# COMMENTS TO AMR SEMINAR #52

**CASE NO. 1 – CONTRIBUTED BY VOLKAN ADSAY:**

**Phil Allen:** Gastrointestinal-type clear cell sarcoma, stomach. Looking at the slide "blind," I thought it was a metastatic malignant melanoma. I should have realized that as an AMR case, it had to be a clear cell sarcoma. Interestingly, this also lacks the giant cells that are a feature of soft tissue clear cell sarcomas.

**Carlos Bacchi:** This is really a fascinating case. Although GIST is an important differential diagnosis in this case, I wasn't favoring much this diagnosis as the cells are uniformly epithelioid; an unusual feature of epithelioid GIST where the neoplastic cell population tends to be not so uniform like in this case. In fact, I was thinking melanoma as the main differential diagnosis. As I wasn't aware of this entity, I confess that I would probably diagnose melanoma especially considering that S-100 protein being strongly positive. The presence of EWS/ATF-1 fusion is very convincing for the diagnosis of clear cell sarcoma of the stomach (according to the literature). Thank you for teaching me about this rare type of neoplasm.

**David Ben-Dor:** The tumor cells have an epithelioid appearance and show variable degrees of nesting. The obvious differential would include by default GIST and, given that this is the AMR slide seminar, something offbeat like melanoma. To be honest, I didn't pick up the clear cell aspect until reviewing the slide after learning the diagnosis. However, my experience is that something like this can occur in large resection specimens due to fixation problems. I never heard of a variant of clear cell sarcoma peculiar to the stomach which is negative for HMB-45; I thought that staining for the latter was the defining characteristic of this group of tumors.

**Gerald Berry:** Beautiful example. I find that my differential diagnosis for non-epithelial neoplasms continues to expand!

**Michele Bisceglia:** Gastrointestinal-type clear cell sarcoma. Welcome to the club, Dr. Adsay. Nice case. It should be in the same spectrum as tumors described by Zambrano et al in 2003. Cases reported by Zambrano were also S-100 +ve and negative for melanocytic markers. Differently from the case here contributed, those cases described by Zambrano et al were "osteoclast-rich" (Zambrano E, Reyes-Mugica M, Franchi A, Rosai J. An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. Int J Surg Pathol. 2003 Apr;11(2):75-81).

**Ira Bleiweiss:** Agree, but I've never seen a case of this in the stomach. Other things also get confused with gastric carcinoid, such as glomus tumor, 2 examples of which I've sent to the seminar in the past.

**John Chan:** Initially, I have not considered the possibility of clear cell sarcoma at all. I seriously thought of epithelioid GIST, and even briefly considered the possibility of glomus tumor. In retrospect, the desmoplastic stroma would be most unusual for GIST.

**Tom Colby:** Agree with diagnosis. New entity for me.

**Kum Cooper:** Beautiful case, thank you. Yes, the morphology does look characteristic and GIST will always need to be ruled out. I have been waiting for this case to come along since reading Christina's paper. However, I guess we will always resort to FISH/cytogenetics to confirm the diagnosis. Welcome to the club!

**Ivan Damjanov:** Without immunohistochemistry, I would have thought that this is a GIST. But I would have been wrong- excellent diagnosis.

**Otto Dietze:** Clear cell sarcoma, convincing histology and IHC.

**Hugo Dominguez-Malagon:** Extraordinary case of clear cell sarcoma of gastrointestinal type; my initial diagnosis was GIST vs a tumor of myoepithelial cells.

**Göran Elmberger:** Thanks for a wonderful case and beautiful description. Illustrates the value of being persistent and well read. I did not know about this entity myself, and it is certainly not described in standard textbooks. Without good molecular laboratory, I guess dx would be pretty much impossible to make. Using commercial FISH test? Specific?
PS. I noted a few osteoclast like giant cells as described by E. Zambrano et al. Thanks!

**Vincenzo Eusebi:** Very interesting case. I would call it an osteoclast rich tumour of the GI tract with features resembling clear cell sarcoma of soft parts [1]. Osteoclast like cells are scattered but present in my section.
(Zambrano E, Reyes-Mujica M, Franchi A, Rosai J (2003) An osteoclast-rich tumor of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: reports of 6 cases of a GIST simulator. Int J Surg Pathol 11:75-81).

**Giovanni Falconieri:** Pretty difficult. Honestly I would not have recognized CCS and add it to my differential. Based on the overall morphology, my only guess would be melanoma, metastatic. Thanks for this contribution and welcome to the Club. Needless to say it, this was a great start.

**Cyril Fisher:** Clear cell sarcoma of GI tract with characteristic morphology and genetic confirmation, great case. A possible primary clear cell sarcoma with EWS-ATF1 has also been reported in GI tract (Hum Pathol 2005; 36: 74) so that both tumor types might occur in this location, provided metastasis is excluded. Welcome to the club.

**Andrew Folpe:** Entirely agree with GI clear cell sarcoma-like tumor. The morphology is essentially identical to that of the 3 cases I have previously seen, with the exception of the absence of osteoclastic giant cells in this example. A question for the AMR members- has anyone seen one of these in soft tissue or other non-GI locations? I strongly suspect that they occur. My guess is that they get labeled as conventional CCS, perhaps even with break-apart EWS FISH "confirmation".

**Christopher Fletcher:** Great example of clear cell sarcoma arising in the GI tract – indeed, on H&E, these lesions more closely resemble conventional melanoma rather than clear cell sarcoma of the type which arises in the extremities – except for the fact that the cytomorphology is relatively more uniform. The genetic and immunohistochemical differences from clear cell sarcoma in the extremities are fascinating, and it is even more remarkable to note that the two fusion genes characterized in clear cell sarcoma (*EWSR1-ATF1* and *EWSR1-CREB1*) have now also been defined as the commonest fusion genes in so-called angiomatoid 'MFH'.

**Jerónimo Forteza Vila:** We agree with the diagnosis. We have a similar case in press in the International Journal of Surgical Pathology.

**Masaharu Fukunaga:** My impression was paraganglioma or malignant melanoma. This is the first time I see gastrointestinal- type clear cell sarcoma. Thank you very much for the informative description.

**Allen Gown:** Beautiful and beautifully well documented example of clear cell sarcoma of the GI type. Absence of melanocytic differentiation is probably a function of the different translocation that occurs in this variant.

**Thomas Krausz:** Before reading the discussion, I was considering epithelioid GIST and some kind of metastatic tumor. I hope I will get the correct diagnosis next time.

**Janez Lamovec:** On H-E slides, I think that most people would diagnose this tumor as a GIST and clear cell sarcoma would be another, more remote possibility. Given the negative immunos for such diagnoses, this may well be a special entity or a variant of either of the two mentioned tumors.

**Thomas Mentzel:** Thank you very much indeed fort his beautiful example of rare clear cell sarcoma arising in visceral location mimicking gastrointestinal stromal tumour.

**Markku Miettinen:** Fully agree on GI clear cell sarcoma and on your comments. These tumors do differ somewhat from GISTs, especially by the nesting pattern, presence of desmoplastic stroma and osteoclast-like giant cells, as seen in the presented case (the latter feature was originally reported by Dr. Rosai's group [Zambrano et al. Int J Surg Pathol 2003;11:75-812]). We have seen approximately 15 cases, many as a byproduct of GIST-studies while screening large numbers of tumors originally considered leiomyosarcoma, especially in the days prior to immunostains. They seem to be more common in the stomach but also occur in the small intestine. As in your case, they often metastasize to lymph nodes much like melanoma and different from GIST, from which I have seen only 2 cases of genuine nodal metastases. Morphology differs from peripheral clear cell sarcoma (smaller cells, less prominent nuclei) and in fact there is some histologic similarity to desmoplastic small round cell tumor in the GI clear cell sarcomas.

**Liz Montgomery:** Thanks so much for this wonderful case. What is also cool is that once one knows this is S100 reactive, the DD of metastatic melanoma is a big one but this lesion is following the rule of translocation sarcomas and displaying monotonous cells with minimal nuclear pleomorphism and no atypical mitoses. It is also more "packed" than some examples of GI tract clear cell sarcoma so easier to recognize as such. I am sure, however, that in the pre immunohistochemical/molecular testing era, we would all have called this epithelioid GIST or even "leiomyoblastoma"! As an aside, we have recently noticed that about a third of epithelioid GISTs show Melan A staining [but of course lack S100 protein].

**Juan Rosai:** Good example of a tumor entity that still needs to be properly categorized. The discussion by Volkan is very good, but it does not tell the whole story. Basically, it would seem that there are four types of melanocyte-related neoplasms that can involve the GI tract:

1- Solitary or multiple metastatic melanoma from a distant source, usually the skin. Not much needs to be said about this situation, which we have all seen.
2- A solitary tumor looking in every respect like a malignant melanoma (pigmented, epithelioid, positive for all the melanocytic markers, the whole works) located somewhere in the GI tract, in a patient without past or present

history of melanoma. Traditionally, these tumors have been generally regarded as being in all likelihood metastatic melanomas from either undetected or regressed primaries, but it is possible that some of them represent primary tumors (Hum Pathol 36: 74-81, 2005). Of course, I am not including in this category the melanomas of esophagus and anal canal.

3- A tumor of the GI tract (usually small bowel or stomach) that looks like clear cell sarcoma/malignant melanoma of soft parts, **including** focal evidence of melanogenesis and immunoreactivity for S-100 protein **and also** for the melanocytic markers, such as HMB-45 and Melan-A.

4- A tumor of the GI tract (again usually located in the small bowel or stomach) that looks like the one described in Category 3 (including strong positivity for S100 protein), except for the fact that it is not pigmented and that it is negative for the melanocytic markers such as HMB-45. We reported on a small series of cases with these features, which contained a scattering of osteoclast-like multinucleated giant cells (Int J Surg Pathol 11: 75-82, 2003).

Tumors in Categories 3 and 4 are associated with a 12, 22 chromosomal translocation involving EWS gene in chromosome 22, analogous to the one in clear cell sarcoma/malignant melanoma of soft parts when occurring at its usual site, i.e., the soft tissue. The most intriguing aspect is that the translocation partner in chromosome12 is sometimes ATF1 (i.e., the one involved in tumors in the soft tissue location) but sometimes a different gene, named CREB1 (Clin Cancr Res 12: 5356-62, 2006). For a while, it seemed like a neat pattern was developing , i.e.:

1- Soft tissue location → full presence of melanocytic markers → EWS- ATF1 gene fusion.

2- GI location → Osteoclast-like giant cells → Absence of melanocytic markers (except for S100 protein) → EWS-CREB1 gene fusion.

However, several exceptions to this attractive scheme have been recorded (Int J Surg Pathol 13: 309, 2005). More cases will need to be studied to get at the bottom of this story. On the basis of the above considerations, it seems to me that Volkan's case fits better Category 4 despite the absence of osteoclast-like giant cells.

**Dominic Spagnolo:** This is indeed a nice example of clear cell sarcoma of the GIT - thank you. I have a similar case in the small intestine, which I will submit in due course as well to the group.

**James Strauchen:** This is a new one to me! Thought of a rhabdoid tumor or met. Thanks for this instructive case!

**Saul Suster:** Thank you Volkan for this great case and welcome to the club! I'm sure I must have seen this before but had no clue at the time of what I was looking at and called it GIST or melanoma. Thank you for the educational discussion. I get the feeling that CCS is going to become the next SFT/PECOma in that we will soon realize it is a ubiquitous neoplasm as we learn to recognize it better. Cesar and I recently got a submission for the *Annals of Diagnostic Pathology* of a case that presented as a primary tumor of the anterior mediastinum.

**Lawrence Weiss:** Nice case, workup, and discussion.

**CASE NO. 2 – CONTRIBUTED BY DAVID BEN-DOR:**

**Phil Allen:** Langerhans cell histiocytosis, cervical lymph node. Some of the Charcot-Leyden crystals can be seen en face and resemble the conventional hexagonal representation of benzene rings, something I had not appreciated before. I look forward to seeing Saul and Cesar's article on paper. Phil Lieberman's big article on Langerhans cell granulomatosis in Am J Surg Pathol 20:519-552, 1996 is encyclopedic and is also of considerable historical interest.

**Carlos Bacchi:** This is a beautiful case indeed with marvelous histology and excellent discussion. Thanks David.

**David Ben-Dor:** This is my case. I was given follow-up shortly after submitting the slides. CT of the abdomen and head performed post-diagnosis were negative; examination of the neck showed multiple enlarged lymph nodes and that of the thorax showed multiple disseminated nodules. Up to receipt of information, he had not yet received any treatment.

**Gerald Berry:** Nice discussion.

**Michele Bisceglia:** Langerhans cell histiocytosis of lymph node. Thank you for this very beautiful case. I am sure of having seen in the past one such case in a peribronchial lymph node; further, around 15 years ago –while spending some weeks in London I was shown another such case by Dr Alsanjari (former registrar with Dr. Cyril Fisher at that time): the latter case was associated with metastatic papillary thyroid carcinoma and was soon after published in the literature (Schofield JB, Alsanjari NA, Davis J, MacLennan KA. Eosinophilic granuloma of lymph nodes associated with metastatic papillary carcinoma of the thyroid. Histopathology. 1992 Feb;20(2):181-3). Would like also to mention (in differential diagnosis) another case I had the opportunity to observe of a neck lymph node, which had tremendous infiltration by eosinophils with necrotizing granulomas, giant cell reaction, huge Charcot-Leyden crystals, and Langerhans cell reactive hyperplasia. I sent this case in consultation to Dr Rosai and to a very experienced hematopathologist, and received 2 different opinions by each of them (reactive likely due to allergic reaction to parasitic-worms infestation by the former and Langerhans cell histiocytosis of the lymph node by the latter). Interestingly, in the history which was given later, this

patient (young boy) had fluctuating lymph adenomegaly. That case was reported as an abstract (M. Bisceglia, P. Paolucci, G. Cenacchi, J. Rosai. Granulomatosi necrotizzante “eosinofila benigna" del linfonodo. Descrizione di un caso. I° Congresso Nazionale della Società Italiana di Anatomia Patologica e Citopatologia Diagnostica. Taormina 6-10 Ottobre, 1998. Pathologica 90: 572-573, 1998).

**Ira Bleiweiss:** Agree. I guess the TB culture was negative.

**Tom Colby:** Agree with diagnosis; classic case. I agree, some of the necrotic granulomas look like Churg-Strauss syndrome, but I have never seen that involve a lymph node. Ronald Dorfman used to say every putative case of Churg-Strauss disease he encountered involving a lymph node turned out to be either Hodgkin’s disease or this condition, Langerhans’ cell histiocytosis. The Charcot-Leyden crystals are an interesting wrinkle.

**Kum Cooper:** Lovely example, David, of LCH involving lymph node with beautiful nuclear morphology. On low power, the eosinophilic abscesses brought on the differential of Kimura's disease (which you included in your discussion).

**Ivan Damjanov:** Agree with your diagnosis. Is this antibody "langerin" any better than CD1a?

**Otto Dietze:** Good example, I remember a case of lymph node involvement with only a few eosinophils and in this patient the course was very aggressive.

**Hugo Dominguez-Malogon:** Completely agree with the diagnosis of Langerhans cell histiocytosis of lymph node, nice discussion.

**Göran Elmberger:** Thanks for submitting a great case and pointing out excellent recent relevant articles. I have more experience from lung lesions but to me the Langerhans cell morphology looks pretty convincing. Also in my slide, 2 necrotizing eosinophilic granulomas are present with true epithelioid histiocyte look. Contrasting cell morphology and probably also contrasting immunophenotype. The interpretation by Tan et all seems reasonable. Are the crystals extracted during routine processing? Value of imprinting! Warthin-Starry??

**Vincenzo Eusebi:** Nice case. Thank you.

**Giovanni Falconieri:** Beautiful case, David. Your discussion is also very instructive and interesting. The best case I have ever seen of LCH. Thanks for this submission.

**Cyril Fisher:** LCH in lymph node - very nice example.

**Christopher Fletcher:** Beautiful example of LCH involving a lymph node – the best that I have personally seen, since I have little experience in this regard.

**Andrew Folpe:** Agree with Langerhans cell histiocytosis, apparently primary in a lymph node. Nice case.

**Jerónimo Forteza Vila:** We agree with your diagnosis.

**Masaharu Fukunaga:** Langerhans cell histiocytosis is first considered. Eosinophilic abscess in a lymph node. Palisaded granuloma with geographic necrosis. The second choice is a parasite disease. Thank you very much for the detailed description of Langerhans cell histiocytosis of lymph node.

**Thomas Krausz:** Beautiful example. On my slide, there is palisading histiocytic reaction around the eosinophilic necrosis. I assume the palisading cells are genuine histiocytes not Langerhans cells.

**Janez Lamovec:** Beautiful case of nodal Langerhans' cell histiocytosis!

**Thomas Mentzel:** A wonderful case of nodal Langerhans cell histiocytosis, showing very nicely the characteristic cytomorphology of histiocytic cells!

**Markku Miettinen:** Fully agree on Langerhans histiocytosis/eosinophilic granuloma of lymph node. Because on constitutional symptoms and apparent widespread disease, association with a primary condition such as Hodgkin's disease should be considered and immunohistochemical tests for CD15/30 could be useful, along with clinical correlation. One of the very first articles of the journal Histopathology also featured an article on this (1977;1:31).

**Liz Montgomery:** Thanks so much for sharing this amazing example. It is nice that we do not need to hunt for the eosinophils.

**Juan Rosai:** Spectacular case of Langerhans’ cell histiocytosis of lymph node. I’d like to point out that one of the first descriptions of Langerhans’ cell histiocytosis in lymph nodes was made by an Argentinian (the famous bone pathologist Fritz Schajowicz) and that the first detailed analysis of Charcot-Leyden crystals in this disease was made by another

Argentinian (my dear teacher Eduardo Lascano). Here is the reference: Lascano EF: A propòsito de los cristales del granuloma eosinòfilo. Arch Soc Arg Anat Norm Patol, 9: 368-372, 1947. I thought of also mentioning that I have seen 4 or 5 cases of Langerhans' cell histiocytosis and Rosai-Dorfman's disease coexisting in the same node but clearly segregated one from the other.

**Dominic Spagnolo:** Stunning example of LCH involving lymph node - thanks.

**James Strauchen:** Langerhans cell histiocytosis. Nice case!

**Saul Suster:** Very classical example, thank you David. Cesar's paper describing 20 cases of LCH in lymph nodes was published late last year and covers the entire spectrum of histopathologic appearances of this condition in lymph nodes (Hum. Pathol 38:1463-1469, 2007). This occurrence is indeed very rare and can be a potential diagnostic pitfall, particularly when the involvement is very focal.

**Lawrence Weiss:** Pretty case. I had not previously seen a case with so much necrosis.

**CASE NO. 3 – CONTRIBUTED BY OFER BEN-ITZHAK:**

**Phil Allen:** Thyroid follicular carcinoma-like tumour of the kidney. It certainly looks like the follicular variant of papillary thyroid carcinoma. I will be very interested in Michal's comments.

**Carlos Baachi:** I believe that your colleague who sent you the case was right. This renal tumor looks like thyroid a lot. In fact it looks like follicular thyroid carcinoma. In this particular differential diagnosis, the absence of expression for TTF1 and thyroglobulin helps in ruling out thyroid as primary site. Nice case. First time I see one. Thanks.

**David Ben-Dor:** On first glance, my impression was a tumor with thyroid features arising in the kidney. But on further examination, I looked for evidence of glomeruli amidst the tubules and as I couldn't find any, I abandoned that and assumed that this was a thyroid tumor arising in the thyroid. So my first thought was borne out. The reaction to this case and the provisional name given it shows that we pathologists are still magnetized by histological appearances as has been the case for the past century; after all with the newfangled immunohistochemical tools used any true biological affinity to thyroid (asides from histophenotype) has been disproven so what's the purpose of stressing the superficial resemblance to thyroid?- it can only make for confusion. Unless someone comes up with something new in the future which would justify the association? I tend to agree with Ofer's conclusion that this is probably a derivative of another established category of renal tumors.

**Gerald Berry:** It certainly looks like a thyroid neoplasm! We haven't encountered this pattern either.

**Michele Bisceglia:** Thyroid follicular carcinoma-like tumor of the kidney (or thyroid-like follicular variant of papillary carcinoma?). Beautiful case. I think this is just the so-called primary thyroid-like follicular carcinoma of the kidney first reported by Amin and Michal. I had the opportunity to see one of Michal's cases. Of course, I look forward to knowing Michal's opinion on your case. To date, we are lucky being helped by immunohistochemistry (thyroglobulin and TTF-1 negativity are of invaluable help): of course, all of us know that not too many years ago to distinguish this case versus true thyroid metastatic tumor to the kidney would have been impossible. Metastases to the kidney from thyroid may also occur either in absence of a clinically known thyroid tumor or many years after the thyroid problem, as was the case of which I am aware, thanks to a friend and lead author of the following article in which the metastasis occurred after 35 years and the pathologist was erroneously told that the patient never was operated on the thyroid nor that she had thyroid neoplasm at the time of renal mets (Insabato L, Di Vizio D, De Rosa G, Prezioso D, Corcione F, Terracciano LM. Renal metastasis from thyroid carcinoma 35 years after detection of the primary tumor. Tumori. 2003 Jan-Feb;89(1):99-101. Review.).

**Ira Bleiweiss:** I've never seen such a case before but it obviously looks like thyroid. I don't see papillary areas on my slide. Is this related to collecting duct carcinoma?

**John Chan:** This is really a most unusual-looking primary tumor of the kidney! It really looks like follicular variant of papillary thyroid carcinoma, including the architecture of the follicles, dark-staining colloid, and nuclear morphology, with the only exception that the nuclei are somewhat chromatin-rich. On second thoughts, perhaps its occurrence should not be too surprising, because the sometimes resemblance of the kidney to thyroid is exemplified by the term "thyroidization" used to describe the tubular changes in chronic pyelonephritis.

**Tom Colby:** Agree with diagnosis, another new entity for me.

**Kum Cooper:** Yes, it is good to have friends; thank you for this educational case. I was not aware of this entity and had forgotten about Mahul and Michal's abstract.

**Ivan Damjanov:** Wow, that was a good diagnosis. I will probably never see another one.

**Otto Dietze:** Thank you for this nice example. I have already forgotten this entity and the publication.

**Hugo Dominguez-Malagon:** Wow, it certainly looks like thyroid; in addition to the other mentioned features similar to renal papillary carcinoma it has foamy cells.

**Göran Elmberger:** Another great case and a new entity to me. In absence of thyroid markers and thyroid tumor, one has to accept this as a new unusual kidney tumor. The interface to normal kidney with gradual non-destructive transition tumor – kidney first made me have doubts on whether this was a true neoplasm or not but the whole picture including described genetical abnormalities is convincing.

**Vincenzo Eusebi:** It seems that kidney shares with the breast some tumors that show features reminiscent of thyroid neoplastic lesions.

**Giovanni Falconieri:** I did not know about this entity (and could not imagine how to handle this at my end); this tumor is nearly identical to a thyroid tumor, including occasional nuclear grooves and inclusions! Thanks for this submission. A terrific mimicker.

**Cyril Fisher:** Aptly-named thyroid carcinoma-like variant of renal carcinoma, a rare and interesting case. Thanks for the useful discussion.

**Christopher Fletcher:** Remarkable and impressive case – I have no personal experience with renal cell carcinoma showing these morphologic features.

**Andrew Folpe:** Really a spectacular case. I have never seen one of these. It's amazing how much it looks like a true thyroid lesion.

**Jerónimo Forteza Vila:** We knew about the report of Jung et al, but we had never seen a similar case in our practice.

**Masaharu Fukunaga:** My impression was papillary carcinoma of the thyroid, metastatic to the kidney. To my surprise, the findings of the immuno studies are not compatible with it. Thank you very much for the unusual case and the detail the literature review.

**Allen Gown:** Thank you for an example of this rare tumor. I wonder if the tumor is positive for expression of PAX-2, a much more renal-specific marker than CD10.

**Thomas Krausz:** I haven't seen this type of renal cell carcinoma before. The resemblance is not only to thyroid follicular carcinoma but also thyroid follicular variant of papillary carcinoma. I assume the colloid-like secretion is biochemically similar to the material one sees in pyelonephritic kidneys.

**Janez Lamovec:** I've never seen or known of such a tumor before, and it really looks like thyroid; thyroid-like changes may be seen in pyelonephritic nephrosclerosis, however.

**Thomas Mentzel:** Thanks a lot for sharing this example of a new tumour entity.

**Michal Michal:** Nice case. Just a paper describing similar tumor appeared (Sterlacci W et al Thyroid follicular carcinoma-like renal tumor: a case report with morphologic, immunophenotypic, cytogenetic, and scintigraphic studies. Virchows Archiv 2008:452:91-95).

**Markku Miettinen:** Fully agree with you. This tries to look like a follicular (variant of papillary thyroid?) carcinoma metastasis to the kidney, although one should think of kidney Ca like that, especially with a TTF negative lesion. Seems to match with Michal's tumors.

**Liz Montgomery:** Thanks for this case of "fake thyroid" kidney cancer. My colleague P. Argani gets lots of rare kidney cancers in his consults and always shows these at high power at our daily conference and tricks us into talking about thyroid lesions and then goes to low power and we all groan. We fall for it every time.

**Juan Rosai:** It sure looks like this tumor ought to be a thyroid carcinoma metastatic to kidney, an occurrence which is well documented in the literature : Cancer 43: 265-268, 1979; End Pathol 10: 265-268, 1999. (Isn't' funny that both papers go from page 265 to 268 ?) In any event, the evidence presented to the contrary is very convincing. Looking at it in retrospect, it has a feature which I haven't seen in thyroid tumors, and that is the presence of a solid central nest or a trabecular bar within the follicle-like structures. I know of two other instances of thyroid-like tumors in other organs, one being the breast tumor that looks like the tall all variant of papillary thyroid carcinoma (Am J Surg Pathol 27: 1114, 003) and the other the tumor of the endolymphatic sac in patients with von Hippel-Lindau syndrome (Cancer 64: 2292, 1989).

**Dominic Spagnolo:** What a beautiful case of renal carcinoma resembling thyroid carcinoma. I, too, think that morphologically it has features more akin to follicular variant of papillary carcinoma. Thank you for the case

**James Strauchen:** Thyroid-like RCC! Resemblance to thyroid is remarkable. What is the colloid-like material? Does it stain for Tamm-Horsfall protein?

**Saul Suster:** Beautiful case! Thank you for the contribution. Although the nuclear features are not the best, the deeply staining secretion certainly enhances the resemblance with the follicular variant of PTC. The older and more sophisticated we get the more we learn how morphology can deceive our eyes and senses.

**Lawrence Weiss:** First case of this that I have ever seen. The name needs to be changed, even if it is a unique renal neoplasm, which I suspect it is.

**CASE NO. 4 – CONTRIBUTED BY GERALD BERRY:**

**Phil Allen:** Acute mononucleosis of the tonsil. I get caught out misdiagnosing lymphoma every time I see one of these, which is only about once every 20 years. Thanks for the contribution but I fear I will never learn.

**Carlos Bacchi:** Nice example of acute mononucleosis simulating morphologically non-Hodgkin lymphoma.

**David Ben-Dor:** It's very important to see cases like this in order to be reminded of the ease with which this entity can be overdiagnosed if the pathologist isn't careful. I must admit that looking at the slide before becoming acquainted with the clinical background I convinced myself that this was a lymphoma (lymphoplasmacytoid?). And even after seeing the patient's age, I didn't think of mononucleosis. The monotonous cells forming sheets actually look more plasmacytoid to me than they resemble immunoblasts, and a lymphoplasmacytoid lymphoma in this age group would probably be unusual which might be a tip-off; I think they're too small for Burkitt lymphoma and there is no starry-sky.

**Michele Bisceglia:** Acute mononucleosis, tonsil. Difficult case without knowing clinical and laboratory data.
It is fully true the statement (aphorism) that "one of the complications of infectious mononucleosis *(for both the patient and the pathologist)* is a lymph node *(as well as any other lymphoid tissue biopsy)* biopsy" (Purtilo DT, 1979 Pathol Annu, 253-299)".

**Ira Bleiweiss:** Agree.

**Thomas Colby:** Agree with diagnosis, similar to other cases I've seen, including the focal necrosis.

**Kum Cooper:** Yes, lovely example. This also looks identical to the early PTLD lesion seen in tonsils in children following transplantation which is also EBV initiated.

**Ivan Damjanov:** Excellent example of IM.

**Otto Dietze:** Without immunostains and clinical history, especially the patient's age, a case like this seems really indistinguishable from "immunoblastic" lymphoma.

**Hugo Dominguez-Malagon:** It really looks worrisome and easily confused with a lymphoma in the absence of clinical information. This case proves the old adage: "the worst complication of mononucleosis is a biopsy".

**Göran Elmberger:** Never saw a histological example of this alarming disease. As you mentioned, clinicians most often recognize and diagnose before making biopsies. However, we do see these cases in our FNA-clinic and the smears do look pretty scary. I guess a dx of immunoblastic lymphoma comes to mind, if the clinical context is not noted. Fortunately, we perform most FNA biopsies ourselves so we have easy access to the clinical picture. Thanks.

**Vincenzo Eusebi:** Very instructive case. Rare to see since usually biopsies are not obtained in mononucleosis.

**Giovanni Falconieri:** The case no (average) pathologist would like to come across. A few years ago, Dr. James Strauchen submitted a similar case to this slide seminar (AMR 39, case 18). It seems, once again, that the worst complication of infectious mononucleosis is a lymph node biopsy. A very instructive case; thank you.

**Cyril Fisher**: Mononucleosis in lymphoid tissue, rare opportunity to have a section of this, many thanks.

**Christopher Fletcher:** Beautiful case of mononucleosis – it is very easy to understand why this disorder could so easily be confused with lymphoma prior to the development of immunohistochemical stains, ISH for EBV and gene rearrangement analyses.

**Andrew Folpe:** An excellent teaching case of an entity we don't really see much of. I shared this with a few trainees, all of whom were sure this was a high-grade lymphoma. I have to admit that I did not immediately jump to

mononucleosis, but I did suspect it was benign/reactive. An excellent example of how careful one needs to be in evaluating any pediatric material.

**Jerónimo Forteza Vila:** We agree with the diagnosis. We must remember that a biopsy can be the worst complication of mononucleosis.

**Masaharu Fukunaga:** My impression was malignant lymphoma, diffuse large cell (immunoblastic), B-cell type. I might make an overdiagnosis. I must be careful in this situation, young age of the patient. Thank you very much for the educational case.

**Allen Gown:** Lovely example of EB-virus related infectious mononucleosis. Pathologists should always be vigilant about this disease, which can (and, unfortunately has) been misdiagnosed as a malignancy.

**Thomas Krausz:** Highly instructive case.

**Janez Lamovec:** Lymphoid proliferation in infectious mononucleosis used to be one of the important differential diagnostic considerations in diagnosing malignant lymphoma. With the help of modern techniques, it is now much easier to exclude such a possibility. On the other hand, these new techniques helped us to observe more subtle morphological details in routine slides and possibly improved our diagnostic abilities in such cases.

**Thomas Mentzel:** Nice to see an example of mononucleosis involving the tonsil.

**Markku Miettinen:** Fully agree with you. Wondered about mononucleosis, also malignant B-cell lymphoma with plasmacytic differentiation, but less likely (EBV tests?).

**Liz Montgomery:** This is a real treat to see a tonsil from a known mononucleosis [EBV] case. Thanks so much.

**Juan Rosai:** Great case of infectious mononucleosis. It is easy to see how this can be overdiagnosed as malignant lymphoma. This reminds me of a fatal case of infectious mononucleosis (fully documented virologically and serologically) I saw in Minnesota many years ago. We showed the case to one of the luminaries of hematopathology, who was visiting the Department, who insisted in looking at the case without the clinical history, and whose immediate reaction was "I wish all hematopathology cases were as easy to diagnose as this immunoblastic sarcoma".

**Dominic Spagnolo:** This is as florid an example of acute mononucleosis I have seen in a while. Thanks.

**James Strauchen:** Acute infectious mononucleosis! I have seen several cases diagnosed as lymphoma, including one case which was diagnosed with immuno at a well known national laboratory as "T-cell-rich diffuse large B-cell lymphoma" of the tonsil in a 17 year old! The clue is often the clinical history, which is usually tonsillitis rather than mass.

**Saul Suster:** Spectacular case! Very easy to misdiagnose this for lymphoma. Thank you for having shared this with us.

**Lawrence Weiss:** It is not uncommon to see acute infectious mononucleosis in consult cases. The history is a give-away.

**CASE NO. 5 – CONTRIBUTED BY MICHELE BISCEGLIA:**

**Phil Allen:** Spontaneous adenomatosis of liver. Thanks for the extensive discussion Michele. I suspect that the classification of these lesions will only get more complex with time.

**Carlos Bacchi:** I am not so familiar with these lesions (nodular hyperplasia and adenomas of the liver). This case is very illustrative of how difficult to diagnosis these entities can be. As usual, Michele's discussion is impeccable. Thanks for the case.

**David Ben-Dor:** I think Michele could form his own slide club based just on his cases, given the amount of material (slides and written) he provides! This exercise shows to what extent people can give differing interpretations to the same slides. I think that a lot of differential diagnosis is semantic, conjectural, and/or hypothetical, and in a given circumstance no one suggested solution can be conclusively proven over any other one, and that many established entities are either biologically the same or closely similar. One can ask whether each and every case has one and only one correct resolution. But try explaining that to the patient if he gets wind of the fact that one consultant did indeed call it malignant!! Whatever this condition is, it apparently is capable of recurring but it doesn't look malignant. The main fear would be massive hemorrhage in the event of a third recurrence.

**Gerald Berry:** Thank you for the detailed discussion.

**Tom Colby:** Agree with diagnosis, have seen at least two other cases of multiple hepatic adenomas (hepatic adenomatosis) unrelated to steroid therapy.

**Kum Cooper:** Michele, an exhaustive write-up…much thanks. Glypican-3 is negative in adenomas and positive in carcinoma (Cancer Cytopath 2007; 111:316.).

**Ivan Damjanov:** I would have no problems calling this adenoma. Excellent review of the problem, Michele.

**Otto Dietze:** Thank you for this excellent presentation and review. I was not aware of the reference of the Bordeaux update and molecular studies of TNFH.

**Göran Elmberger:** Thanks, Michele, for a great update on benign hepatocellular proliferations. Our hospital system (The Karolinska University Hospital) is now stressing profiliation amongst its 4 nodes. Sadly, I don't get to see any liver pathology any more.

**Vincenzo Eusebi:** Michele thank you very much for your learned handout.

**Giovanni Falconieri:** Always pleased to learn from you, Michele. Thanks for going over a difficult and controversial subject. I do not have much experience with this subject, but it seems that there are cases in which it may be difficult to draw a line not only between HCC and adenomas, but FNH and HCC/Adenoma; the case you have brought to our attention just reflects the issue.

**Andrew Folpe:** Hepatocellular adenomas. Lacks the proliferating bile ductules of true FNH.

**Jerónimo Forteza Vila:** Very interesting case.

**Masaharu Fukunaga:** A very interesting case, Michele. Thank you very much for detailed description. My first impression of the first slide was fibrolamellar hepatocellular carcinoma.

**Allen Gown:** Interesting case. Results of IHC studies for CD34 and glypican might be informative in this case. Greatly facilitates the accuracy of distinguishing between malignant hepatic lesions and benign mimicker.

**Thomas Krausz:** I agree with all that there is no carcinoma. Using good old fashioned criteria, I would have called the 1999 lesion as you did, focal nodular hyperplasia and the 2006 nodules as "hyperplastic nodules" perhaps regenerative or some other unknown etiology. The new classification appears a bit complex, but I don't regard myself as an expert on this field. Perhaps I want too much, like clonality studies to be convinced about multiple adenomas/adenomatosis.

**Thomas Mentzel:** Thanks a lot, Michele, for this interesting case and especially for the excellent discussion!

**Markku Miettinen:** I was thinking well-differentiated hepatocellular carcinoma; not in my field of expertise, however. After reading your text, I believe adenoma is probably a better diagnosis.

**Liz Montgomery:** The first biopsy looks like FNH but the other 2 are impossible!

**Juan Rosai:** I have very little to add to the scholarly discussion by Michele Bisceglia. I think that the nodules are definitely not hepatocellular carcinomas, and I eventually convinced myself that they look better for hepatocellular adenomas than for focal nodular hyperplasia.

**Dominic Spagnolo:** Thanks, Michele, for this typically in-depth review of the issues relating to hepatic adenomas and FNH. I can't argue with your final interpretation.

**James Strauchen:** Multiple hepatic adenomas versus focal nodular hyperplasia. Thank you for the excellent discussion.

**Saul Suster:** Very difficult case! Thank you for the learned discussion. Don't know that any of our current understanding of these lesions makes any sense to me and I get the feeling that much of what we think we know about these lesions is arbitrary and that the arguments could go both ways.

**Lawrence Weiss:** I was completely unaware of the molecular studies in adenoma. Thank you for the wonderful discussion.

**CASE NO. 6 – CONTRIBUTED BY THOMAS COLBY:**

**Phil Allen:** Iatrogenic pulmonary emboli of various materials, probably polyvinyl alcohol, tris-acryl gelatin microspherules and possibly, cyanoacrylate, right upper lobe of lung in a patient with cystic fibrosis. Thanks for the discussion Tom. Gelfoam is the usual agent used here for therapeutic embolization.

**Carlos Baachi:** Great case with fascinating histology and excellent discuss about iatrogenic causes of pulmonary emboli.

**David Ben-Dor:** My first thought was that there was occlusion of bronchial lumina by impacted mucinous plugs (given the history of cystic fibrosis) - at least where the material stained bluish. I didn't see anything birefringent using polarized light. There is also what looks like a large granuloma whose constituent histiocytes seem to have clear or granular cytoplasm- is this related to the iatrogenic lesions or to the underlying disease?

**Gerald Berry:** Agree.

**Michele Bisceglia:** Therapeutic pulmonary embolization for arteriovenous malformation. Never seen one in the lung. It is similar to some analogous reaction I frequently see in neurosurgical specimens of brain vascular lesions or richly vascularized tumors (meningeal tumors) previously treated by embolization. The material in the lumen has a slight birefringent reticular aspect on polariscope.

**Ira Bleiweiss:** Agree; very odd foreign material. The lymph nodes are obviously "sentinel" nodes and are reminders that sentinel nodes are equal opportunity employers - They drain anything: foreign or native, biologic or not, benign or malignant.

**Kum Cooper:** Thank you, Tom, for this unusual and gross example. Yes, I recall the case that Kelly used for the evening conference.

**Ivan Damjanov:** Agree. Thanks for including Dr Butnor's discussion.

**Otto Dietze:** The identification of the origin and type of embolized material seems to me an evolving problem, especially in consideration of legal aspects.

**Hugo Dominguez-Malogon:** Nice case of iatrogenic pulmonary emboli, and a good discussion.

**Göran Elmberger:** Great case. Only saw similar findings in juvenile angiofibroma of the nasopharynx and in extraadrenal paragangliomas glomus type in old times when we had a daring skilful ENT surgeon, Dr. Mendel, taking them on. Today, expectation seems to be the rule.

**Vincenzo Eusebi:** Pulmonary emboli with foreign material. Thank you for the discussion and references.

**Giovanni Falconieri:** A quite unusual case, given the history and peculiar clinical context. Thanks for this contribution. I believe that the issue presented by Tom has great practical importance. I have had some medicolegal experience with sudden post operative death due to fat embolism in patients who underwent bone prosthetic surgery and lipoplasty. The demonstration of lipid material in small vessels, mostly capillaries, is crucial to the correct interpretation. The club members may be interested to go back to AMR case 26-4 by contributed by Dr. Chan.

**Cyril Fisher:** Amazing appearance. The discussion says it all.

**Andrew Folpe:** I don't have a better explanation than previous embolization, but it seems odd to me that the material should be in the airways and (apparently) in the alveolar tissue. I could find only one or two intravascular foci.

**Jerónimo Forteza-Vila:** We agree with this unusual diagnosis.

**Masaharu Fukunaga:** Thank you very much for a very unusual case and the discussion.

**Allen Gown:** Thank you for that very complete and detailed summary of etiologies of pulmonary emboli.

**Thomas Krausz:** Dramatic morphology. Seen it at other sites but not in lung before.

**Janez Lamovec:** Most interesting lesion. My experience with iatrogenic causes of pulmonary emboli is limited to fat and bone marrow embolism.

**Thomas Mentzel:** Many thanks for this unusual case.

**Markku Miettinen:** Thank you for this beautiful problem. I believe in your interpretation of foreign body material. Initially, thought a Hydatid cyst, even focally with nice hooklet-like structures, having recently seen a case from a rancher from Wyoming in soft tissues of groin.

**Juan Rosai:** Spectacular case. I have never seen so many nuclei in foreign-body-type giant cells. And, as usual, there is not a single one undergoing mitosis!

**Dominic Spagnolo:** Spectacular example of foreign material embolic to lung with associated suppurative granulomatous response.

**James Strauchen:** Granulomatous reaction to iatrogenic foreign material. Remarkable case! There also appears to be an abscess-like component.

**Saul Suster:** Spectacular case – had never seen this! Live and learn....

**Lawrence Weiss:** Spectacular case! And thank Dr. Butnor for a very complete discussion.

**CASE NO. 7 – CONTRIBUTED BY GÖRAN ELMBERGER:**

**Phil Allen:** Sclerosing mucoepidermoid carcinoma with eosinophilia associated with Hashimoto's thyroiditis and oncocytic adenoma, right lobe of thyroid. An excellent case. Thanks for the contribution.

**Carlos Bacchi:** This is really a nice example of thyroid sclerosing mucoepidermoid carcinoma with eosinophilia.

**David Ben-Dor:** This is a fascinating slide especially as I've never seen an example of this tumor in the flesh. The squamoid/intermediate element is obvious. What is particularly interesting is the distorted follicle-like structures which are lined by squamoid cells with interspersed mucin secreting cells (which I had to look for). I assume these are thyroid follicles whose lining was replaced by the tumor, but the pink material in the lumens isn't colloid but something that only *looks like* colloid? This is reminiscent of the thyroid like tumor of the kidney seen earlier in this seminar, but this lesion actually in the thyroid (i.e. a true thyroid tumor with pseudo-colloid). But again this is the never-never land of slide club pathology. On a somewhat different track, years ago I had a repeat FNA from a thyroid nodule interpreted on the first FNA as an adenomatous follicular nodule. The second examination was atypical and the subsequent resection showed a squamous proliferation in the form of nests as seen here. My interpretation was a follicular lesion with squamous metaplasia secondary to the trauma of the original FNA. In retrospect I wonder if I didn't overlook a tumor as seen in this case.

**Gerald Berry:** Agree. Beautiful example

**Michele Bisceglia:** Thyroid sclerosing mucoepidermoid carcinoma with eosinophilia, Hashimoto's thyroiditis, and oncocytic adenoma/adenomatoid oncocytic nodule. Nice case. Never seen a personal case. One such case of this type of tumor was presented in Naples in 2003 at an Italian Congress of anatomic pathologists by Dr. Franco Fedeli (La Spezia, Italy), stating that up to that time only 20 cases had been previously published, most in females and on Hashimoto's background. The issue of eosinophilia is interesting. Classical (non-lymphoid) tumors with tissue eosinophilia are large cell carcinoma of the lung (sometimes even accompanied by blood eosinophilia). Dr. Falconieri has a case of squamous carcinoma of the pharynx with marked intratumoral eosinophilia.

**Ira Bleiweiss:** New one to me. Very few "mucocytes" in my slide.

**John Chan:** I am not sure how best to label this thyroid lesion. It certainly has many of the morphologic features of sclerosing mucoepidermoid carcinoma with eosinophilia, but this lesion is non-invasive and lacks nuclear atypia. I just wonder whether this could have been "sclerosing mucoepidermoid *metaplasia* with eosinophilia" instead. In the cases of thyroid sclerosing mucoepidermoid carcinoma with eosinophilia that I have seen (diagnosed based on at least presence of definite invasion +/- nuclear atypia), there are also sometimes foci for which I cannot decide whether they are part of the carcinoma or part of the metaplastic process in the background.

**Thomas Colby:** Agree with diagnoses.

**Kum Cooper:** Thank you. I have been waiting for one of these "SMECE" tumors to come along since reading John's paper in the early 90's. Beautiful example and certainly fits the descriptive title of this tumor.

**Ivan Damjanov:** Excellent diagnosis, just like the index case and the others you referred to.

**Otto Dietze:** I can only remember one case of thyroid mucoepidermoid thyroid carcinoma in 3 decades, and it did not show this association of eosinophilia and thyroiditis. It was originally misdiagnosed as an undifferentiated carcinoma in a small biopsy, and we became aware of this after the patient did well for several years.

**Hugo Dominguez-Malogon:** A classic example of thyroid sclerosing mucoepidermoid carcinoma, thank you.

**Vincenzo Eusebi:** Another rare case. Sclerosing mucoepidermoid carcinoma of thyroid with eosinophilia in a background of Hashimoto's thyroiditis. Salivary gland MEC are different but share the same name.

**Giovanni Falconieri:** Sclerosing mucoepidermoid carcinoma with eosinophilia of thyroid, finally I have got one! Thanks for this contribution.

**Christopher Fletcher:** I am no thyroid expert, but my recollection was that sclerosing mucoepidermoid carcinoma was much more sclerotic and also much more infiltrative than this. Can we be certain that this isn't simply very florid squamous metaplasia in the setting of thyroiditis?

**Cyril Fisher:** Sclerosing mucoepidermoid carcinoma , excellent and rare case.

**Andrew Folpe:** Agree with mucoepidermoid CA of the thyroid. Thanks for sending in such a rare lesion.

**Jerónimo Forteza Vila:** We had never seen a similar case previously.

**Masaharu Fukunaga:** Thyroid sclerosing mucoepidermoid carcinoma with eosinophilia. Thank you very much for sharing an interesting case, Goran. This is the first time I see this type of tumor.

**Thomas Krausz:** Agree with diagnosis (superb case), though it is diagnostically challenging seeing such a tumor in the thyroid. Sclerosing mucoepidermoid carcinoma with eosinophilia has also been described in a more appropriate site for such an entity, in salivary gland.

**Janez Lamovec:** Low grade sclerosing mucoepidermoid carcinoma; agree with the diagnosis. I only wonder whether the lymphocytic thyroiditis with accompanying changes (oxyphilic follicular epithelium) is extensive enough to label it as Hashimoto thyroiditis.

**Thomas Mentzel:** Thanks for this example of a rare entity that I've never seen before.

**Michal Michal:** Nice case. One can more than suspect that the tumor has origin in solid cell nests (SCN). I have a case with such hyperplasia of SCN that I was unable to decide whether to call it a tumor or not.

**Markku Miettinen:** Without being very familiar with recent developments, would have thought that this is a "squamous cell adenoma",? derivative of thyroid solid cells nests, the high molecular weight keratin and p63-positive nests in thyroid commonly seen in Hashimoto thyroiditis. Independent oncocytic adenoma, thyroiditis.

**Juan Rosai:** Nice example of the thyroid tumor type we reported some years ago as sclerosing mucoepidermoid carcinoma with eosinophilia. We had previously presented the work at a USCAP meeting under the name of "sclerosing squamoid tumor with eosinophilia", which in retrospect I like it better. Although these tumors (including this particular example) often have squamous as well as mucinous foci, I don't think they have anything to do with bona-fide mucoepidermoid carcinoma of salivary glands. I suspect they are related to papillary carcinomas. The first case I ever saw had nice psammoma bodies.

**Dominic Spagnolo:** I have not routinely encountered one of these sclerosing mucoepidermoid carcinomas with eosinophilia - thank you for the case.

**James Strauchen:** Sclerosing mucoepidermoid carcinoma of the thyroid with eosinophilia. I will definitely add this to my teaching collection.

**Saul Suster:** Great case – thanks for sharing it. I had only seen one of the cases reported by Drs. Chan and Rosai but have not come across another one since. Must be indeed very rare.

**Lawrence Weiss:** Very peculiar. Very metaplastic-like.

**CASE NO. 8 – CONTRIBUTED BY GIOVANNI FALCONIERI:**

**Phil Allen:** Cellular fibroepithelial tumour with malignant stroma, ?adenosarcoma; ?atypical phylloides tumor. I suspect that tumors like this have in the past been called low-grade phylloides tumors, but I agree that adenosarcoma seems to be a more accurate, descriptive name.

**Carlos Baachi:** I would favor low-grade malignant phyllodes tumor, but I would like to hear the opinion of more experienced members of the club about how to label this lesion.

**David Ben-Dor:** I'm in favor of a low grade entity such as periductal stromal tumor as publicized by Burga and Tavassoli at the AFIP (AJSP 2003). I realize that you considered this and ruled it out, possibly due to the fact that in the publication the stromal component is described (in the abstract) as spindle celled with "variable atypia" without mention of the pleomorphic and multinucleated cells prominent in this specimen. But that entity is a precedent for breast lesions with benign epithelium and atypical/malignant stroma and lacking the characteristic phyllodes architecture, so it would be a good "home" for this lesion in the absence of anything better. The lesion is well delimited and without stromal invasion and in random perusal of the slide I didn't notice mitoses or atypical mitoses (I'm sure they're there but finding them requires more careful examination). I suspect and hope the patient will do well. (See also my comment for case 12 below).

**Gerald Berry:** I think the lesion is basically a phylloides tumor with markedly typical stromal cells. The widespread distribution of the atypia but lack of division figures warrants classification as borderline phylloides tumor.

**Michele Bisceglia:** Cellular fibroepithelial tumor with malignant stroma (? Adenosarcoma; ?atypical phyllodes tumor). I think this is a malignant phyllodes tumor: highly pleomorphic and mitoses, partly atypical. The phylloid growth pattern is focally visible. However, it is morphologically unusual and I have never seen a similar one. Thank you, Falco.

**Ira Bleiweiss:** I did not receive a slide; however, I have seen a few cases which I think fit what you describe. I think they should be classified as histologically malignant phyllodes. Excision with negative margins should be adequate treatment.

**John Chan:** Although the architecture is somewhat unusual (epithelial component assuming a blunt duct adenosis appearance), I would have labeled this fibroepithelial tumor as phyllodes tumor because: (1) there are at least some foci with a leaf-like (phyllodes) pattern; and (2) there are areas with condensation of stromal cells around the epithelial units.

**Thomas Colby:** Essentially agree with diagnosis. Architecturally this looks like fibroadenoma with a malignant stroma, and I (in my ignorance of things mammary) would probably classify this as a phyllodes tumor. I think it should be managed as a malignant stromal tumor.

**Kum Cooper:** Low grade malignant phyllodes tumor. Follow-up for recurrence.

**Ivan Damjanov:** I would sign out this case as malignant or at least atypical phyllodes tumor.

**Hugo Dominguez-Malogon:** The tumor is well circumscribed and does not show the typical folia of phyllodes tumor. I do not have a precise name for it, perhaps "fibroadenoma with bizarre stroma", my guess is that it will behave as a benign lesion.

**Göran Elmberger:** Difficult case. Clearly as suggested, a fibroepithelial breast lesion probably best classified as a phyllodes tumor. To me, the problem is in assigning grade. The striking (bizarre) nuclear pleomorphism is possibly indicating a more malignant potential but features such as modest stromal hypercellularity, intermediate number of mitoses, well circumscribed margin and uniform stromal distribution would make me classify the lesion as most probably of borderline grade according to 3 tiered grading schedule suggested by WHO.

**Vincenzo Eusebi:** Never seen such remarkable nuclear atypia. I would call this lesion in my surgical routine as fibroepithelial tumour with atypical stroma. I am not convinced at all that this lesion is malignant. It is relatively small (1.7 cm, microscopic size) has circumscribed margins and no stromal overgrowth.

**Cyril Fisher:** Adenosarcoma seems a good term.

**Christopher Fletcher:** Particularly given the length of some of these epithelial-lined clefts, I think that I personally would have called this a phyllodes tumour.

**Andrew Folpe:** I would call this a phyllodes tumor with sarcomatous stroma. It's interesting inasmuch as there is no stromal overgrowth, which typically accompanies these types of stromal changes.

**Jerónimo Forteza Vila:** We agree with the diagnosis.

**Masaharu Fukunaga:** I would call this case a phyllodes tumor, histologically a borderline lesion. Although pleomorphism is remarkable and cellularity is high, no mitotic figures are seen. It is an unusual beast lesion.

**Allen Gown:** Agree that this is a difficult lesion to subclassify though it clearly represents a stromal tumor of the breast on the malignant spectrum of things. With all the retained and hyperplastic ductal units, however, the term adenosarcoma might well be appropriate.

**Thomas Krausz:** I agree that this is histologically rather unusual. I would like to call it adenosarcoma but the term is not used in breast, so with a bit of compromise, I would diagnose it as an unusual variant of cystosarcoma phyllodes.

**Janez Lamovec:** Fibroepithelial tumor of the breast with sarcomatous stroma, akin to phyllodes tumor. In our experience with phyllodes tumors, there are some cases with a stromal component that fit into PT (cellularity, pleomorphism, mitoses, etc) but lack well developed leaves; however, changing the well established name of phyllodes tumor into something else would not much improve our knowledge of their biological behavior, so we tend to classify them as a variant of PT. The same applies to so-called periductal stromal tumors. Given the small size of the present tumor and apparent free margins, I think that no additional treatment is necessary. However, one may not be absolutely confident as to prognostication of phyllodes tumors in spite of numerous claims of importance of this or that morphological/immunohistochemical/molecular factor in predicting their biological behavior.

**Thomas Mentzel:** Given the atypical and proliferative activity of the mesenchymal component as well as the lack of a clear phyllodes tumour, I would label this case as an adenosarcoma.

**Michal Michal:** The stroma looks like a "sarcomatous PASH". Inspiring case

**Markku Miettinen:** Could be regarded as malignant phyllodes tumor variant. Atypical mitoses and "super atypia" noted. I am in agreement with you. Small size may be mitigating factor, but cannot ignore potential based on these histologic features.

**Liz Montgomery:** It looks like a cross between a periductal stromal tumor and a phyllodes tumor. Seems like it should do well with a complete excision despite the horrible looking stromal cells!

**Juan Rosai:** I would interpret this breast lesion as a pleomorphic or giant cell variant of phyllodes tumor. The stromal component is clearly neoplastic, and the epithelium is making pretty good clefts. It does not look like the fibroadenoma with bizarre giant cells reported in Am J Surg Pathol 10: 823-827, 1986). For one thing, it has too many mitoses, some of them atypical.

**Dominic Spagnolo:** I agree that this does not fit neatly into a specific category of breast fibroepithelial tumors. Your suggestion of "adenosarcoma" seems apt. If excision is complete, then there will likely be a good outcome long term.

**James Strauchen:** Phyllodes-like tumor with marked stromal atypia. What do you think, Ira?

**Saul Suster:** Another ideal playground for the "name-givers"! Have fun!

**Lawrence Weiss:** I would consider this tumor to be a phyllodes tumor, and a malignant one given the mitotic rate and the atypical mitoses, and am glad to hear that the margins are negative. I think that the patient should be closely followed.

**CASE NO. 9 – CONTRIBUTED BY MASAHARU FUKUNAGA:**

**Phil Allen:** Papillary squamo-transitional cell carcinoma of the uterine cervix. I agree with the diagnosis. I suspect that the deep invasion portends a bad prognosis.

**Carlos Baachi:** This is a nice example of papillary squamotransitional cell carcinoma of the uterine cervix. Thanks for sending the case.

**David Ben-Dor:** The ability of the endocervical mucosa to undergo metaplastic changes mimicking transitional epithelium (or the more modern term urothelium) is also demonstrated by the condition of "transitional cell metaplasia" found in the cervices of older women. I think transitional is merely a descriptive term and a tumor like this shouldn't be biologically different from typical squamous cell carcinomas of this area, though it behooves the pathologist to insure that bladder tumor is ruled out. The problem with transitional metaplasia is not to overdiagnose dysplasia. I agree that the phenotypical histological features of transitional cell tumors as seen in the bladder are well developed in this case and that the tumor would otherwise be compatible with a urothelial tumor (i.e. if in the right place).

**Gerald Berry:** It looks like a high grade nonkeratinizing squamous carcinoma to me.

**Michele Bisceglia:** Papillary squamotransitional cell carcinoma of the uterine cervix. I would have called it squamous cell carcinoma with papillary architecture. Thank you, Masa, for contributing this case and pointing out this peculiar type/variant of tumor.

**Ira Bleiweiss:** Agree.

**Thomas Colby:** I would have probably called this squamous carcinoma, but agree that it does have a papillary squamo-transitional appearance. This is a new entity for me, although it shouldn't be given the 1997 AJSP reference.

**Kum Cooper:** Masa, I would have probably signed this out as papillary and invasive squamous cell carcinoma of the cervix in Africa (where as you know this is epidemic). I have read about the squamo-transitional carcinomas as described but never made that diagnosis. The problem as you point out is papillary SCC which is also well described. I wonder if the "transitional" areas show true urothelial differentiation: uroplakin, thrombomodulin etc. CK 20 is usually positive in TCC's. The other point of course is that transitional metaplasia is seen in older women.

**Ivan Damjanov:** I think that this is an excellent diagnosis, although I would have signed it out routinely as papillary squamous cell carcinoma.

**Otto Dietze:** I agree with the diagnosis; however I cannot add a similar observation from my own experience.

**Hugo Dominguez-Malagon:** Papillary squamotransitional carcinoma, this particular case has high grade features such as comedo necrosis and vascular invasion. The WHO classification makes a distinction but it not considered as a separate entity, and the behavior is similar to regular squamous cell carcinoma.

**Göran Elmberger:** Good case for opening an interesting discussion. I basically agree with the suggested diagnosis of papillary squamotransitional carcinoma. However, I find it difficult to find the rationale for not classifying this lesion as non-keratinizing squamous cell carcinoma with a component of papillary squamous cell carcinoma. I guess this is merely of academic interest, but still. For non-keratinizing squamous cell carcinoma, I could see features such as "epidermoid" growth (basal palisading and cytoplasmic maturation centrally within nests), isolated cell keratinization and focally prominent intercellular bridges. Immunohistochemical phenotyping might add in difficult situations, but I suspect that even after an extensive differential marker study focusing on squamoid and transitional differentiation, doubt might persist. Should we integrate IHC findings in our interpretation rather than as recommended in many situations just go by routine stains? Time for paradigm shift? What about more extensive investigation, such as expression profiling – any help??

**Vincenzo Eusebi:** Papillary squamotransitional cell carcinoma.

**Giovanni Falconieri:** Honestly, my interpretation was poorly differentiated squamous carcinoma, and that was it. We do not have the ob-gyn clinic, hence I have basically forgotten almost all about these lesions including customary ones.

**Cyril Fisher:** Papillary squamotransitional cell carcinoma of cervix, as described, very nice slide.

**Christopher Fletcher:** I have no personal experience with lesions of this type.

**Andrew Folpe:** Being only a humble small town soft tissue pathologist, I'd probably just call this a non-keratinizing SCC and go about my day, unaware of this WHO approved entity.

**Jerónimo Forteza Vila:** We agree with the diagnosis.

**Thomas Krausz:** Agree with diagnosis. Beautiful example. It would be interesting to know what makes the phenotype of this tumor primarily transitional rather than squamous at this anatomic site. I assume demonstration of HPV 16 would help to distinguish this primary cervical tumor from a metastatic malignant Brenner tumor.

**Janez Lamovec:** Most of the tumor appears transitional and in some foci squamotransitional (the morphology of epithelial cells being in between the two types) but well developed squamous cell differentiation is not evident. We saw one similar case recently.

**Thomas Mentzel:** I do believe as well that papillary squamotransitional cell carcinoma represents the best diagnosis, many thanks.

**Markku Miettinen:** Non-keratinizing squamous cell carcinoma would have been my terminology, I am afraid all of these went under this name in my (historical) gyn-pathology practice, but surely your diagnosis may match the reference you mentioned. It would of interest to know whether these tumors have true urothelial markers such as uroplakins.

**Juan Rosai:** I agree that it looks like the case reported by Koening et al, but I wonder how much of an "entity" this is, as opposed to a morphologic variation in the theme of squamous cell carcinoma of the cervix.

**Elvio Silva:** Agree with the papillary component, which could be important in biopsies. I prefer the diagnosis of poorly-differentiated squamous cell carcinoma. I doubt the transitional component

**Dominic Spagnolo:** I agree with the categorization as squamotransitional according to the current classifications, but I have a problem in justifying the "transitional" other than the superficial resemblance to transitional epithelium; the papillary element cytologically looks like squamous carcinoma in-situ of the cervix.

**James Strauchen:** Papillary squamous cell carcinoma of the cervix. I was unaware of the entity of squamotransitional cell carcinoma but the term seems apt for this histology.

**Saul Suster:** I can certainly see the close resemblance with a high-grade urothelial carcinoma. Do not recall having seen this before. Thank you for sharing the case.

**Lawrence Weiss:** I would have called this a squamous cell carcinoma and gone on to the next case. I doubt that there will be biologic significance to this very interesting histologic pattern.

**CASE NO. 10 – CONTRIBUTED BY THOMAS KRAUZ:**

**Phil Allen:** Well differentiated malignant mesothelioma with low nuclear grade and prominent papillary pattern. I showed this case to Dr Doug Henderson, who has just completed the manuscript of a chapter on mesothelioma for the latest edition of Dail and Hammar's lung book. He thinks that the status of well differentiated papillary mesothelioma is still not clear. He believes this is different from the very well differentiated tumors and is malignant because there is invasion of fat, a stromal reaction to tumour cells, and is too cellular, large and diffuse to be the same as the tumors described as benign, well differentiated papillary mesotheliomas. However, as it is well differentiated, the clinical course could be protracted, but he warns that he has seen mesotheliomas that were not as histologically alarming as this which killed within a few months.

**Carlos Bacchi:** As this lesion has potential for malignant behavior, I would agree with the diagnosis of epithelioid papillary low-grade mesothelioma, but I am not sure if more radical treatment such as chemotherapy would be beneficial in this neoplasm.

**David Ben-Dor:** I think a good part of the practice of pathology is dealing with semantics. The problem begins with the sloppy assignment of names to lesions by well meaning individuals. Even if the problem gets sorted out on the level of cognitive rationality, there are still residues from past misunderstandings which muddy the waters. Another possible aspect of the problem is the psychological difficulty in assigning a diagnosis of malignancy to such a well differentiated and bland looking lesion, with the attendant psychological implications for the patient, so this diagnostic term could be a way of having your cake and eating it too. Is there really such a thing as a benign mesothelial epithelioid tumor or aren't most of them reactive/hyperplastic (which is what Rosai thinks the original "papillary mesothelioma" really is)? I agree that this is a low grade malignant neoplasm. I'm not sure how well the clinicians would grasp the differentiation between the entities discussed here; if I had to report a "papillary mesothelioma" as defined originally, I would call it descriptively a benign papillary mesothelial proliferation in order not to have to go through the agony of making sure that the clinician understood that the term "mesothelioma" shouldn't be taken literally. Does anyone call Spitz nevi "juvenile melanomas" anymore? By the way, I found a small focus of lymphoid parenchyma in 10a and a psammoma body calcification in 10b.

**Gerald Berry:** Whatever the term that is used in this case, I think a detailed explanation of the terminology and prediction of the recurring nature of this lesion would be necessary. I think your term is a good one as it encompasses the low grade but likely biologic behavior.

**Michele Bisceglia:** Epithelioid malignant mesothelioma, low nuclear grade, with prominent papillary pattern. Honestly and based only on the slides submitted, I would have call this case as "well-differentiated papillary mesothelioma", but this does not mean that I would have been right. In my opinion, you are one of the most prominent experts on mesothelial tumors, so you must be right. Further, taken into account the entire clinical (operative) information and the rest of your pathologic data (focal invasiveness), agree that this case should be diagnosed as you did. In the Weiss-Enzinger textbook, it is stated that when these tumors are widespread they are more likely to pursue a progressive clinical course and cannot be regarded as benign.

**Ira Bleiweiss:** I would call this well-differentiated papillary mesothelioma. How is the patient doing? Sometimes "time" is the best diagnostician.

**John Chan:** Agree with interpretation of malignant mesothelioma, because the architecture is too complex and focally too solid for well differentiated papillary mesothelioma.

**Thomas Colby:** Malignant mesothelioma, epithelioid type. Too cellular and complex for a well-differentiated papillary mesothelioma. To me, this is a fully malignant mesothelioma that should be managed as such.

**Kum Cooper:** Thomas, I would have called the first lesion a well-differentiated papillary mesothelioma (good prognosis, circumscribed and solitary). However, the history of multiple lesions subsequently places this firmly in the epithelioid malignant category. Interesting that you use the term "low grade". Is there an evolving multi-step pathogenesis for

mesothelioma? (Similar to serous carcinomas of the ovary ala the Johns Hopkins group). The first tumor does have a central sclerosing focus with solid nests. Is this evolving into a high grade? Thank you for this challenging case.

**Ivan Damjanov:** I agree with you , although I do not remember that I made a diagnosis of "low nuclear grade mesothelioma", except those in the scrotum.

**Otto Dietze:** To make a definite diagnosis from my personal experience without consultation of a reference center is difficult, and I believe that most oncologists would expect a second opinion in such cases; however the morphology of this tumor and the diagnosis is convincing.

**Hugo Dominguez-Malogon:** I agree that this tumor should be considered malignant, and called malignant mesothelioma, epithelioid, papillary, with low grade nuclei.

**Göran Elmberger:** Interesting case. I would personally go along with the suggested diagnosis of epithelioid mesothelioma with tubulopapillary pattern of growth. I realize the differential towards WDPM is difficult and that there might be a continuous spectrum in morphology as well as in biology within these lesions. However, even the WDPM is generally classified as a tumor of low-grade malignant potential rather than a benign entity. Furthermore, malignant transformations such as one I have seen are well described. Is there really any difference between low malignant potential and borderline? These words are often used with basically the same connotation – "I do not know exactly how this tumor in this individual will behave in the long run". We only know the outcome in an individual case after long-time follow-up! Uncertain malignant potential??? PMUMP???

**Vincenzo Eusebi:** Thank you Thomas. I entirely agree with the diagnosis of epithelioid malignant mesothelioma with papillary pattern.

**Giovanni Falconieri**: Low grade papillary mesothelioma, malignant. I have no hesitation in labeling it as you did.

**Cyril Fisher:** I would term this malignant mesothelioma while acknowledging that it is cytologically well differentiated. Well differentiated (but not benign) papillary mesothelioma is recognized to progress, even after many years, especially when there are multiple lesions. It seems best to regard all these as malignant from the outset while noting that there is a spectrum of morphology and behavior. The introduction of a borderline /intermediate category is likely to be confusing for clinicians - should these cases be treated with chemotherapy from the outset?

**Christopher Fletcher:** Given your description of the presence of convincing invasion elsewhere, then personally I would label this as malignant mesothelioma, epithelial type with a prominent papillary pattern, just as you suggest.

**Andrew Folpe:** Very cool case. Completely agree with epithelioid malignant mesothelioma, showing relatively low nuclear grade. The low-power architecture of this lesion is interesting- could it have arisen in a (benign) multicystic peritoneal mesothelioma?

**Jerónimo Forteza Vila:** In a first moment, we diagnosed it as a benign tumor.

**Masaharu Fukunaga:** A- well-differentiated papillary mesothelioma; B- Basically same histology of A with a solid arrangement. There is no frank evidence of stromal invasion and nuclear atypia and no mitotic figures, but because of multiple lesions, it has malignant potential. I agree your diagnosis. I wonder how to differentiate "well-differentiated papillary mesothelioma" from "epithelioid malignant mesothelioma, low nuclear grade". I understood most of the former has a benign clinical course and some show a malignant behavior.

**Allen Gown:** These are problematic cases, and the nomenclature used should convey to the oncologist the low (but non-zero) malignant potential of this tumor; I would sign this out as a low grade epithelioid mesothelioma.

**Janez Lamovec:** With this extent of papillary mesothelial proliferation, I would not be willing to call this benign in spite of low grade nuclei, rare mitoses etc. Many years ago, we had a more diffuse type of similarly "benign" but more diffuse mesothelial hyperplasia that was by some considered to be reactive. We sent that case to Dr. Churg who diagnosed it as malignant mesothelioma, low grade. The patient had a protracted course for many years but eventually succumbed to the disease.

**Thomas Mentzel:** Given the extension of the neoplasm and the presence of small areas showing early invasion, I think the diagnosis should be low-grade malignant mesothelioma with a prominent papillary pattern.

**Markku Miettinen:** A tumor with histologically adenomatoid and well-differentiated papillary mesothelioma-like features. As a multifocal process both designations of "uncertain malignant potential" and low-grade malignant would be appropriate. This might well be a precursor lesion for diffuse malignant mesothelioma, as well-differentiated papillary mesothelioma (sometimes) might be. Slide 10B does show more solid (compacted?) features yet still with bland cytology.

**Liz Montgomery:** Cases like this are impossible since the available lesion is so bland but, anecdotally, we have seen similar lesions recur as overtly malignant ones that are easy to diagnose. It seems best to handle this one as you did since, despite the bland cytology, it looks too cellular and solid and seems to be invading a bit. This is a little too "interesting" for "well-differentiated papillary mesothelioma" as initially described.

**Juan Rosai:** Beautiful case of papillary mesothelioma. This is the kind of tumor that occurs much more often in the peritoneum than in the pleura. It may be well-differentiated all right, but one should not equate this with benignancy, as I learned the hard way with several cases. As far as the terminology is concerned, I would call it a malignant epithelial (or epithelioid) mesothelioma, well-differentiated papillary type (low-grade).

**Dominic Spagnolo:** I would call this well differentiated papillary epithelioid malignant mesothelioma. I would always include a comment as to the biological potential of the lesion, so there is no misunderstanding by the clinician. The points you raise are important practical issues.

**James Strauchen:** Tubulopapillary diffuse epithelioid malignant mesothelioma. I agree this is "too much" for a well differentiated papillary mesothelioma.

**Saul Suster:** I agree with your assessment that this is malignant based on multifocality and focal infiltration of fat and I would have also called it malignant mesothelioma. Despite the low-grade morphology, I think this is going to be a problem for management. Anecdotally, we've seen low-grade lesions in the peritoneal surface eventually becoming widely invasive with poor outcome. Hopefully, you will give us some clinical follow-up on this case.

**Lawrence Weiss:** I think that this is a borderline lesion. We have seen a very similar case within the last year. I think that it will probably behave well, but cannot be considered to be benign. I think that there is room for a transitional entity.

**CASE NO. 11 – CONTRIBUTED BY THOMAS MENTZEL:**

**Phil Allen:** Lupus panniculitis, right hip. I wonder if there was any immunofluorescent or serological support for a diagnosis of lupus panniculitis and if this was the only lesion clinically apparent.

**Carlos Baachi:** This is a very challenging case. I confess that I didn't think about lupus at all but after reading Thomas' discussion, I am convinced that this panniculitis could well be related to lupus. Great case.

**David Ben-Dor:** It's interesting to observe that the epidermis and dermis are relatively normal. Given the fact of a mass lesion and the deep lymphoplasmacytic infiltrates, I would have worried about ruling out a lymphoma. I apologize for and am embarrassed by my ignorance, but I don't know what the significance of CD123 cells are. On the other hand, I was happy to learn about the role of the T regs and the fact that documenting a lack of them is helpful in confirming the diagnosis of autoimmune disease. Sounds like a useful tool for working these cases up but is this known to non-dermatopathologists? Is there a history or are there other clinical manifestations of lupus and can this lesion be the first or only manifestation of the disease?

**Gerald Berry:** Agree. I am curious, was the history of lupus provided at the time of surgery?

**Michele Bisceglia:** Lupus panniculitis (lupus erythematosus profundus). Difficult case, and brilliant/elegant diagnosis. Hope that such a case does not occur in my practice or if this is to happen that at least I could know in advance that the patient has lupus erythematosus.

**Thomas Colby:** Difficult case for me, favor inflammatory over neoplastic (either peculiar liposarcoma or lymphoma). Indeed a profound case of (lupus) profundus. Was the patient proven to have lupus, or can that diagnosis be made from the histology and the distinctive immunohistochemistry?

**Kum Cooper:** Lupus was furthest from my mind! Interesting presentation. Thank you, Thomas, for this education.

**Ivan Damjanov:** Excellent diagnosis - well documented.

**Otto Dietze:** Thank you for this contribution. Although the infiltrate with a considerable amount of plasma cells seems to me reactive and not neoplastic, the tumor like growth and fibrosis is a feature I have never seen is LE.

**Hugo Dominguez-Malagon:** Nice case of lupus panniculitis, thank you.

**Göran Elmberger:** Thanks for an unusual but educational case.

**Vincenzo Eusebi:** Thank you very much, Thomas, for this very difficult case. At the beginning, I also had taken in consideration an inflammatory liposarcoma, but I think you are right.

**Giovanni Falconieri:** Difficult case. Because of the "bottom heavy" lymphoid infiltration, I would initially favor a lymphoproliferative disorder although some microscopic features, including the polyphenotypic infiltrate, go better along with an inflammatory condition.

**Christopher Fletcher:** Appearances are consistent with a very florid example of lupus panniculitis (certainly the most florid I have seen or recognized). Did the patient have any evidence of SLE or discoid lupus?

**Andrew Folpe:** I couldn't do much better than "lobular panniculitis". I would definitely want to rule out a lymphoma, but the infiltrate does seem very mixed. Lupus panniculitis seems reasonable- did she prove to have SLE?

**Jerónimo Forteza Vila:** We had also thought about lupus panniculitis or panniculitic lymphoma as a differential diagnosis.

**Masaharu Fukunaga:** I have never seen this type of panniculitis. Thanks, Thomas, for the unusual lesion and detail description of the immunostaining.

**Thomas Krausz:** Diagnostically difficult case. In the context of the clinical history of a solitary lesion, I would have considered an inflammatory pseudotumor. Reading the very educational discussion, I am convinced about the diagnosis provided by Thomas Mentzel.

**Markku Miettinen:** Lupus panniculitis, fully agree with you. Lack of atypical large cell component may separate it from panniculitic T-cell lymphoma (however, my experience of the latter is only 1-2 cases.)

**Liz Montgomery:** Thanks for this case that was initially called "inflammatory liposarcoma". I do not know the first thing about lupus panniculitis and the phenotype of the lymphoid cells in it and how they progress to T cell lymphoma, but the deep parts of this lesion, with the storiform appearance and foamy appearance to the spindly cells, remind me of soft tissue Rosai-Dorfman disease (perhaps this was on my mind since I had one yesterday that had been called high grade sarcoma but could be diagnosed as RDD on the H&E alone). I could not tell whether I was seeing emperipolesis or odd tissue retraction but would have also checked an S100 stain.

**Juan Rosai:** After reading the history and glancing at the case on low power, I was sure it had to be an inflammatory liposarcoma. However, I searched and searched for atypical stromal cells (lipoblastic or otherwise) without finding any, and, therefore, I came to accept the proposed diagnosis of panniculitis. Whether it is necessarily due to lupus erythematosus, I cannot say.

**Dominic Spagnolo:** Very nice case of lupus profundus. At first low power glance, I thought it was going to be Rosai-Dorfman disease.

**James Strauchen:** Lupus panniculitis ("lupus profundus"). Nice example. The presence of relatively numerous plasma cells is another feature favoring lupus panniculitis over subcutaneous panniculitis T-cell lymphoma.

**Saul Suster:** This must be the most dramatic case of lupus profundus I've ever seen! The sclerosing stromal reaction is another feature I was not expecting in this condition. In some areas there is angiocentric and perineurial involvement by lymphoid cells. Is it possible that a lymphoproliferative process could arise from a lesion of lupus panniculitis? I think in a case like this it would have certainly been interesting and worthwhile to further study the infiltrate for B-cell gene rearrangements. Were there any clinical features or laboratory findings supportive of a diagnosis of lupus in this patient?

**Lawrence Weiss:** It is hard to assess this case without having seen the immunos. In my experience, lupus profundus does not have "numerous" CD20-positive cells. Were the plasma cells polyclonal? Were Ig gene rearrangements performed?

**CASE NO. 12 – CONTRIBUTED BY ELIZABETH MONTGOMERY:**

**Phil Allen:** Giant cell angiofibroma (giant cell rich solitary fibrous tumour), soft tissue of neck near base of skull. I agree with the diagnosis.

**Carlos Bacchi:** Nice example of giant cell angiofibroma.

**David Ben-Dor:** Am I the only member to whom this entity is not "certainly well known"? Maybe this is apples and oranges, but the stromal cells on this slide bring to mind those in the breast lesion presented by Falconieri earlier (case 8) maybe even being weirder looking here.

**Gerald Berry:** Agree. Nice example.

**Michele Bisceglia:** Giant cell angiofibroma (giant cell rich solitary fibrous tumor). Nice and typical case in extraorbital location.

**Ira Bleiweiss:** Agree.

**Thomas Colby:** Agree with diagnosis.

**Kum Cooper:** Just as we begin to recognize this tumor, Louis Guillou is now telling us that this is a variant of SFT!

**Ivan Damjanov:** We all agree about what this is but then there are problems on how to call it. In any case, I prefer giant cell angiofibroma than solitary fibrous tumor.

**Otto Dietze:** I agree, CD34 has facilitated this diagnosis in the last years.

**Hugo Dominguez-Malogon:** Completely agree with the diagnosis of giant cell rich solitary fibrous tumor, thank you for the case.

**Göran Elmberger:** Thanks for interesting case. Kind of reminiscent to the SFT, I usually see i.e.: those in lung and pleura with the exception of the giant cells!

**Vincenzo Eusebi:** Giant cell angiofibroma. Agree.

**Giovanni Falconieri**: I agree with the microscopic interpretation, the differential may also include a meningothelial tumor because of the location. Thank you for this contribution, I have finally one of such lesions in my collection.

**Andrew Folpe:** Giant cell angiofibroma. Very nice example.

**Cyril Fisher:** Extraorbital giant cell angiofibroma, nice case. This lesion is cropping up in a few places other than the orbit but as a supposed variant of SFT its scarcity and localization compared with the ubiquity of SFT is surprising.

**Christopher Fletcher:** Indeed this is a beautiful example of what we first described as giant cell angiofibroma – many thanks Elizabeth! It seems remarkable that the first group of cases with this morphology were all located in the orbital region, although, of course, they have subsequently been identified in other head and neck or more distal locations. It does indeed seem logical nowadays to regard this as a pattern of degenerative alteration in SFT, as suggested by Louis Guillou some years ago.

**Jerónimo Forteza Vila:** We agree with the diagnosis.

**Masaharu Fukunaga:** Giant cell angiofibroma, thanks, Elizabeth for the beautiful case.

**Allen Gown:** Another member of the CD34-positive mesenchymal club.

**Thomas Krausz:** Agree with diagnosis. Beautiful example.

**Janez Lamovec:** What a fantastic case of giant cell angiofibroma. Thank you for sharing it with us.

**Thomas Mentzel:** Thanks a lot for this nice example showing features of extraorbital giant cell angiofibroma.

**Markku Miettinen:** Fully agree on giant cell angiofibroma type of solitary fibrous tumor, a very nice example.

**Juan Rosai:** Nice example of the entity described as giant cell angiofibroma. I like the idea of it being related to solitary fibrous tumor, although the type of multinucleated giant cells present in it remind me more of those one finds in polypoid lesions located beneath squamous epithelia, such as vulva, vagina, cervix, anus, nasal cavity and oral cavity, and which have been given a variety of names, one of which (in the oral cavity) happens to be giant cell fibroma (Oral Surg Oral Med Oral Pathol 53: 582-586, 1982).

**Dominic Spagnolo:** This is a very nice example of giant cell angiofibroma with prototypical findings. Thanks for the case.

**James Strauchen:** Giant cell angiofibroma (giant cell rich variant of solitary fibrous tumor)! I am not sure how much has actually been learned. I think we may have just changed the names!

**Saul Suster:** Very beautiful example of this tumor. I also agree with the interpretation that this likely corresponds to a variant of solitary fibrous tumor. We have seen examples of pleural SFT's showing similar multinucleated and bizarre cells.

**Lawrence Weiss:** Nice case.

**CASE NO. 13 – CONTRIBUTED BY GIUSEPPE PELOSI:**

**Phil Allen:** "Triphasic" neuroendocrine carcinoma with rhabdomyomatous and myofibroblastic differentiation, right upper lobe. I have never seen a similar case. Thanks for the extensive discussion and references.

**Carlos Baachi:** I agree that this case is a carcinosarcoma. I don't recall seeing cases like this before as primary tumor in the lung. It is unusual indeed.

**David Ben-Dor:** It wasn't obvious to me that this was small cell carcinoma, since in places there seems to be a bit too much cytoplasm, the cells look spindly, and some of the nuclei look a little vesicular. Purely on morphologic ground, I probably would have called this spindle cell carcinoma in the aggregate.

**Gerald Berry:** The biphasic nature of the neoplasm suggests a carcinosarcoma with neuroendocrine differentiation. Both components would be expected to behave aggressively.

**Michele Bisceglia:** Combined small-cell carcinoma with skeletal muscle differentiation and spindle cell sarcoma component of myofibroblastic type. Giuseppe, I think this case is unique and I predict that you will have a hard time putting 2 cases together. The only experience I have with small cell tumors with immunohistochemical myogenic differentiation (desmin and myogenin +) is with a Merkel cell tumor and with 2 cases of SCC of the urinary bladder, apart from 2-3 cases of anaplastic medulloblastoma (myo-medulloblastoma based on immunohistochemistry without rhabdoid differentiation on morphology).

**Ira Bleiweiss:** Agree. I've never seen this combination before.

**Thomas Colby:** I would probably have called this a sarcomatoid carcinoma including a small cell component and a spindled component. I have seen a few cases like this in the past, and have not worked them up as extensively immunohistochemically so I could have missed muscle differentiation. In some of the cases I worked up previously, the "small cell" component didn't show the immunohistochemistry of small cell carcinoma, and I have been left with making a more descriptive diagnosis. I will keep an eye out for these cases in my practice. In terms of management, I think consideration should be given to post-surgical adjuvant therapy (for the small cell component).

**Kum Cooper:** Combined small cell carcinoma.

**Ivan Damjanov:** Carcinosarcoma would be my preferred diagnosis for this bad tumor.

**Otto Dietze:** I cannot add a similar observation, agree with the diagnosis. Thanks for the good discussion.

**Hugo Dominguez-Malogon:** The only discussion would be the many names that could be applied to this neoplasm, I prefer the simplest: "sarcomatoid carcinoma" that goes along with the concept you mentioned: "the sarcomatous component is derived from carcinoma elements according to a process of metaplasia".

**Göran Elmberger:** Hard case to classify. Given the results of IHC, I would concur with the suggested diagnosis of small cell carcinoma, combined type. The "small cell" component in itself is kind of intermediate between classical small cell and large cell neuroendocrine carcinoma. I guess we are dealing with a morphological continuum. The association with spindle cell carcinoma is probably unusual and certainly not in my recollection.

**Vincenzo Eusebi:** Very convincing sarcomatoid small cell carcinoma of the lung. I am surprised that myogenin is not positive in some cells of the spindle cell component.

**Giovanni Falconieri:** Great case and outstanding presentation! I agree with your assessment, this tumor looks pretty much like a "carcinosarcoma" or a "biphasic/collision tumor" according to a time-honored but still effective nomenclature. Not surprisingly, small cells co-express myogenic markers, and this is reflected in the abortive rhabdoid features. I have pulled out from my file a similar case seen more than 10 years ago in a 65 year-old man: the tumor was an endobronchial, polypoid small cell carcinoma growing in intimate association with a malignant, spindle and pleomorphic/sarcomatoid cell component that displayed a myofibroblastic phenotype (actins+, vimentin+, keratin and EMA negative). Electron microscopy demonstrated neuroendocrine granules in the epithelial cells. No further studies had been done at that time; however, the epithelial cells looked just small and packed just like those seen in ordinary small cell lung cancer. By the way, the patient died 6 months later and an autopsy revealed a classic metastatic pattern associated with small cell lung carcinoma. Microscopic evaluation of autopsy specimen was not so much enlightening due to postmortem and chemotherapy induced tissue changes. If this information suffices for the purposes, I'll feel delighted to join you in this venture! Just let me know how you wish to move along. Again, thanks for contributing this excellent case.

**Christopher Fletcher:** In my personal experience, this is a unique case. On H&E, in the absence of immuno-histochemical or ultrastructural data, one would have thought that this represented a combination of neuroendocrine carcinoma and sarcomatoid carcinoma. I have encountered a couple of cases of small cell carcinoma with "conventional" heterologous rhabdomyoblastic differentiation, but I have not seen a spindle cell sarcomatous component associated with a neuroendocrine tumour in the lung.

**Andrew Folpe:** Agree with high-grade neuroendocrine carcinoma with sarcomatous differentiation. I don't see any rhabdomyoblasts, but it sounds like you have convincing IHC evidence of rhabdomyoblastic differentiation. Very interesting case.

**Jerónimo Forteza Vila:** We have also thought of synovial sarcoma.

**Masaharu Fukunaga:** Agree. Carcinosarcoma or sarcomatoid carcinoma, composed of neuroendocrine carcinoma and spindle cell sarcoma. It is not clear that there is rhabdomyosarcomatous differentiation in the HE slide. Thank you very much for the detailed description.

**Allen Gown:** Strange and wonderful case; I have never seen anything quite like it! But if I do, I'll be sure to send it to you!

**Thomas Krausz:** I have never seen a carcinosarcoma of the lung where the carcinomatous component was small cell type. The sarcomatoid myofibroblastic component does not look high grade to me (on its own it reminds me of inflammatory myofibroblastic tumor, which of course does not make sense in this context). I would do a range of keratins to see whether the spindle cells express some of them in order to exclude sarcomatoid carcinoma. I did not see rhabdomyoblastic differentiation on H&E.

**Janez Lamovec:** Multi phenotypic immunoprofile in carcinosarcoma somewhat similar to desmoplastic small cell round cell tumors although with different morphological features of carcinomatous component and with sarcomatous stroma. Never seen a similar case.

**Thomas Mentzel:** What an interesting case, and I do agree with the interpretation of this unusual neoplasm as a sarcomatous high-grade neuroendocrine carcinoma.

**Markku Miettinen:** Although I initially thought of nonkeratinizing squamous cell carcinoma with sarcomatoid transformation, I agree with your interpretation. Also wonder if there is any squamous differentiation noting your neuroendocrine marker and CD56-positivity for small cell/neuroendocrine Ca. Could not catch rhabdomyoblastic differentiation histologically but certainty it could be there (reported at least in Merkel by Eusebi), and some other carcinomas also. Never seen exactly this combination.

**Liz Montgomery:** This case is very interesting and looks like a sarcomatoid carcinoma in which the overtly epithelial component has small cell features. Presumably the epithelial component must elaborate all sorts of molecules exerting autocrine and paracrine and weird differentiation factors to inform the crazy differentiation in the spindly component.

**Juan Rosai:** Spectacular case of the tumor type that has been called either sarcomatoid carcinoma or sarcomatoid carcinoma depending on the type of tissue present, and the bias that one may have for a descriptive versus a histogenetic approach. A particularly intriguing combination is that in which the epithelial component exhibits neuroendocrine differentiation and the sarcoma-like component exhibits skeletal muscle differentiation, such as that seen in this tumor. This case also confirms the old adage that if a malignant tumor in an adult shows clearcut skeletal muscle differentiation, the chances are overwhelming that it is something other than a rhabdomyosarcoma.

**Dominic Spagnolo:** I would have called this a carcinosarcoma (combined high grade neuroendocrine CA and high grade sarcoma). The occurrence of rhabdomyoblastic features in the epithelial cells immunohistochemically and apparently ultrastructurally is certainly unusual. One wonders how often this might occur in pure neuroendocrine carcinoma. I have not encountered this before.

**James Strauchen:** Combined small cell carcinoma/pleomorphic spindle cell carcinoma ("carcinosarcoma"). I have not seen this particular combination before!

**Saul Suster:** This looks like a pulmonary carcinosarcoma with a neuroendocrine carcinoma epithelial component. We saw many of these in the files at the AFIP with Cesar. As an interesting aside, I have never seen the combination of skeletal muscle + epithelial differentiation in the same cell. If this is the case, then this is truly a reportable case.

**Lawrence Weiss:** I have never seen a case like this before.

**CASE NO. 14 – CONTRIBUTED BY SANTIAGO RAMON Y CAJAL:**

**Phil Allen:** Primary osteosarcoma of the right atrium with undifferentiated metastases in the left fronto-parietal region of the brain and soft tissues of the right leg, presenting as an apparent primary brain tumour. I am surprised that the presenting metastasis was in the brain rather than in the lung when the primary was on the right side of the heart. The presentation is more like one would expect from a left atrial sarcoma.

**Carlos Baachi:** High-grade spindle cell sarcoma of unknown histogenesis. I would like to hear other member's opinion in this case.

**David Ben-Dor:** The fascicle does mention the possibility of primary osteosarcoma of the heart. I was wondering why it would be surprising for a tumor in the heart to embolize to peripheral sites until I re-read the description, and realized that the tumor was in the *right* heart, so this pattern in the absence of lung involvement does seem odd at least anatomically (unless the tumor grew through the septum and was exposed to the interior of the left atrium). The serpiginous necrotic areas bordered by palisading tumor cells remind me of high grade astrocytoma.

**Gerald Berry:** We have encountered this kind of scenario before. I think that the distinction between a primary cardiac osteosarcoma and primary musculoskeletal osteosarcoma should be sorted out by the radiologists. Primary cardiac tumors generally present with symptoms and signs of CHF or thromboembolism.

**Michele Bisceglia:** Metastasis of sarcoma. Difficult case, Santiago. Taking everything into account, high grade sarcoma in my opinion would be the diagnosis on this slide.

**Ira Bleiweiss:** I guess the discussion is academic, but why didn't you consider the leg tumor the primary?

**Tom Colby:** A difficult problem; doing pathology can be humbling can't it? Based on anecdote-based medicine (rather than evidence-based medicine), I would agree that the heart is likely the primary, and that it shows a variety of differentiation (similar to the one that can be encountered in pulmonary artery sarcomas).

**Kum Cooper:** Thank you for this educational case. I would have signed this out as a gliosarcoma!

**Ivan Damjanov:** Metastatic sarcoma, but the nature of sarcoma is debatable.

**Otto Dietze:** High grade sarcoma, exact classification of the type seems difficult to me.

**Hugo Dominguez-Malogon:** High grade spindle cell sarcoma with osteoclasts. The possibility of osteosarcoma as the primary tumor is a good one.

**Göran Elmberger:** High grade sarcoma with spindle cells, epithelioid cells and osteoclast-like giant cells. TTF1+? Thyroid or lung lesion? I guess this would be a case for clinicians and radiologists to contribute regarding discussion on primary site.

**Vincenzo Eusebi:** Brain metastasis from high grade tumour.

**Giovanni Falconieri:** I agree with your interpretation. Heart and larger intrathoracic vessel sarcomas may have a chondro- and/or osteosarcomatous phenotype. The rapid clinical evolution goes well along to the natural history of these tumors.

**Christopher Fletcher:** Given the detailed clinical history provided, this would appear to be metastatic sarcoma, consistent with spread from a primary tumour in the heart (which may well have been osteosarcoma, although no osteoid is evident in this brain metastasis). In my experience, primary sarcomas of the heart may quite often present with metastases in unusual locations. For example, I have seen several cases which have been associated with multifocal metastasis in the small bowel, either before, at, or soon after the time of primary presentation.

**Andrew Folpe:** Agree with metastatic sarcoma. I'd want to see the primary tumor for classification of the metastasis, but for the time being would be content with "undifferentiated sarcoma with osteoclastic giant cells". Certainly this could be part of an osteosarcoma.

**Jerónimo Forteza Vila:** We think that the first possibility is an origin in soft tissue with metastasis in brain and heart. Are there lung metastasis?

**Masaharu Fukunaga:** High grade sarcoma, a very difficult case. No osteoid or cartilaginous elements are seen in the slide. No differentiation is observed. Thanks, Santiago.

**Allen Gown:** It is odd that you describe TTF1 expression, even weak and in a subpopulation of the tumor cells; while TTF-1 can be expressed, rarely, in non-lung carcinomas. TTF-1 expression in mesenchymal tumors is, in my experience,

exceedingly rare.

**Thomas Krausz:** I agree that this is a metastatic sarcoma. I would consider metastatic MPNST with heterologous osteosarcomatous differentiation over osteosarcoma.

**Janez Lamovec:** Predominantly spindle cell sarcoma with osteoclast-like giant cells. I don't think that this can be diagnosed as osteosarcoma but in regard to heart tumor it may well be so.

**Thomas Mentzel:** The slide shows features of a high-grade sarcoma and it would be interesting to see the other lesions as well.

**Markku Miettinen:** Agree on high grade sarcoma, type unclear. This perivascular collar pattern occurs in many high grade tumors especially in MPNST, bad GISTs, among others. In this context, it probably means an intimal (? myofibroblastic) sarcoma of the heart with embolic metastases into brain and leg. Such sarcomas can also have chondroosseous (osteosarcomatous differentiation). Your case matches with many in our series of pulmonary artery intimal sarcomas, and similar tumors no doubt also occur in the heart (atrium) also.

**Liz Montgomery:** My brilliant diagnosis is "high grade sarcoma". If it started in the heart, maybe "intimal sarcoma" since such lesions can display osseous differentiation.

**Juan Rosai:** I don't think one can say anything other than high-grade pleomorphic sarcoma, not otherwise specified. The osteoclast-like multinucleated giant cells made me think of leiomyosarcoma, but the immunohistochemical profile does not support it. I suspect the primary tumor is the mass located in the heart. The fact that prior radiologic studies showed calcifications in the cardiac area is of interest in this regard. It reminds me of a case discussed at a Seminar of the Penrose Cancer Hospital in 1969 by Averill Liebow, who diagnosed it initially as osteoma of the atrium but which developed into a high-grade sarcoma with invasion of the lung and killed the patient.

**Dominic Spagnolo:** Was the tumor in the limb the primary site? Has that been excluded?

**James Strauchen:** Sarcoma, NOS. The combination of positivities for TTF-1 and CD10 is perplexing. According to the AFIP Fascicle, cardiac osteosarcoma invariably involves the left atrium.

**Saul Suster:** Looks like high-grade sarcoma, NOS in the metastasis. Would be interesting to compare this with sections of the heart tumor.

**Lawrence Weiss:** Metastatic sarcoma would not have been my primary thought. I would have considered it to be a primary sarcoma.

**CASE NO. 15 – CONTRIBUTED BY JOSHUA SICKEL:**

**Phil Allen:** Necrotizing eosinophilic myocarditis with eosinophilic vasculitis and foci of myocardial infarction consistent with Churg-Strauss syndrome. A very convincing case. Thanks for the contribution.

**Carlos Baachi:** Spectacular case Josh! Amazing the degree of vasculitis with eosinophilia involving the heart.

**David Ben-Dor:** Beautiful demonstration of eosinophilic vasculitis involving vessels of varying sizes (not limited to any one size group as are other vasculitides). Granulomas found after searching.

**Gerald Berry:** I agree with the diagnosis of eosinophilic myocarditis. The important distinction when faced with this pattern is to distinguish it from hypersensitivity myocarditis, which is a drug-related disorder. The abundant myocyte damage and necrosis and the interstitial distribution between myocytes are key points. In our experience of eosinophilic myocarditis (3-4 cases), none had a connective tissue disorder or vasculitis. The treatment is aggressive immunosuppression at our institution.

**Michele Bisceglia:** Necrotizing eosinophilic myocarditis with associated vasculitis, consistent with Churg-Strauss syndrome. Thank you, Josh. Very rare case. Never seen in this location.

**Ira Bleiweiss:** We don't see this, even here in the original home of Drs. Churg and Strauss.

**Thomas Colby:** I agree with diagnosis and discussion. Now this is a case I can wet my pants over!

**Kum Cooper:** Beautiful case. Thank you. The descriptive terminology "allergic angitis and granulomatosis" is so appropriate for this case. I assume she had peripheral eosinophilia as well.

**Ivan Damjanov:** I agree with the diagnosis of Churg-Strauss syndrome. It can be highly variable despite the claims to the contrary.

**Otto Dietze:** I have never seen a case of myocarditis in CSS, thanks for this unique contribution.

**Hugo Dominguez-Malogon:** Churg-Strauss involving the myocardium, the case is spectacular. Thank you.

**Göran Elmberger:** Beautiful text-book case! Unfortunately one usually only encounters these case just in text books and in the AMR club! Thanks.

**Vincenzo Eusebi:** Thank you. I agree.

**Giovanni Falconieri:** Extraordinary case, thanks for this presentation and the thorough review of CSS. Very useful and didactic slide.

**Cyril Fisher:** What a striking appearance. Fascinating case.

**Christopher Fletcher:** Amazing, impressive and entirely convincing case, the like of which I have not previously seen – many thanks.

**Andrew Folpe:** Eosinophilic vasculitis involving the heart. Very unusual case.

**Jerónimo Forteza Vila:** We agree with the diagnosis.

**Masaharu Fukunaga:** A very fulminating case. This is my first time to see CSS. Thank you very much for the case and the informative comments.

**Thomas Krausz:** Agree with diagnosis. Beautiful example.

**Thomas Mentzel:** A nice case of Churg-Strauss syndrome with extensive necrotizing eosinophilic myocarditis.

**Markku Miettinen:** Agree on eosinophilic myocarditis and now also seeing the focal vasculitis. This disease is new to me - never seen in soft tissues.

**Liz Montgomery:** Oooo. A cousin to our prior GI tract case.

**Juan Rosai:** I guess the Churg-Strauss syndrome exists after all. I have been told that Averill Liebow did not believe in the existence of this entity, which meant that none of his many distinguished disciples (Katzenstein, Carrington, Saldana, Feldman) and the disciples of those disciples (Askin, Colby) did not believe in it either.

**Dominic Spagnolo:** Great example of Churg-Strauss syndrome involving the heart. I suspect in many places a post-mortem examination would not have been done!

**James Strauchen:** Churg-Strauss! Spectacular case! The incidence of Churg-Strauss may be rising due to the widespread use of steroid-sparing leukotriene receptor antagonists (montelukast) in asthma. We recently saw a case diagnosed on endocardial biopsy.

**Saul Suster:** Great case, thank you for contributing it. Is Churg-Strauss a vanishing syndrome? I don't recall having seen another case for ages.

**Lawrence Weiss:** Holy cow!!!!!!!!! How was this person walking around? Josh, I would love to get a slide of the adrenal on this case.

**CASE NO. 16 – CONTRIBUTED BY DOMINIC SPAGNOLO:**

**Phil Allen:** Sclerosing stromal tumour, right ovary. This is the first one of these I can remember seeing. There are enough pseudolipoblasts in the sections to trigger a misdiagnosis of ovarian liposarcoma.

**Carlos Baachi:** Agree.

**David Ben-Dor:** I see this entity once in a while and have never seen a case with this extent of sheet like proliferation of round almost epithelioid cells. In fact these look somewhat deciduoid. But there are areas in the periphery where the typical pseudolobular organization is preserved. How about a good old fashioned mucin stain to rule out Krukenberg?-

the keratin positivity of the cells here doesn't help in that regard and in fact surprised me. Is the latter accepted?- I looked in some of the recent general pathology and gynecology textbooks I have and didn't see this mentioned.

**Gerald Berry:** Agree. Nice case.

**Michele Bisceglia:** Sclerosing stromal tumor of the ovary. Rare case. This tumor seems to have variable histology; and in my experience, the diagnosis should be difficult. As a matter of fact, although I was able 20 years ago (assuming that anyone should have been less experienced in the past than he is to date) to correctly ad quickly diagnose one such case which had a typical morphology (as one can see illustrated in textbooks); and notwithstanding I had the opportunity to see another typical case few years ago, still I "managed" to misinterpret the most recent one I observed last year which was composed of multinodular pseudo fibromatous bilateral ovarian masses (marked hyperplasia of the collagen-producing spindle cells with only scattered -singly or in minute nests or cords- of inhibin alpha +ve small round cells which looked like granulosa cells). My erroneous diagnosis was corrected by a more experienced and gene-specialized pathologist. Now I see another histology in your case. I am not bored with these cases. Thank you, Dom.

**Ira Bleiweiss:** Agree.

**John Chan:** In this case, the pseudolobules have more plump ovoid cells and many less spindly cells compared with the average case of sclerosing stromal tumor of ovary. With so many vacuolated/signet ring cells, this case shows overlap with so-called signet ring stromal tumor.

**Thomas Colby:** I agree with diagnosis.

**Kum Cooper:** Dom, the ones I have encountered have been predominantly spindled with the lobulation and peripheral HPC-like blood vessels. Have never seen so many luteinized cells before…and clearly they belong as they merge imperceptibly with the background spindle cells.

**Ivan Damjanov:** I agree.

**Otto Dietze:** Nice case, I did not see a similar one within the last years and think that it is rare within the group of sex cord stroma tumors.

**Hugo Dominguez-Malagon:** Agree with the diagnosis, thank you.

**Göran Elmberger:** Interesting case. Agree with diagnosis. Being more versatile in H&N and pulmonary pathology I see some resemblance to SFT. CD34? Belonging to same group of tumors?

**Vincenzo Eusebi:** I agree. Thank you.

**Giovanni Falconieri:** As already commented on Masa's case, I do not see too much Gyn pathology specimens, Dom. I have memories of a few cases of ovarian SST; none, however, so small as the case you have presented. Nevertheless, I am in total agreement with your interpretation.

**Cyril Fisher:** Sclerosing stromal tumor, unusual example. The few I have seen have not had this degree of luteinization.

**Christopher Fletcher:** Convincing case. When these lesions are much less luteinized, they may quite closely resemble a solitary fibrous tumour.

**Andrew Folpe:** Looks good for a lipidized sclerosing stromal tumor. Thanks for contributing it!

**Jerónimo Forteza Vila:** Thank you so much for this interesting case.

**Masaharu Fukunaga:** A very beautiful case. Thanks, Dominic. I encounter this type of tumor one or twice a year.

**Thomas Krausz:** The few cases of sclerosing stromal tumors of the ovary I have seen before were substantially larger, and contained much less luteinizing cells. On the submitted case I was also considering a diagnosis of luteinized thecoma. Perhaps this case can be called luteinized variant of sclerosing stromal tumor.

**Thomas Mentzel:** This represents for me a quite difficult case given the coexpression of epithelial, myogenic and melanocytic markers (did tumour cells stain positively for HMB-45, NKIC3 and MiTF1 ?). Because cases of PEComa may show prominent sclerosis (as it has been reported recently by Dr. Fletcher), I was thinking on a PEComa with aberrant expression of epithelial markers ???

**Michal Michal:** Beautiful case. There are even transitions to the signet ring stromal tumor of the ovary (*I.Ramzy: Signet ring stromal tumor of ovary. Cancer 1976: 38:166-172. G.R.Dickersin, R.H.Young, R.E.Scully. Signet ring stromal and related tumors of the ovary. Ultrastruct Pathol 1995:19:401-419*)

**Markku Miettinen:** PEComa like features, would have considered this a PEComa without being much aware of this rare ovarian tumor, without being in disagreement with you. By its Melanin A positivity, this tumor (sclerosing stromal tumor of ovary) might intersect with PEComa, even perhaps be a PEComa variant. HMB45 would also be of interest to evaluate possible relationship with PEComa.

**Liz Montgomery:** I thought the luteinized cells made it hard but the backdrop seemed good for sclerosing stromal tumor of ovary.

**Juan Rosai:** I would not argue too much with the diagnosis offered, although – like the contributor – I have never seen a case of ovarian sclerosing stromal tumor with so many luteinized cells. I confess having a hell of a time telling apart this tumor from a luteinized fibrothecoma and a so-called stromal luteoma.

**Elvio Silva:** The nodularity and fibrotic stroma would favor the diagnosis of sclerosing stromal tumor. However, it is rare to see groups of luteinized cells and the vascular pattern is not clear. It is difficult to determine if there are different variants of a rare and poorly understood tumor like this one.

**James Strauchen:** I can believe that! I thought this might be a hilus cell tumor due to the foamy, lipid-laden cells.

**Saul Suster:** Thank you for this unusual example of this tumor. I don't get to see too many cases of ovarian tumors.

**Lawrence Weiss:** I have also not seen the extensive luteinized component before.

**CASE NO. 17 – CONTRIBUTED BY SAUL SUSTER:**

**Phil Allen:** Undiagnosed, histologically bland, 8 cm epithelial tumour with insular pattern and fibrovascular stroma, serosa of sigmoid colon, female aged 63. Sorry Saul. I don't know what this is either. I don't think it is a mesothelioma, and I can't, for the life of me, think what it could be but it looks as though it is an "entity".

**Carlos Bacchi:** Granulosa cell tumor??

**David Ben-Dor:** By default, given the location (and in the absence of anything definitely contradictory from the immuno point of view assuming I didn't miss anything), mesothelioma which apparently didn't consult the textbook before deciding what it should look like.

**Ofer Ben-Itzhak:** I received this case from Dr. Groisman to help with some immunostains. At that time, Dr. Groisman informed me that the cytokeratin was strongly positive, and EMA, cytokeratin 5/6, cytokeratin 7, calretinin and S100 were all positive. CD117, CD99, ER, PR, melan A, vimentin and p63 were all negative. He asked for inhibin (due to resemblance to granulosa cell tumor) which was negative. I also performed WT1 which showed definite nuclear staining of tumor cells at the periphery of the mass and D2-40 which was positive. Thus, we thought this might be a localized mesothelioma, with unusual histologic and clinical characteristics. Histologically the extensive nuclear grooves are unusual in mesothelioma, although reported in reactive mesothelial hyperplasia (Ng, Collins: Diagnostic significance and possible pitfalls of nuclear grooves in extrathyroid cytology. Diagn. Cytopathol. 16:57, 1997). The basement-membrane like globules are very rare in mesothelioma (PAS-D positive basement-membrane globules, not similar to those in our case, were reported in 2 cases by Adams et al: Malignant mesothelioma: PAS-diastase positivity and inversion of polarity in intravascular tumor. Histopathol 41:260, 2002), and of course, the low-grade nuclear features and the relative circumscription of the tumor are unusual. Clinically, the solitary large peritoneal lesion is unusual and we did not know whether the tumor is definitely a "malignant-mesothelioma" or "of uncertain malignant potential". However, we received help from the clinical follow-up. PET-CT demonstrated two other peritoneal lesions, and operation by oncologic surgeon at another hospital (5 months following the previous operation) disclosed multiple peritoneal nodules (of 0.2 cm to 1.2 cm) of the same tumor (which were also CK+, calretinin+). Thus, the widespread peritoneal dissemination is consistent with diffuse peritoneal mesothelioma.

**Gerald Berry:** Carcinoma; NOS!

**Michele Bisceglia:** Sorry, Saul. I cannot help. I do not know what this case is. Look forward to hearing others' opinions and seeing if they disregard or do not disregard the positivity you mentioned of mesothelial markers. Once I heard of a true localized mesothelioma.

**Ira Bleiweiss:** ???? but cytologically the cells remind me of granulosa cell tumor. The pattern and immuno are against this, though.

**John Chan:** I am not sure what this tumor is. The cytologic features (including the sharp cell borders) and the close association with amorphous hyaline stroma do suggest mesothelial differentiation, which apparently is further supported by the immunostains (cytokeratin, D2-40, mesothelin, calretinin, CA125 and WT1). But then with the circumscription, unusual growth pattern and practically absence of mitotic figures, I am somewhat reluctant to label this as a malignant mesothelioma. Perhaps "mesothelioma of uncertain malignant potential", for the time being?

**Thomas Colby:** ? localized mesothelioma or peculiar adenomatoid tumor. It's surprising it was not noted at the time of TAH/BSO, but perhaps that had been transvaginal surgery in a lesion like this could have been missed. I don't know about some of the positive immunostains and whether they would be against mesothelial differentiation. I'm not sure that I've seen a mesothelioma that looks like this. If this were in the chest, I agree that thymoma would need to be considered.

**Kum Cooper:** Sorry, Saul, I do not have any better solutions. I too like ectopic hamartomatous thymoma!

**Ivan Damjanov:** On the basis of nuclear morphology, I initially thought that this is a granulosa cell tumor, but with all the immunohistochemistry I think that this is most likely a localized mesothelioma or mixed mullerian tumor of peritoneal origin.

**Otto Dietze:** Sorry, no really good ideas, I hope that the follow-up can help us.

**Hugo Dominguez-Malogon:** Difficult case, at the beginning I thought of a granulosa cell tumor but the immunos are not compatible; perhaps mesothelioma???

**Göran Elmberger:** I do not know. Anastomosing trabecular growth. Epithelioid cells with coffee bean nuclei. Peculiar vascularity in stroma. IHC does not exclude mesothelial tumor. Benign localized mesothelioma? Unusual adenomatoid tumor?? S100?? GIST?? GANT?? Ectopic meningioma??? Transitional cell metaplasia of Müllerian epithelium???

**Giovanni Falconieri**: Difficult case, Saul. I feel as frustrated as you. The only thing that comes to my mind is something close to granulosa cell tumor of the ovary given the cord/trabecular arrangement of tumor cells and the striking indentation of their nuclei. I would certainly try to obtain more clinical information and further insight from the total hysterectomy specimen as to be sure that anything has not been overlooked or left behind at the time of gross dissection of the ovaries. Granulosa cell tumors may display a variety of gross appearance, including cysts and cavitation.

**Christopher Fletcher:** The nuclear grooves, sharply defined cell borders and syncytial growth pattern are very striking but, at least to me, not distinctive in this context. One might wonder about the possibility of an unusual metastasis. In truth, I have no useful idea for this case.

**Andrew Folpe:** The morphology and the immunophenotype seem to me to point towards a mesothelial tumor. I would probably call this a localized mesothelioma, commenting that the prognosis might be relatively favorable, given the growth pattern and low-grade cytology.

**Jerónimo Forteza Vila:** We think that a good alternative is a histiocytic cell tumor. We propose doing a CD1a stain and even an ultrastructural study looking for Birbeck's granules.

**Masaharu Fukunaga:** It is a very interesting case, and looks like an extrapancreatic solid cystic tumor.

**Allen Gown:** Good lord, the histology and immunophenotype do not compute to a diagnosis! Did you look for expression of GI tract related proteins (CDX-2, villin)?

**Thomas Krausz:** I agree it looks strange/diagnostically challenging. I started with granulosa cell tumor, however, it is not exactly right and the immuno-result is somewhat against this diagnosis. I would repeat the inhibin. I would also consider a diagnosis of localized variant of malignant mesothelioma, low nuclear grade. I am looking forward to seeing Tom Colby's comment whether any of the localized malignant mesotheliomas in their series showed resemblance to the submitted case. I have observed nuclear grooves in some peritoneal mesotheliomas before.

**Janez Lamovec:** With all these immuno results it's difficult to accommodate this tumor into any sound category. It is probably not a mesothelioma (some people here thought of it), it is not any kind of sex cord-stromal ovarian tumor (one rarely see such clear and numerous nuclear grooves but immuno is against the idea). I don't know. It appears to be a low grade neoplasm.

**Thomas Mentzel:** Given the reported clinicopathological and immunohistochemical findings, I was also thinking on an unusual (benign looking) peritoneal mesothelioma.

**Michal Michal:** Beautiful case. I would still stay with the diagnosis of a weird "solid variant" of papillary mesothelioma. Many of these have cytology having cleaved nuclear morphology similar to granulosa cell tumors of the ovary (compare it

with the cytology of case 10 of Thomas Krausz). Immunoprofile is typical for mesothelial lesion. Slides for this case were forwarded to Dr. Ondrej Ondic, and the following are his comments: "Based on H&E, I suppose one can see it as Brenner tumor. I am not sure if immuno does strongly militate against this diagnosis. A revision of ovarian tumor would be of help. If positive, we could consider serosal colonic mass as being a metastasis/implant of ovarian primary Brenner tumor. In any case, I would be really grateful for a note when this case will be signed the final diagnosis".

**Markku Miettinen:** Agreeing with your consideration would diagnose it as localized mesothelioma, provided this is indeed localized. Solid makeup and mitotic activity make it one notch up from case 10 in this seminar, thus would consider it (at least) low-grade malignant. Marker profile seems to be in agreement with this. Central lack of WT1 may reflect loss of antigen/antigen recovery in less rapidly fixed central portions of the tumor.

**Liz Montgomery:** Egads. Has peculiar meningothelial look and, of course, the nuclear grooves bring various gynecologic lesions to mind. I suspect it will behave indolently but hope it is all out.

**Juan Rosai:** Bizarre case indeed. I was very impressed by the numerous longitudinal grooves in the nuclei of the tumor cells, which made me think of granulosa cell tumor and proliferating Brenner tumor, but neither the topography nor the immunohistochemical profile fit. Like Saul, I have never seen a mesothelioma looking like this, yet I wonder whether it could be one. The location is OK, there exists a localized form, and the immunoprofile is not bad (positivity for CK 5/6, mesothelin, calretinin and WT-1). Furthermore, mesothelial cells can make very good nuclear grooves (as I have seen in cases of MICE).

**Dominic Spagnolo:** I'm afraid I can't do any better. On the blind, I had exactly the same thought that it looked thymic, and even meningeal crossed my thinking. But I haven't a clue. It doesn't look like any mesothelioma I've ever seen, but I can't think of an alternative.

**James Strauchen:** No idea! The grooved nuclei are reminiscent of a granulosa cell tumor; however, the immuno seems to point toward a mesothelial origin. I have never seen a mesothelioma with this appearance.

**Saul Suster:** This is my case (actually Ofer Ben-Itzhak's case, who shared it with me and out of frustration I decided to submit it to the Club). I appreciate all the comments and agree with the majority opinion that the most sensible diagnosis for this case would be that of an unusual morphologic variant of localized malignant mesothelioma. However, this would be a diagnosis by default, in my opinion. The presence of multiple additional peritoneal nodules certainly speaks in favor of a more aggressive, non-localized process, but certainly does not guarantee a diagnosis of malignant mesothelioma because GIST and ovarian and other tumors can grow in the same fashion. What I would have found most convincing here would have been a good ultrastructural study. Since the tumor appears to be very low-grade (and presumably well-differentiated), I would have expected to find good microvilli lining the cell surfaces. Making a diagnosis based solely on results of immunohistochemical stains has always made me quite nervous, particularly when the morphologic features don't fit. If additional surgery is performed on this tumor, it would be great to obtain some tissue for electron microscopy – it might contain the clue to a definitive diagnosis in this case (could be confirmatory of mesothelioma!).

**Lawrence Weiss:** Looks like it could be mesothelial to me, so - malignant mesothelioma.

**QUIZ CASE NO. 1 – CONTRIBUTED BY SAUL SUSTER:**
(Case contributed by Dr. Vladimir Osipov, Medical College of Wisconsin).

**Phil Allen:** To me, this looks like fibrosarcomatous transformation of dermatofibrosarcoma protuberans with metaplastic bone. I can find no published accounts of bone in dermatofibrosarcoma protuberans but that does not put me off the diagnosis. After all, giant cell fibroblastoma cells in dermatofibrosarcoma protuberans were missed for about 70 years. I did find one account of osteoclast-like giant cells in dermatofibrosarcoma protuberans. (Aspiration cytology of fibrosarcomatous variant of dermatofibrosarcoma protuberans with osteoclastlike giant cells in the chest wall: a case report. Acta Cytol (United States), Nov-Dec 2005, 49(6) p644-9. Kim L; Park IS; Han JY; Kim JM; Chu YC). Cytogenetics or molecular studies might be of diagnostic assistance. This is a large tumour (5 cm) so surgical excision with adequate margins would leave a huge defect. I note that imatinib is now approved for treatment of dermatofibrosarcoma protuberans in the United States.

**Carlos Bacchi:** DFSP with fibrosarcomatous transformation and metaplastic bone.

**Gerald Berry:** I think this best fits into DFSP with transformation to fibrosarcoma with metaplastic bone.

**Michele Bisceglia:** Fibrosarcomatous transformation of DFSP with metaplastic bone (or focal "osseous differentiation") to extraskeletal osteosarcoma. I think this case was initially a DFSP and that now it has a fibrosarcomatous and osteosarcomatous component. Putting everything together I would call it fibroblastic osteosarcomatous transformation of DFSP (or, DFSP with high grade sarcomatous transformation –fibrosarcoma and osteosarcoma, which in this context would be the same thing). Probably this event has never previously been described. I do not think this case arose as fibrosarcomatous extraskeletal osteosarcoma (with DFSP features).

**Ira Bleiweiss:** Extraskeletal osteosarcoma.

**Thomas Colby:** DFSP/Fibrosarcoma with central degenerative fibrinous change and (probably metaplastic) bone.

**Kum Cooper:** Fibrosarcomatous DFSP with osseous metaplasia.

**Otto Dietze:** I favor osteoid metaplasia in a fibrosarcomatous transformed DFSP.

**Hugo Dominguez-Malogon:** I would favor dedifferentiated DFSP with fibrosarcomatous and osteosarcomatous areas.

**Göran Elmberger:** I would prefer the diagnosis of fibrosarcomatous transformation of DFSP with metaplastic ossification. I would base this decision on location and the fact that larger parts of the tumor show a classical DFSP look. The positivity of CD34 reinforces my impression. The alternative of extra skeletal osteosarcoma seems less likely but I gladly admit I am an amateur with soft tissue.

**Giovanni Falconieri:** I feel comfortable with fibrosarcoma ex-DFSP.

**Christopher Fletcher:** Given the organoid appearance of this lesion (even in the component infiltrating fat, there is a rather whorled architecture and in the fascicular areas, there is alternating hyper- and hypo-cellularity), then I would suspect that this might in fact represent MPNST with heterologous osteosarcomatous differentiation (in which context the osteosarcomatous component has no known prognostic relevance). The appearances of the component infiltrating adipose tissue do not look quite right for DFSP to me.

**Andrew Folpe:** DFSP with sarcomatous change, showing in part osteosarcomatous differentiation. I would expect this to behave like a typical fibrosarcomatous DFSP.

**Jerónimo Forteza Vila:** We agree with the alternative of a malignant transformation of a DFSP.

**Masaharu Fukunaga:** Soft tissue well-differentiated osteosarcoma.

**Janez Lamovec:** I would rather think of extraosseous fibroblastic osteosarcoma in DFSP. Tumor cells form woven bone, focally filigree pattern of its deposition is seen; so I don't think that this is a simple metaplastic bone. On the other hand, I don't understand why the treatment should be more aggressive whatever you call this tumor, since generally grade is probably more important than type of sarcoma in such setting.

**Thomas Mentzel:** For me, the lesion looks like fibrosarcomatous DFSP with ossification.

**Elizabeth Montgomery:** To me - DFSP with fibrosarcomatous transformation and zones of osseous matrix formation rather than extraskeletal osteosarcoma.

**Markku Miettinen:** Combination of fibrosarcoma and extraskeletal osteosarcoma. Seems to be intermediate to high grade per French criteria (mitotic count close to 20/ 10 HPFs, some necrosis in the osseous component). Cannot be sure of treatment, but high-grade protocol should be considered depending on circumstances. Cannot rule out relationship with/derivation from DFSP (? skin connection, history, COLIA-PDGF fusion/rearrangement studies?). The overlying limited amount of skin showed no evidence for DFSP. However, even some subcutaneous fibrosarcomas might be DFSP-derived. Also, MPNSTs could have this morphology, including heterologous differentiation.

**Juan Rosai:** I would interpret this case as a dermatofibrosarcoma protuberans that has gone bad (tumor progression, dedifferentiation), the high-grade foci looking like fibrosarcoma and extraskeletal osteosarcoma.

**Dominic Spagnolo:** This should not be regarded as an extra-osseous osteosarcoma in my opinion. I would regard it as a DFSP with low grade fibrosarcomatous transformation, with osseous metaplasia occurring within the fibrosarcomatous element, as may occur in primary fibrosarcomas uncommonly; complete resection should be the aim here.

**James Strauchen:** DFSP with fibrosarcomatous transformation and osseous metaplasia.

**Saul Suster:** The reason why I submitted this case was not only for the rarity of the bony component but also because this case posed unique problems for patient management. An outside consultant who saw the case made a diagnosis of extraskeletal osteosarcoma. A radical amputation was contemplated as befits an osteosarcoma. A more conservative approach, however, was recommended by us. The million-dollar question here is whether this tumor is going to behave as an extraskeletal osteosarcoma or a DFSP with fibrosarcomatous transformation. Although they are both high grade tumors, the implications of a diagnosis of extraskeletal osteosarcoma are obviously direr. Another consideration was, if the bony component represents osteosarcomatous transformation, shouldn't the histology of the bony component be taken into account for grading. The bony component in this tumor more closely resembles a well-differentiated parosteal osteosarcoma than a conventional high-grade extraskeletal osteosarcoma. Would it not be logical to assume then that an

extraskeletal “parosteal-type” osteosarcoma would behave in a more indolent fashion than a full-blown high-grade osteosarcoma? In either case, I suppose these are questions that only the long-term follow-up will be able to clarify in this case. In the meanwhile, I took solace from seeing the wide range of opinions of the members of the club regarding the interpretation of this tumor, which ranged from DFSP to high-grade extraskeletal osteosarcoma (and even MPNST!), although the majority of the opinions do seem to lean in favor of a DFSP with fibrosarcomatous transformation and osseous metaplasia (17) rather than an extraskeletal osteosarcoma (5).

**Lawrence Weiss:** DFSP with fibrosarcomatous and osteosarcomatous transformation.

# FOLLOW-UP COMMENTS TO AMR SEMINAR #51

**CASE NO. 17 – CONTRIBUTED BY PAUL WAKELY, M.D.**

**Contributed by**: Paul E. Wakely, Jr., M.D.
In the last paragraph of my comments, I mentioned that I was not completely convinced that the atypical stromal cells in this esophageal polyp represented lipoblasts. Many club members who were more perceptive than I, however, were convinced that these were lipoblasts, and suggested additional testing. Therefore, I want to publicly acknowledge the help of Thomas Krausz whose lab performed the mdm2 and cdk4 immunostaining of this specimen for me, and demonstrated that indeed many of these large hyperchromatic cells stain positively with both antibodies. I also sent slides to Dr. Julia Bridge (U. of Nebraska) whose lab demonstrated positive amplification of mdm2 gene region at 12q15 in 64% of interphase cells using FISH methodology with the LSI MDM2 DNA probe. Thus, the correct interpretation of this case is well-differentiated liposarcoma with rhabdomyomatous differentiation arising in a giant fibrovascular polyp of the esophagus. I want to express my gratitude to all members for their instructive comments and guidance on this case.