LiVolsi later changed the title of her paper to “Warthin-like PTC” at the time of publication in response to the criticism leveled by some of the attendees that the lesions should not be considered benign given that some of her cases had metastasized to lymph nodes.

Ady Yosepovich - It looked familiar, did not know it exists in the thyroid....

**CASE NO.13 – CONTRIBUTED BY MARKKU MIEITTINEN**

Abbass Agaimy - Very interesting case that is identical to my case in this seminar. Nice to see the striking similarity of the cases and the phenotype-genotype correlation, thanks Markku.

Phil Allen - Uterine leiomyoma associated with hereditary leiomyomatosis and renal cell cancer. These uterine leiomyomas certainly look different from ordinary fibroids. I hope I can remember the pattern in cases I see one of these rare cases at this Hospital.

David Ben-Dor - I wonder what the statistical odds are to see two examples of what is a rare condition in the same seminar (assuming that Saul didn’t engineer this). This would have flown right by me- in truth there is some atypia but not severe enough to begin to worry about malignancy especially since other than the somewhat enlarged vesicular nuclei there is no necrosis. Maybe I would have excused this as “progesterone induced changes” or found some other subterfuge. How many labs can perform the required procedure to make the diagnosis?

Ira Bleiweiss - Just like case 1!!! (or the alleged case 1 in my set)

Alberto Cavazza - Fantastic: putting together this case and case n. 1, I hope I will be able to recognize this lesion in the future (at least I will spend more time in my next uterine leiomyomas!).

Thomas Colby - Agree with diagnosis. I guess I am marginally trainable. I thought this had some similarities to Case 1 but again I was thinking about PECOMAs and other strange smooth muscle tumors.....and it IS a strange SMT.

Kum Cooper - This is so exciting - two cases in one seminar. Looks very much like Abbas’ case. Thank you Markku.

Hugo Dominguez Malagon - Nice case of hereditary leiomyomatosis RCC syndrome, good discussion.

Goran Elmberger - Role of duplicates. At least got this one right.

Giovanni Falconieri - Sorry, impossible to comment on. This goes far beyond my intellectual capability.

Franco Fedeli - I can notice that pathology related to enzymatic alterations are now emerging, in fact this particular slide seminar includes two examples of this entity.

Jeronimo Forteza - It suggests the association of other tumours with HLRCC syndrome. More specifically leiomyomas and leiomyomatosis.
Maria Pia Foschini - Uterine leiomyoma associated with HLRCC syndrome. This case is similar to case 1, and it was useful to see, in order to better understand the disease.

Masaharu Fukunaga - Another case of uterine leiomyoma associated with HLRCC syndrome. Wonderful case. Thank you, Markku

Ondrej Hes - This is very interesting case. I am sure that HLRCC will be a hot topic in the near future. We have had a wrong approach in searching for HLRCC patients. Originally such tumors were supposed to be so called "papillary RCC, type 2"...also there are limited possibilities in using immunohistochemistry (non-commercial antibody 2SC and FH). Actually we know that RCC can be papillary but also tubular, tubulocystic or mixed. The important feature is the prominent, deep red nucleolus. Such cases are mostly submitted for FH mutation analysis, which is the most reliable method (altogether with morphology) right now. We have searched for female patients with leiomyomas (age under 30) and RCC. Only 4 patients out of several hundred with leiomyomas were found (none has been proved as LH RCC syndrome).

Thomas Krausz - Great case. I have seen only cutaneous examples before. I agree, morphologically this is a rather distinctive leiomyoma, richly vascular with HPC-like vessels and striking number of cytoplasmic inclusions.

Janez Lamovec - Two extraordinary lesions in one seminar!

Thomas Mentzel - Rare things always come in clusters – see Case 1.

Liz Montgomery – This case looks so boring for such a fancy history!!! It’s nice to see this case and see the slightly altered cytologic features. One hopes that this would allow us to suggest the syndrome when we don’t know the patient has it and organize testing for loss of fumarate hydratase.

Fredrik Petersson - On my section, features were less prominent than in case 1. Seems to be a few “tumorlets” in the surrounding myometrium. Was IHC-FH done? Cutaneous lesions ??

Santiago Ramón y Cajal - HLRCC syndrome associated with leiomyoma. Thank you very much, Markku. It is important not diagnose it as malignant.

Brian Rubin - What was the probability that we would have two HLRCC leiomyomas submitted in one slide seminar? Nice case.

James Strauchen - Wow! What are the chances of having two in the same AMR slide seminar (see case 1).

Saul Suster – Very interesting case – thanks for the education, and 2 similar cases in the same seminar!

Ady Yosepovich - thank you for this unusual case.

CASE NO.14 – CONTRIBUTED BY ELIZABETH MONTGOMERY

Abbas Agaimy – Very interesting case and spectacular case presented by Liz Montgomery. While I am delighted that my views on the occurrence of NF-1-like phenotype in constitutional MMR deficiency and juvenile-like polyps in NF1 patients have been accepted by Liz on one side, I am glad to have been alerted to an even more unique and exceptionally rare occurrence of concomitant juvenile polyposis (SMAD4 germline mutated) in a patient with proven NF1 (current slide of Liz). The email communication pointed out by Liz on this topic resulted in another short publication about the same topic in Histopathology (see Brosens et al’s letter and Agaimy & Vieth’s reply). I fully agree with the comments by Liz and the content of their letter.

Phil Allen - Gastric (inflammatory/hyperplastic) polyposis associated with neurofibromatosis type I. Will these new discoveries ever cease?

David Ben-Dor - for me this is the most garden variety hyperplastic gastric polyp. It shows that ignorance is truly bliss (and is conducive to sleep which is very important for my personal health but not for the patient's).
Ira Bleiweiss - Agree.

Alberto Cavazza – I thought of a juvenile polyp, but I ignored many of the details of this topic. Thanks for the discussion.

Thomas Colby - Agree with diagnosis.

Kum Cooper - Thank you, Professor Montgomery for that erudite education on NF1-associated gastric polyps. We see a handful of NF patients here at Penn; but I have not come across these polyps.

Hugo Dominguez Malagon - Hyperplastic polyp of stomach, I was unaware of its association with NF-1.

Goran Elmberger - Interesting case. Molecular testing indication??

Giovanni Falconieri - Interesting case, agree that history is much more intriguing than the slide itself although I am always cautious with polyps of stomach as long as they may conceal some unexpected finding.

Franco Fedeli - Gastric polyposis in association with NF1. Interesting case that I’m sure that Abbas Agaimy is going to find very cool.

Jeronimo Forteza - An interesting case of how morphology and genetic alterations are associated.

Maria Pia Foschini - Gastric polyposis associated with NF1. As discussed, this case is similar to non-neoplastic gastric polyps arising in different conditions. The correct diagnosis is not simple without knowledge that the patient is affected by NF1. Several types of polyps can be encountered in the GI tract of patients with NF (Ann Acad Med Singapore 2004;33:797-9; Am J Med Genetics 2004;127A:298-301), but I wonder if the pathologist cannot suspect NF syndrome just based on the polyps!

Masaharu Fukunaga - Gastric polyposis in association with NF1. This is my first time to see it. Thank you Liz.

Thomas Krausz - Highly educational case, especially in view of the clinical context and the clinical differential diagnostic considerations.

Janez Lamovec - Partly hyperplastic, partly juvenile polyps; I was not aware of NF1 associated gastric polyps. This is getting more and more complex.

Thomas Mentzel - Many thanks for sharing this rare case.

Liz Montgomery - This is my case and the story has expanded!!! For years, I had been seeing gastric polyps from this patient and was not given the history of NF1 and kept making comments in my reports that the patient might have gastric juvenile polyposis. When we learned that the patient has NF1, we found Abbas' nice series but one of my colleagues was concerned that this poor patient actually had both NF1 and juvenile polyposis and he organized genetic testing for juvenile polyposis and found that the patient had a SMAD4 mutation as well as his NF1 alteration. My colleague was quite excited about this since we wondered if some of the cases reported by Abbas might also have this pair of alterations since some of the patients Abbas reported had a phenotype like the one in juvenile polyposis and he sent a letter - it will be cool to learn whether Abbas knows anything more now about his patients he reported. Would be really interesting if some of his patients were “double hitters” as well! Kind of an interesting idea but of course all these little polyps are rare and odd. I was able to find another old case report about the simultaneous occurrence of NF1 and something like juvenile polyposis. On the other hand, the SMAD4 gene and NF1 gene live on different chromosomes and I am not clever enough to think of a reason why the two syndromes would tend to occur together, but since our understanding of these types of gastric polyps is not great, maybe there IS an association but no one has been able to really figure it out!!! Anyway, this case was very interesting to me but not just for the morphology.


Fredrik Petersson - Hyperplastic alright. Good educational points.

Santiago Ramón y Cajal - Agree. Thank you very much.

Brian Rubin – Cool case. NF1 really is a fascinating tumor syndrome. I wonder if the polyps arise due to dysfunction of the wall of the gut or if the polyps arise due to intrinsic problems to one or more cell types in the polyps themselves.

James Strauchen - Thank you! I was unaware of this form of gastric polyposis associated with NF-1!

Saul Suster – Way out of my league!

CASE NO.15 – CONTRIBUTED BY FREDRIK PETERSSON

Abbas Agaimy - My initial impression was Perineurioma too; would stain such lesions always for MUC4 to avoid overseeing perineurioma-like LGFMS. Thanks Fredrik for sharing this nice case.

Phil Allen - Probable soft tissue perineurioma, subcutis of the arm. The only perineurioma that I am comfortable with is the very rare intraneural perineurioma, probably because in most other cases, the diagnosis rests on a single immunohistochemical stain (in the absence of electron microscopy). In this case, we have the variable expression of EMA and the poor old CD34 stain bestows her favours far too liberally to trust her much. I doubt that it is an angiomatoid (malignant) fibrous histiocytoma or a solitary fibrous tumour.

David Ben-Dor - I wish I had the requisite understanding of soft tissue tumor pathology to make any kind of constructive comment. In my slide the onion whorling is well developed and prominent but only locally; otherwise there are foci of angry looking hyperchromatic cells which look ominous.

Ira Bleiweiss - Again, I leave it to the soft tissue gurus.

Alberto Cavazza - Thanks for the beautiful discussion. Perineurioma is my best guess.

Thomas Colby - An insoluble problem with a very nice detailed discussion. How about perineurioma with SFT-like stroma?

Kum Cooper - Thank you for Fred for this interesting case. Composite intraneural and sclerosing perineurioma is my morphological interpretation. Look forward to Jason’s comments!

Hugo Dominguez Malagon - Solitary fibrous tumor vs. sclerosing perineurioma, was GLUT-1 performed in this case?
Goran Elmberger - Sorry no dedicated opinion on this one.

Giovanni Falconieri - Quite difficult, Fredrik. On the overall, the perineurioid pattern seems to predominate yet several phenotypic and immuno evidences conflict. Shall look forward to reading the opinions of the soft tissue guru. Thank you for the excellent case outline and discussion.

Franco Fedeli - Challenging case. EMA positivity is very suggestive for perineurioma. In addiction, it’s very notable the perivascular arrangement of lymphoid cells.

Jeronimo Forteza - I agree with your diagnosis.

Maria Pia Foschini - Soft tissue perineuroma with extensive CD34-positivity or angiomatoid fibrous hystiocytoma with extensive perineurioma-like pattern and EMA and CD34 expression. This is a quite difficult case. It has some similarities with a case that we reported some years ago and interpreted as hypertrophic neuritis. (Bilateral hypertrophic brachial plexus neuritis: a pathological and electrophysiological study. M. Stumpo, M.P. Foschini, M. Poppi, G. Cenacchi, P. Martinelli. Surgical Neurology, 52(5):458-464, 1999.). Hypertrophic neuritis is characterized by cells disposed in an "onion bulb fashion" around axons. Among the differential diagnoses, perineuroma was considered. At a difference with the present case, our case lacked the prominent vascular proliferation. Nevertheless, I would suggest hypertrophic neuritis among the possible diagnoses for this case.

Masaharu Fukunaga - I prefer perineuroma with focal sclerosis, Thank you for the detailed discussion, Fredrik.

Thomas Krausz - Difficult, especially in view of the conflicting immuno-results. However, my differential also includes perineuroma, SFT and angiofibroma of soft tissue. I don’t think that this is angiomatoid fibrous hystiocytoma.

Janez Lamovec - Morphologically, this appears as a combined perineurioma-SFT tumor, although immuno excludes SFT. On H&E, I would not consider angiomatoid FH and translocation studies might be helpful to exclude such, to me quite improbable possibility. As far as CD34 expression is concerned, the list of CD34 positive is expanding and expanding.

Thomas Mentzel - I was thinking on solitary fibrous tumour as well, however, given the lack of STAT6 nuclear expression, the diagnosis of perineurioma seems better (and perineuriomas stain in about half of the cases positively for EMA, as many fibroblastic neoplasms).

Markku Miettinen - I like preneurioma with CD34+, as previously reported by Hornick and Fletcher. But not all perineurioma forms are CD34+.

Liz Montgomery - This looks like a solitary fibrous tumor with meningothelial whorls to me. It’s very cute whatever it is.

Santiago Ramón y Cajal - Difficult differential diagnosis with the hematoxylin eosin. Initially diagnosed it as a benign tumor from the group of miopericitomas and secondly, a nerve sheath tumor with predominant perineural component.

Brian Rubin - Excellent case and discussion. I think the lesion is a perineurioma. I agree with Jason Hornick, Chris Fletcher and you (Fredrik) that perineuriomas have a range of differentiation and I have also found that CD34 immunoreactivity can be quite extensive. You can also see CD34 immunoreactivity in neurofibromas and Schwannomas for that matter. Some perfectly obvious perineuriomas are negative for EMA and in speaking about it with Jason, he and Chris Fletcher sign them out as something to the effect of “benign fibroblastic neoplasm with features of perineuroma”. I was one of the co-authors on Steve Billing’s study so I saw all of the cases, some of which were from my consult files. The major difference in our cases is that they had a dense population of chronic inflammatory cells simulating a lymph node surrounding the lesion but a couple of them really did look a lot like perineuriomas. I’d be happy to do EWSR1 FISH on your case if you want!

Saul Suster – I agree with perineurioma, sclerosing/involuting phase. A GLUT-1 stains would have been helpful; conversely, electron microscopy could easily resolve the issue here.
James Strauchten - Thank you for the elegant discussion and review!

CASE NO.16 – CONTRIBUTED BY MURRAY RESNICK

Abbas Agaimy – Very well presented and discussed case on rare findings in the liver, thanks for teaching us on this.

Phil Allen - Extensive centrilobular congestion and necrosis with interface calcification in an 80-year-old female with hypertensive/ischaemic heart failure, chronic renal disease and diabetes. Our local liver man, Dr Tony Thomas, who is neither a gnome nor an elf, has not previously seen this kind of calcification. I don’t suppose the patient took a few paracetamol tablets before she was admitted to hospital.

David Ben-Dor - when I first saw the slide (before reading the handout) my differential diagnosis was between bizarre degenerating nuclei and calcifications. Even after learning of the diagnosis and seeing the slide once more I can't help but notice that while some of the deep blue deposits look homogeneous and without any internal structure some are disintegrating and have “granular” features mimicking chromatin. Food for thought.

Ira Bleiweiss - Agree.

Alberto Cavazza - Nice case, I have never seen this degree of calcification in ischemic injury of the liver.

Thomas Colby - Agree with diagnosis (after second review). I had been concerned about bacteria in a profoundly immunosuppressed patient with some associated calcifications but I guess all those tiny calcifications that are about the size of bacteria are probably calcified organelles of some type, perhaps mitochondria. I am probably a member of the minority since I thoroughly enjoy these non-neoplastic cases.

Kum Cooper - Welcome to the AMR Murray! Some of the calcification seems to be intracellular; most of which are undergoing necrosis. Interesting case. Never seen anything like it.

Hugo Dominguez Malagon - Spectacular case of hepatic necrosis with extensive calcification, thank you.

Goran Elmberger - Interesting pathophysiological discussion.

Giovanni Falconieri - An unusual finding, I do not have memory of these changes. I am afraid I have not recognized or misinterpreted them as post mortem artifacts whenever I come across. A very educating case of general anatomic pathology

Franco Fedeli - Thank you for sharing this peculiar case. In my opinion these calcifications appear more dystrophic than metastatic.

Jeronimo Forteza - The calcification of centrilobular necrosis in cases in which there is no hypercalcemia could be related with the intensity of the ischemia, but may also be linked with other aetiologies. Diabetic livers are possibly more sensitive to necrosis due to changes in mediators of this process.

Maria Pia Foschini - Extensive centrilobular congestion and necrosis with diffuse hepatocellular calcification. This is a very rare feature of hepatocellular necrosis. Calcium deposits have been described also in association with hepatocellular carcinoma (Wang CE et al. World Journal of Gastroenterology 2014;20(43)16377-80).

Masaharu Fukunaga - I have never seen such a liver with prominent calcification. Its etiology is very interesting.

Ondrej Hes - I have seen one autopsy case with extensive calcification within liver in patient with Caroli disease (congenital dilatation of the intrahepatic bile ducts). However, calcifications in this case were not of hepatocellular origin but were located mostly in dilated lumina. Another experience when I came across extensive calcification was hydatid cyst of the liver (very rare finding in Central Europe).
**Thomas Krausz** - Purely on morphological ground I favor dystrophic calcification.

**Janez Lamovec** - In our experience, osteoclast-like giant cells in sarcomatoid spindle cell component of metaplastic carcinomas that are not associated with osteoplasia are quite rare. However, we have seen pure spindle cell metaplastic carcinomas with osteoclast-like giant cells without any admixed component of high grade IDC. On the other hand, I am not aware of any report of IDC with osteoclast-like giant cells associated with metaplastic carcinoma component.

**Thomas Mentzel** - An unusual phenomenon indeed.

**Liz Montgomery** – This is a really crazy case with all the calcification. Thanks for sharing it.

**Fredrik Petersson** - Peculiar pattern of calcification, indeed. Some weakly basophilic ring-shaped/bug-like structures.

**Santiago Ramón y Cajal** - Very interesting case. Thank you very much.

**Brian Rubin** - Interesting. Thanks for educating me about calcifications in the liver.

**James Strauchen** - Wow, calcified hepatocytes. Never seen that before!

**CASE NO.17 – CONTRIBUTED BY SAUL SUSHER**

**Abbas Agaimy** - Nice and very rare example of fibrothymolipoma, thanks Saul for brief and excellent discussion.

**Phil Allen** - Thymofibrolipoma, anterior mediastinum. This is the first one that I have seen. Many thanks for the contribution, Saul.

**David Ben-Dor** - aside from the obvious adipose tissue component I was intrigued by a fibrous tissue component containing epithelial cells which form structures composed of two parallel layers of small epithelial cells which I can only describe as canalicular and which reminded me of canalicular adenomas which are uniquely found in one of the lips. Is this type of epithelium seen in normal thymus? - not that I know of. The fibrous and epithelial tissue seem to be growing in tandem as would be seen in a biphasic tumor. I don't know what the significance of any of this is. I found Hassall's corpuscles only in one portion of the slide which shows more typical lymphocyte rich thymic parenchyma. I don't see any marked demarcation between the former and latter aspects of the lesion. To my understanding the parenchymal component of a thymolipoma would look like routine thymus with a lymphoid component.

**Ira Bleiweiss** - I don't see anything ominous for malignancy in any of this. Agree.

**Alberto Cavazza** - Very nice case, I thought of a thymolipoma but I forgot the paper of Dr. Moran on thymofibrolipoma and I buy this diagnosis.

**Thomas Colby** - Agree with diagnosis. A very lovely histologic example.

**Kum Cooper** - Thanks Saul. My initial impression was that of thymolipoma (not having read Cesar's paper!); then the epithelial component (strands) reminded me of ectopic hamartomatous thymoma. So I was pleased to read that you consider a hamartomatous component too!

**Hugo Dominguez Malagon** - My limited experience made me think in thymolipoma, thanks for illustrating me.

**Goran Elmberger** - New to me.

**Giovanni Falconieri** - Don't know this microscopic entity. My impression was of an hamartomatous lesion and could not perceive a significant amount of fibrous tissue.
Franco Fedeli - Rare case. In some aspects this lesion reminds of me the morphology of the so called ectopic hamartomatous thymoma.

Jeronimo Forteza - Thank you for sharing this interesting case.

Maria Pia Foschini - Thymofibrolipoma. I agree with Saul’s interpretation that it is most probably a hamartoma. The morphology is very bland and very similar to the normal epithelial thymic component. I am afraid that in a small biopsy it could give the impression of being normal thymus!

Masaharu Fukunaga - Thank you for sharing the interesting and the rare case of thymofibrolipoma. I have never seen before. The comment is very informative.

Thomas Krausz - Great case, I hope will not come across this entity on a biopsy specimen.

Thomas Mentzel - Many thanks for this case that looks like ectopic hamartomatous thymoma.

Fredrik Petersson - Got the thymolipoma part. Looked in vain for evidence of thymoliposarcoma.

Santiago Ramón y Cajal - Thank you, Saul. Agree that it may represent a hamartomatous lesion

Brian Rubin - Very interesting case. I agree with you that it does not have the features of a liposarcoma. However, I may be biased due to my subspecialty interest but atypical lipomatous tumor/well differentiated liposarcoma of the mediastinum including thymus is not that rare.

James Strauchen - Thymo(fibro)lipoma! Very nice case!

CASE NO.18 — CONTRIBUTED BY ADY YOSEPOVICH

Abbas Agaimy – Teaching example of metaplastic breast carcinoma with diverse appearance, thanks Ady.

Phil Allen - High grade metaplastic carcinoma with osteoclast-like giant cells, right breast. I have seen one or two cases like this over the years.

David Ben-Dor - I guess that for the oncologists this would be a unique type of triple-negative tumor. Did you do CK 5/6 which is often positive in spindle cell breast carcinomas? I remember seeing osteoclastic type giant cells in a leiomyosarcoma and also in a bladder carcinoma (later included in a series published by Amin and Epstein). I don't know if anyone knows what they really mean (asides from arousing the interest of the pathologist).

Ira Bleiweiss - Agree. I've seen a few cases of breast carcinoma containing benign looking osteoclast like giant cells, typically accompanied by hematopoietic cells (even grossly having a brownish tinge, like bone marrow). Ady - If they are really eating the tumor cells, maybe you've discovered a new treatment for breast cancer. You could patent them and retire!!

Alberto Cavazza - Nice case. Probably I would diagnosis this case simply as sarcomatoid carcinoma.

Thomas Colby - Agree with diagnosis. Osteoclastic giant cells appear to be making a comeback.

Kum Cooper - Interesting case Ady. What was her BRCA status? Also with the secretory activity I wonder if this is high grade variant of secretory carcinoma (I just made that up!). Be interesting to check the ETV1 FISH status.

Hugo Dominguez Malagon - Sarcomatoid carcinoma or if you wish metaplastic carcinoma with osteoclastic giant cells, they have been described in many tumors, like bladder, pancreas and lung, probably representing a reactive phenomenon of the stroma rather than neoplastic cells.
Goran Elmberger - Medullary carcinoma?? FV-PTC?

Giovanni Falconieri - Agree with your interpretation, my slide shows all the microscopic features of a pleomorphic carcinoma with osteoclast-like giant cells. I think I have seen this in slide seminars but I have not memory of it in my practice.

Franco Fedeli - I find this case very didactic, showing the possible presence of osteoclastic-like giant cells in this tumor (Hum Pathol: 21, 1142-1150, 1990). In addition, I consider this finding a possible feature of the sarcomatous carcinomas in other organs too.

Jeronimo Forteza - A very interesting case. I agree with the diagnosis.

Maria Pia Foschini - High grade metaplastic carcinoma with mesenchymal differentiation (carcinosarcoma) and osteoclast-like giant cells. Osteoclast-like giant cells (OGC) can be seen in breast carcinomas. A complete and detailed description was offered by Holland R and van Haelst UJ (Cancer. 1984 May 1;53(9):1963-73. Mammary carcinoma with osteoclast-like giant cells. Additional observations on six cases.). In the original paper OGC were associated with low grade carcinomas of the breast. Subsequently the spectrum of breast carcinomas associated with OGC has been widened. The hypothesis of a host reaction to the tumor cells is supported by the immunohistochemical profile of the OGC, that suggest the histiocytic nature. In addition OGC accompany the tumor cells also when lymph-node metastases appear and in a case of multifocal invasive breast carcinoma (Richter G et al. Journal of Medical Case Reports 2011;5:85).

Masaharu Fukunaga - High grade metaplastic carcinoma, I agree. However, mesenchymal differentiation is not clear and it seems be sarcomatous features.

Ondrej Hes - Great case, I haven´t seen similar cases yet in breast. In urothelial carcinomas it is not common, but occasionally present phenomenon, ie “osteoclasts” on the background of more typical TCC (not sarcomatoid). Very rarely it is possible to find tumors (mostly in the renal pelvis) which are nearly identical with giant cell tumor of bone. In a minority of such cases it is not possible to find even a small urothelial component (however I believe it is sample error).

Thomas Krausz - Agree with diagnosis.

Thomas Mentzel - The osteoclast-like giant cells are a reactive component.

Fredrik Petersson - Metaplastic breast carcinoma – carcinosarcoma agree.

Brian Rubin - I always get messed up on the nomenclature. What is meant by “of carcinosarcoma subtype”. Does that mean that it is a metaplastic carcinoma with areas that look like carcinoma and other areas that look like sarcoma? Anyway, I agree with the diagnosis of metaplastic carcinoma with osteoclast-type multinucleate cells. They are definitely "feeding" on something. They really like blood so they are often found at the edges of blood pools – think aneurysmal bone cyst. However, in this case it’s not clear what attracted them to the lesion.

James Strauchen - Metaplastic carcinoma. Thank you!

**QUIZ CASE NO.1 – CONTRIBUTED BY ABBAS AGAIMY**

Abbas Agaimy - My case: this patient has a history of breast carcinoma and now presented with this very unusual thyroid pathology. I signed the case as extensive bilateral microfollicular adenomatosis of the thyroid. In my experience, such findings in conjunction with breast cancer should alert to the possibility of Cowden disease. This has been discussed in the report, but results of further investigations are not communicated yet. The thyroid pathology in Cowden disease is variable and follicular carcinomas as well as adenomatous goiters are well described. Might be of value to stain such cases with PTEN antibody. I presented this case hoping to hear the comments of Dr. Rosai and those with deep experience in thyroid pathology on this unusual case.
Phil Allen - Don’t know. Histologically bland, multinodular, follicular lesion involving the entire thyroid. I do not think it is metastatic breast carcinoma nor does it look like a multinodular goiter. I would have thought that a follicular thyroid carcinoma that is so widespread would have exhibited extensive vascular invasion.

David Ben-Dor - obviously it can’t be so simple since it’s a quiz case but if it came to my just like that without a history why not call it microfollicular adenomas? - though there is a marked discrepancy in the size of the nodules and they are well demarcated from the surrounding normal looking thyroid parenchyma. If metastatic breast, then what is the primary tumor? Doesn't look like tubular carcinoma which in any case is rather indolent and wouldn't be expected to recur many years afterwards as a thyroid metastasis. Some kind of odd genetic syndrome? The nuclei aren’t diagnostic for papillary carcinoma.

Alberto Cavazza - The nodules have some nuclear features of papillary carcinoma, but at the end I think they are not. I considered the possibility that they are composed of elements different from follicular thyroid cells and probably I would do a couple of immunostains. At the end my guess is a peculiar multinodular hyperplasia of the thyroid, but probably I am missing something.

Thomas Colby - Multinodular microfollicular hyperplasia

Kum Cooper - Multinodular adenomatous goiter (with focal FVPTC) with the blessing of Dr LiVolsi who has seen about 10 cases of this entity!


Giovanni Falconieri - Mmmmm .... Wonder where the trick is, it looks just a microfollicular hyperplastic goiter, but I am missing something. I am sure!

Franco Fedeli - Very challenging case. The histologic findings remind me in some aspects a nodular hyperplasia of the thyroid. Could it be related to any genetic alteration? Are neuroendocrine markers negative?

Jeronimo Forteza - The morphology of this case recalls a hyalinizing trabecular tumour in its malignant version?

Maria Pia Foschini - F 63: Previous diagnosis of breast carcinoma, presents with a diffusely enlarged thyroid gland. Unusual proliferation of small glands forming nodules of various dimensions. As a first hypothesis I would favor a thyroid follicular proliferation. Nevertheless, even if it has no features of breast carcinoma, I would ask for ER and PR receptors. In addition, I would search for calcitonin positivity to exclude a follicular type medullary carcinoma.

Masaharu Fukunaga - It seems to be identical to case 1. Uterine leiomyoma associated with HLRCC syndrome.

Hugo Dominguez Malagon - Nodular goiter with microfollicular nodules vs. nodular C-cell hyperplasia.

Janez Lamovec - Instead a quiz case, I received another slide of regular case No. 1 (Abbas’ case)

Markku Miettinen - Primary thyroid lesion. Cannot be convinced of papillary carcinoma even if some grooves are present. Immunostains should resolve breast vs. thyroid if any doubt (TTF1, GATA3).

Fredrik Petersson - My slide is the same as Case 1.

Santiago Ramón y Cajal - In my slide, I saw basically multiple thyroid nodules in the context of a nodular adenomatous hyperplasia. I wondered history and previous treatments.

Brian Rubin - Could this be some sort of nodular c cell hyperplasia? The cells look neuroendocrine. I also considered an unusual intrathyroidal parathyroid proliferation and lastly a very odd medullary carcinoma (but the cells looks benign).

Saul Suster – My slide is the same as Case 1 – Abbas, could I get another recut from this rare and excellent case! My apologies for the mishap in triaging the slides!
James Strauchen - Florid nodular hyperplasia.

Paul Wakely - ? Micronodular hyperplasia

QUIZ CASE NO. 2 – CONTRIBUTED BY ALBERTO MARCHEVSKI

Alberto Marchevski – My case: Bronchiolitis obliterans (BO) (chronic rejection). The case shows severe fibrosis centered around bronchioles. Some of the bronchioles show complete obliteration by fibrosis, while others show mostly peribronchiolar fibrosis. The pathologic changes are very patchy and multiple sections are often needed to be able to diagnose bronchiolitis obliterans (BO). Pathologists should be aware of this potential problem and take adequate tissue samples or discuss the limitations of biopsies, particularly transbronchial biopsies, with pulmonologists in cases that are not diagnostic pathologically after comprehensive evaluation.

Chronic allograft rejection remains as a major source of morbidity and mortality after lung transplantation, and often results in respiratory failure and death after the first year following lung or heart-lung transplants. Patients present with progressive dyspnea and worsening decrease in forced expiratory volume in one second (FEV1). The condition is usually diagnosed clinically on the basis of pulmonary function tests and imaging studies as bronchiolitis obliterans syndrome or BOS. Chest CT shows evidence of air trapping. Transbronchial biopsies have low sensitivity (approximately 15%-17%) with a specificity of 94.5% and are mostly useful to exclude other conditions such as acute cellular rejection, infectious pneumonias and others.

There is no adequate therapy for BO. Patients are often treated with azithromycin, cyclosporine or tacrolimus, all immunosuppressors that can slow the progression of decline in respiratory insufficiency in some patients but do not reverse the fibrotic process. Pulmonologists also attempt to prevent the development of BO by attempting to avoid various clinical problems that have been associated with an increase incidence of BOS and BO such as repeated episodes of acute cellular rejection, gastrointestinal reflux, infections such as influenza, CMV and pneumococcus and others. Pulmonary re-transplantation can be attempted in selected patients.

David Ben-Dor - I can only say that I hope my lungs are in as good shape as this slide looks to me!

Alberto Cavazza - Difficult case. I think there are subtle alterations of the small and medium-sized airways, with ulceration of a bronchiolar epithelium and large areas in which I do not recognize bronchioles (maybe they are replaced by small scars). As an indirect sign, there are focal peribronchial/peribronchiolar accumulations of foamy macrophages (which are probably small foci of obstructive pneumonia). At the end, I think this patient had a constrictive bronchiolitis as an expression of chronic rejection. To confirm this hypothesis, it would be interesting to know if the patient had an obstructive syndrome, as I suspect she did.

Thomas Colby - Obliterative bronchiolitis with somewhat patchy involvement of what appear to be bronchioles and small bronchi.

Kum Cooper - Chronic rejection involving large airways and hypertensive changes of arteries.

Hugo Dominguez Malagon - Lymphangioleiomyomatosis vs rejection with perivascular and peribronchial fibrosis.

Giovanni Falconieri - Patchy desquamative pneumonia? Minimal changes?

Franco Fedeli - Challenging case. Although I’m not an expert in transplant pathology, I can notice the presence of an inflammatory and necrotic injury to the bronchial wall. Could it be related to the reject of the organ?

Jeronimo Forteza - Hyperplasia with hyalinization of the muscle layer of the vascular walls? Hyperplasia of neuroendocrine cells?

Maria Pia Foschini - Patient with previous systemic and lung hypertension. The lung section shows minute glomeruloid vessels along the fibrous septa, suggestive of recurrence of pulmonary hypertension. In addition, some alveoli are filled with macrophages having a finely granular and foamy cytoplasm. As the patient has been, most
probably, treated with immunosuppressive therapy for the previous lung and renal transplantation, I would check these macrophages for opportunistic infection, such as atypical mycobacteriosis.

**Masaharu Fukunaga** - Peribronchial fibrosis with intraalveolar histiocytic infiltrates. I have no idea of the diagnosis.

**Janez Lamovec** – Patchy perivascular and interstitial fibrosis and sclerosing bronchitis – I don’t know how to classify this lesion.

**Markku Miettinen** - Changes seem somewhat subtle with perivascular and peribronchial fibrosis.

**Fredrik Petersson** - Have to pass on this.

**Santiago Ramón y Cajal** - A subtle case, initially raised me a diagnosis of chronic rejection.

**Brian Rubin** - I cheated and shared this case with one of my pulmonary pathology colleagues since I couldn’t make much sense of it. He wondered whether the emboli in the capillaries with the associated giant cell reaction were silicone or other foreign material. He also noted foci of obliterative bronchiolitis (hope I spelled it correctly). We were both struck by the macrophages but in the end we figured they were a red herring.

**James Strauchen** - Vanishing bronchioles.

**Paul Wakely** - I must be missing something since this looks like histologically normal lung with some foci of extramedullary erythropoiesis.
Follow-up to AMR Seminar #56; case 17 (Contributed by Dr. Dominic Spagnolo). This was a controversial splenic marginal zone hyperplasia vs marginal zone lymphoma. Colleagues who opined at the time may be interested to learn of the patient's course. Seven years post-splenectomy, and after several uneventful pregnancies, the patient remains well, although she is anxious and always concerned she has something sinister going on. Her attending haematologist is convinced she does not have a lymphoma. She recently was found to have prominent lymphoid tissue in the hypopharynx, post-nasal space and base of tongue, and had mild/moderate cervical adenopathy. Multiple biopsies of these sites were performed elsewhere, and cervical nodes excised. Similar to the splenectomy of 2008, the nodes showed the same unusual pattern of prominent mantle/marginal zone hyperplasia, albeit more patchy than the uniform changes in the spleen. The other biopsy sites revealed unremarkable (reactive) lymphoid tissue. The expanded follicles in the node are clearly polyclonal - there is no light chain restriction. Molecular studies clearly show only polyclonal IgH, Ig-kappa and Ig-Lambda gene rearrangements. I repeated the light chain immunostains (all clearly polyclonal) and molecular assays on 3 splenic paraffin blocks from 2008, using our more sensitive assays (Biomed-2 primers, capillary electrophoresis and Genescan analysis of electropherograms), confirming again that there are only polyclonal gene rearrangements. I can only conclude that there is no lymphoma. As to the cause of this unusual pattern of florid hyperplasia, I remain clueless. I have noted in her lab reports (done elsewhere) that she has some mild polyclonal elevation of serum IgA and IgG levels; there is no autoimmune disease documented, though I have suggested this again be investigated by serology etc. There are no clinical grounds to suggest that there is any underlying immunodeficiency, nor is there any family history of such. But I have suggested to the haematologist that a specialist Immunologist review might be prudent.