COMMENTS TO AMR SEMINAR #64

CASE NO. 1 – CONTRIBUTED BY VOLKAN ADSAY, M.D.:

Phil Allen - The answer has not been included in the circulated information. It looks like colonic dysmotility caused by patchy atrophy and fibrosis of the muscularis propria in a patient with rheumatoid arthritis/systemic lupus erythematosus. I have just read in Odze's textbook that this kind of dysmotility may be associated with disseminated lupus as well as with scleroderma.

David Ben-Dor - I'm looking at this without having the handout available (it didn't download). But without any further information it looks normal. I'm anxiously awaiting the punch line for this. But one thing I can say at this point- the histology is beautiful. I usually don't get such good preservation of colonic mucosa except in small biopsies. I assume this reflects your adherence to proper practices: open the specimen as soon as possible, fixation while pinned to a board, and all the other good things you're supposed to do which I don't.

Michele Bisceglia - This case should be intended as a "Quiz case". The clinical history along with the absence of any apparent mechanical cause of intestinal obstruction induces one to think of intestinal pseudoobstruction. On the other hand chronic intestinal pseudo-obstruction can also be an accompanying manifestation of both SLE and RA. However in case of involvement of the intestine in these connective tissue diseases one should see vasculitis or inflammation or fibrosis or degeneration of smooth muscle cells of the muscularis propria at histology, all of these being absent in this case. However in my view one can suspect herein a scarcity of the submucosal and myenteric ganglion cells and plexuses, and maybe this can be the effect of an autoimmune attack against these autonomic nervous structures, or maybe the inflammation burned out or it is in the relevant autonomic ganglia, outside the intestinal walls. Maybe this is also imagination. Also of interest would be to investigate the distribution of the interstitial cells of Cajal as a possible cause of the intestinal problem in this case. Finally, the gallstones which were found in this patient could also be the effect of the same disease affecting the colon, due to biliary dysmotility. Do not exclude I "missed the boat" in regard to this case, and that the diagnosis is completely different. In conclusion, Volkan. I look forward to hearing from you.

Ira Bleiweiss - Hmm. No clue

Thomas Colby - Visceral myopathy consistent with that associated with connective tissue disease (albeit usually scleroderma).

Kumarasen Cooper - Selective hollow visceral outer muscularis propria myopathy. ?autoimmune ganglioneuropathy ? mitochondrial myopathy (MNGIE) (American Journal of Pathology, Vol. 173, No. 4, October 2008)

Otto Dietze - Disturbance of collagen deposition in vascular rheumatic disease.

Hugo Dominguez-Malagon - I see prominent myenteric plexuses with inflammatory cells in the neighborhood, the mucosa is unremarkable.

Göran Elmberger - Quiz case? Atrophy muscularis propria, ganglionitis and neuronal vacuolization noted. Idiopathic ganglionitis? Autoimmune associated ganglionitis (SLE; RA)? (GE)

Vincenzo Eusebi - I would go for a visceral myopathy. This is for the lack of inflammatory changes; vacuolization of myoenteric plexus; atrophy of the external circular stratus.

Giovanni Falconieri - Is that supposed to be the quiz case? I must admit that without clinical history I would just sign it out as "unremarkable", and passed to the next slide in the tray. With the hindsight of history I might notice some depauperation of ganglion cells where they are supposed to be seen (?Hirschsprung) yet I am sure I am missing the point.

Franco Fedeli - No diagnosis given by Volkan. I personally think this is a case of chronic intestinal dysmotility, probably due to intestinal neuropathic damage for some reason, either related or unrelated to the two systemic connective tissue diseases which the patient was affected with and/or the relevant therapies she was given.

Christopher D.M. Fletcher - Other than some rather hypoplastic-looking bowel, I have difficulty in seeing any definite abnormality in this section and obviously am missing something – perhaps something informative in the history that has been withheld? I look forward to being educated.

Andrew Folpe - Segment of small bowel with apparent loss of the longitudinal layer. I have no idea!!!

Jerónimo Forteza - Naturally, an alteration at level of Auerbach's plexus is a possibility. However, we cannot determine it just by H&E. We can see ballonization in the cytoplasm of neural cells as can be observed in illnesses such as Tay-Sachs. In any case, this is just a speculative comment.

Masaharu Fukunaga - The muscularis propria is very thin and atrophic. There is no inflammation.

Thomas Krausz - The outer layer of the muscularis propria lost most of the muscle fibers and "converted" to a fibrotic band. Rare ganglion cells in the myenteric plexus appear degenerated. No vasculitis.

Janez Lamovec - Sclerosis and atrophy of outer layer of muscularis propria – ?visceral myopathy, ?systemic sclerosis.

Markku Miettinen - Difficult case. External muscle layer looks atrophic and possibly surrounded by a fibrous zone. Considered drug-induced pathology (steroids?).

Juan Rosai - Part of the paperwork on this case seems to be missing. There is a clinical history but not discussion or diagnostic impressions by the contributor. I must confess that I was not too impressed with the morphologic changes in this specimen from the bowel. The only alteration I saw was a meager mononuclear infiltrate along the Auerbach plexus. I suspect this is secondary to this patient's immune-mediated disease, most specifically to the vasculitis that often accompanies this group of conditions. In any event, I would appreciate receiving a copy of Volkan's impressions on the case.

Brian Rubin – I thought the myenteric plexus looked normal. I shared the case with one of the GI pathologists in our group and we both thought the outer longitudinal layer looked atrophic but that was all we really saw. The best we could do was a chronic intestinal pseudo-obstruction (visceral myopathy) secondary to RA or lupus.

Dominic Spagnolo - Sounds like some form of intestinal pseudo-obstruction, with attenuated muscularis propria and extensive fibrosis of the outer muscularis. ?secondary to underlying autoimmune conditions, or ?primary. But way outside my comfort zone.

James A. Strauchen - Colonic muscularis atrophy ? autoimmune.

Ady Yosepovich - the muscularis propria is atrophic, apart from that did not see anything abnormal. Ganglion cells are normal – could this be due to denervation? Drug effect?

CASE NO. 2 – CONTRUIBUTED BY CARLOS BACCHI, M.D.:

Volkan Adsay - Very nice example.

Abbas Agaimy - Very impressive case! Never knew about its existence but being taught by your wonderful case, I was able to diagnose my own case just a few weeks later. I have seen in our new case that the population of cells strongly expressing ALK are not all positive for CD30 and the tumor looked just like featuring two cell populations. The H&E impression is that of classical HL. Thank you for teaching me.

Phil Allen - ALK and CD30 positive anaplastic large cell lymphoma mimicking nodular sclerosing Hodgkin's lymphoma with null phenotype. Even in the H&E, this looks more malignant than the usual nodular sclerosing Hodgkin's disease. Thanks for the contribution. Despite this helpful lesson, I will continue to slough off lymphomas to someone else.

David Ben-Dor - It's cases like this which make me wonder whether as a general pathologist with a limited availability of immunohistochemistry I should be signing out any lymphomas, even those which look obvious (as this one would) and straightforward. The suggestion of using EMA is a good one (though it doesn't rule out NLPHD); how about CD43?- I assume that the latter would be negative in Hodgkin's cells.

Michele Bisceglia - ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin lymphoma with null phenotype. Indeed this case mimics NSHD histologically (as well as clinically, speaking of a cervical lymph node in a young girl). Do not recall having seen a similar case in the past, and if I did, I missed it. Thank you, Carlos, for sharing this case.

Thomas Colby - Agree with diagnosis. A good mimic of Hodgkin lymphoma but not quite right.

Kumarasen Cooper - Thank you Carlos. Beautiful differential of NSHD vs ALCL. I wonder how many of these were previously called "syncytial variant" of NSHD? In the very old days NSHD was subtyped as Type I and II (Histopathology). Yes, both lacunar cells and horseshoe/donut cells are present confounding the distinction and IHC is mandatory. But as you astutely point out that the sinus involvement is characteristic of ALCL. I have also seen nodular LPHD evolve into ALCL sequentially (in Africa of course).

Otto Dietze - ALK Lymphoma. The blast –rich proliferation in the H&E slide are suspicious for this diagnosis.

Hugo Dominguez-Malagon - Agree with the diagnosis, anaplastic lymphoma resembling NSHL, there are hallmark cells, mummified cells and lacunar cells, the inflammatory infiltrate resembles HL.

Göran Elmberger - Thanks for showing this beautiful case and bringing up the ddx of HD nodular sclerosis type. Guess we all need to include ALK in the panel. From a general pathologist's perspective also metastatic carcinoma and melanoma needs to be considered in the broad differential diagnosis. ALK translocations are not exclusive to NHL's. Had a great experience with those together with John Wing Chan in Nebraska 1994 optimizing a RT-PCR nested assay during a visiting professorship – my first experience of molecular pathology. Thanks John and Carlos... (GE)

Vincenzo Eusebi - Difficult case to diagnose. Probably I would have missed it.

Giovanni Falconieri - Quite a case Carlos. HD was on the top of my differential. Very difficult even with the aid of an extended IHC panel. Thanks for sharing with us this challenging case and congratulations for your excellent hemepath skill. Thank you also for coming to Italy in October and my utmost appreciation again to Franco Fedeli for inviting you. We have all great memories of your sharp eyes at the Bologna grand round.

Franco Fedeli - ALK-positive anaplastic large cell lymphoma mimicking nodular sclerosis Hodgkin lymphoma with null phenotype. Nice case, Carlos. Nice description and nice discussion. Agree. I assume EMA was also positive in this case. It is very interesting to study gene expression profiling of ALCL: cellular origin, pathogenesis and relation to HL (Eckerle s et al. Leukemia 2009 Nov;23;(11):2129-38)

Christopher D.M. Fletcher - The cytology of the large atypical cells would certainly seem to fit better with ALCL than with Hodgkin lymphoma – this is a very pretty case.

Andrew Folpe - NS Hodgkin lymphoma vs ALCL. I'd need stains, and to show to an actual hematopathologist.

Jerónimo Forteza - I agree with the diagnosis. Immunohistochemistry plays a key role in differential diagnosis; however, diagnosis can be reached via H&E (hallmark cells). Notabily, some ALK+ Hodgkin-like anaplastic large cell lymphomas can mimic the nodular sclerosis form of classical Hodgkin lymphoma.

Masaharu Fukunaga - A wonderful educational case. Thank you very much for sharing it.

Thomas Krausz - I agree, there is morphologic overlap with Hodgkin's disease. Without the sheets of large, rather monotonous neoplastic cells, I would have fallen into the trap. This is diagnostically quite a challenging case.

Janez Lamovec - Very tricky case. I thought it was nodular sclerosis

Markku Miettinen - Totally agreeable as an anaplastic large cell lymphoma based on reported results. Histologically only as a large cell lymphoma.

Thomas Mentzel - Many thanks for the nice case and the interesting discussion!

Fredrik Petersson - Low-power NS, Hodgkin-like, but as pointed out cytological features and growth pattern; sinusoidal/sheet-like, made me abandon that alternative (in favour of ALCL or metastatic melanoma – perhaps also malignant LCH/Langerhans cell sarcoma or even histiocytic sarcoma) could be contemplated on H&E. Convincing IHC.

Juan Rosai - I enjoyed looking at this case and reading the erudite discussion by Dr. Bacchi. I am not at all surprised that some observers (including yours truly) initially thought this was Hodgkin's lymphoma. As a matter of fact, one could have a lengthy discussion as to whether this case should still be considered a form of Hodgkin disease based on the morphology, although I know most would consider that sacrilegious. Yet, it seems to me that there is too much splitting going on in the hematolymphoid field. In any event, I am sure that Funes would have gone along with the contributor's interpretation, but that Borges would have not (see Jorge Luis Borges: Funes the memorious).

Brian Rubin – Cool case.

Dominic Spagnolo - Spectacular case of NS Hodgkin-like ALCL. The cytological features are a good tip-off.

James A. Strauchen - ALCL mimicking NSHD. Hallmark cells more easily found than classic RS cells typical of ALCL.

Saul Suster – pretty spectacular case. In the absence of ALK positivity I would have also considered first a Hodgkin lymphoma!

Ady Yosepovich - very nice case – actually as I understand it one cannot make a diagnosis of Hodgkin's without immunos?

CASE NO. 3 – CONTRIBUTED BY DAVID BEN-DOR, M.D.:

Volkan Adsay - Very nice case. Allowed us to have a nice discussion with our residents about how it is very unusual for germ-cell tumors to divert from midline, but at the same time, the importance of reviewing tumor cases as "unknown" because unusual things happen (Man from Istanbul phenomenon, as discussed).

Abbas Agaimy - very tricky case and a true pitfall if one doesn't think of it. Thanks.

Phil Allen - After seeing the previous case, I also made a diagnosis of lymphoma. Thanks for the discussion. The presumed disruption of normal lymphatic communications caused by the orchiopexy must be the explanation for the contralateral inguinal node metastasis.

Michele Bisceglia - Thank you, David. Nice case. Agree on everything you said. I was particularly interested in your literature search concerning with lymphatic spread of seminoma to inguinal lymph nodes (both ipsilateral and contralateral). Indeed when something strange occurs in the behaviour of a tumor we usually quote the motto "*tumors do not read books*" and this is correct. However I personally think that the tumor in your case is an exception to the rule, which escapes the quoted motto. In my view, when educated people look at a primary or metastatic tumor in an inguinal lymph node they do not think of seminoma (unless on follow-up, when you are told the patient had seminoma). In humans, lymphatic efferents from testes do not have any connection with lymphatics draining to either ipsilateral or contralateral inguinal nodes. These (functional or anatomical) abnormal connections are always secondary to either surgery in the genital area or to obstruction of the normal testicular lymphatic outflow routes. So – like you - I also do not understand the "anatomic logic" based on which some authors think seminoma can (occasionally) spread to inguinal node "via the spermatic cord". The lymphatics of the spermatic cord, including those from testes which are contained in the spermatic cord itself, go to para-aortic (and preaortic) lymph nodes always (this is said based on all the available major standard textbooks of normal systematic and topographic human anatomy).

Ira Bleiweiss - Seminoma vs malignant lymphoma (except for the normal background lymphocytes).

Thomas Colby - Agree with diagnosis. Seminoma is usually easy because of the location/presentation but when those are unusual, it can be much more difficult. We just recently had a seminoma present as a periduodenal mass and we did not make the correct diagnosis until resection (and fortunately resection was the treatment of choice for that variant of metastatic seminoma).

Kumarasen Cooper - David, thank you for the educational instruction and great write-up. This reminds me of a case I saw in Vermont in a 40 yr. old year man who presented with a cervical lymph node (was the husband of a medical secretary). I too followed the lymphoma, carcinoma, melanoma, histiocytic route. The cells in my case were much more smaller, uniform and discohesive. The penny only dropped after 28 IHC with OCT3/4 positivity. The testis, removed a week later, looked like classical seminoma and the lymph node metastasis was clearly suboptimal fixation/processing.

Otto Dietze - I have never seen a similar case of inguinal spread of seminoma.

Hugo Dominguez-Malagon - Agree with seminoma. Round cell tumor with clear cytoplasm, vesicular nuclei and spiky nucleoli, besides granulomata are seen.

Göran Elmberger - Never trust a clinician when it gets to case information!! In these cases of BFUM tumors I always follow the good advice to start out broad – historically - with a panel including CK, S100, CD45 and Vimentin. Seeing cases like this and a recent case I had with a liver metastasis of an extracranial dedifferentiated ependymoma maybe would argue for a slightly wider approach including Sall4 as germ cell marker and GFAP… Amazing to me that someone can work up cases like this based on HE alone like obviously John Chan.

Vincenzo Eusebi - Seminoma. Thank you for the interesting and helpful discussion on this difficult case.

Giovanni Falconieri - Terrific case, David. Another lesson from the "man of Istanbul", no question about that. I came across a comparable case many years ago. The patient had a lump in the supraclavicular soft tissue and the clinician forced us into a diagnosis of lymphoma since there was no other evidence of disease elsewhere. Yet the overall microscopic and IHC were in overt conflict with any lymphoma we were aware of. At that time we could not take advantage of the OCT4 and SALL4 nowadays available, and the PLAP worked a little bit lousily. We were not trusted by our colleagues hence we also sent the case in consultation to John Chan who confirmed that this case was seminoma. And guess what? A 2 cm lump in the testis was later found! A further challenge in your case is the quite

unique clinical background. Thank you again. As a corollary to the Istanbul story, an old saying from Saul regarding our fellow physicians whom we are referring to: "Trust! But verify …. "

Franco Fedeli - Interesting case, David, and what a detailed report you made of an unusual presentation of a common tumor! I saw a case of dysgerminoma presenting in a lymph-node only with a granulomatous reaction.

Cyril Fisher - Seminoma in unexpected location. We sometimes see retroperitoneal primary seminomas that cause difficulty if the diagnosis is not thought of.

Christopher D.M. Fletcher - The histology certainly fits well for a germ cell tumor and, as John Chan pointed out, the large rounded nuclei would also fit well with the final diagnosis. An educational case.

Andrew Folpe - Anaplastic malignant neoplasm in lymph node. Would have to work up.

Jerónimo Forteza - Nuclei morphology and the lack of cell modulation did not make me think of a lymphoma as first diagnosis but of a metastatic disease. The case is very well demonstrated with the immunhistochemichal study.

Masaharu Fukunaga - Thank you for the interesting case and description in detail. My first impression was lymphoma.

Ondrej Hes - As lymphoma ignorant, my first suggestion was metastasis of germ cell tumor (being mostly GU pathologist). Was there any OCT3/4 positivity? I found this marker more sensitive for seminoma, than SALL4, which is, in my opinion, more useful for the detection of yolk sac tumor. Very nice case, thank you for submitting it.

Thomas Krausz - Without previous history of testicular tumor I agree, metastatic seminoma can be a diagnostic challenge in various anatomic locations. I remember cases where on needle core biopsies of retroperitoneal mass only a few viable neoplastic cells of seminoma were present in an inflammatory/necrotic background. The referring pathologist in most of these instances worried about lymphoma.

Thomas Mentzel - What a case! I would never think of this diagnosis in these circumstances – many thanks indeed.

Markku Miettinen - Looks good for seminoma.

Fredrik Petersson - Also my direct first impression was hemato-lymphoid. I had metastatic melanoma in the back of my mind, but not - given the location - seminoma. Seeing the slides again; cells very well compatible with seminoma. Re-arrangement of the lymph drainage post surgery – very educational. Missed that. Bitten by the Istanbul man (again).

Juan Rosai - Great case. I think one of the important clues is the appearance of the nucleoli (very large, basophilic, with markedly irregular edges and dispersed). This is a seminoma all right, although I suspect that people who believe in the entity of anaplastic seminoma (I did once, and I still do a little bit) would have placed this tumor in that category.

Brian Rubin – Interesting. Thanks for a fantastic discussion. I did not realize that surgical manipulation could alter the pattern of metastasis but it makes sense. Thanks also for sharing John Chan's comments about the granulomas in seminoma – nice diagnostic pearl.

Dominic Spagnolo - Very tricky clinical scenario for a metastatic seminoma – one to remember.

James A. Strauchen - Seminoma mimicking lymphoma. Zones of lymphocytes and histiocytes typical of seminoma.

Saul Suster – Very nice case of metastatic seminoma to an unusual location! The irregular, "spiked" nucleoli (betraying the presence of nucleolonemmata) are a helpful clue for diagnosis. Easy to misdiagnose this for something else!

Ady Yosepovich - David – thank you for this teaching case and for the beautiful presentation. The head of surgery must be instructed to perform a physical examination on his patients before operating them….

CASE NO. 4 – CONTRIBUTED BY GERALD BERRY, M.D.:

Volkan Adsay - Great case.

Abbas Agaimy - Pretty case, never seen this before. Thanks.

Phil Allen - Congenital peribronchial myofibroblastic tumor (3.5 cm), right middle lobe, male aged nine weeks. These cases are getting too hard for me. Thanks for the contribution and the diagnosis.

David Ben-Dor - Thanks. Patients such as this aren't operated on at my hospital so this is the only opportunity we have of seeing cases such as this.

Michele Bisceglia - Congenital peribronchial myofibroblastic tumor. This is the first case I see, thank you very much for sharing it with us. Although somewhat different morphologically, by instinct one can make an analogy with some other congenital tumors of other parts of the body such as congenital mesoblastic nephroma (cellular variant) and congenital infantile fibrosarcoma. Did anyone perform any genetic studies on this tumor, investigating trisomy 11 and t(12;15) (p13;q25), the translocation associated with ETV6-NTRK3 gene fusion?

Ira Bleiweiss - New one for me.

Thomas Colby - Agree with diagnosis. Spectacular case. I think this is only the second one of these that I have seen and I am supposed to know something about lung disease.

Kumarasen Cooper - Thanks Gerry. It reminded me of cellular mesoblastic nephroma. Could this be part of the infantile fibrosarcomas? FISH for the ETV6 break-apart probe would resolve that? t(12;15) ETV6-NTRK3.

Otto Dietze - My first impression was (for me) an unknown type of pulmonary blastoma, however I am convinced of the diagnosis and have not seen anything similar before.

Hugo Dominguez-Malagon - Very illustrative case of congenital peribronchial myofibroblastic tumor, this is the first case I see.

Göran Elmberger - Thanks for great case. Never got to see one of those before even after 20 years as pulmonary pathologist at Karolinska. Maybe our pediatric pathologist got one.

Vincenzo Eusebi - Difficult case. This to me seems to be an embryonal stromal neoplasm. I do not have a better name.

Giovanni Falconieri - Impossible case, Dr. Berry. Thank you. I have found this very educative. An extraordinary piece of collectible item.

Franco Fedeli - Congenital peribronchial myofibroblastic tumor. Never seen such a case before. From the tumor name and some relevant synonyms you cited, and from the fact it is "cured by complete surgical excision" only, I understand that, despite the morphology, this tumor has a low grade clinical behaviour.

Cyril Fisher - Congenital peribronchial myofibroblastic tumor. I was not familiar with this entity. Great slide, many thanks.

Christopher D.M. Fletcher - I am very glad to have had an opportunity to see an example of this rare 'entity', the nomenclature of which has been confusing. Taking into account the prominent stromal vessels, many of which are branching, one might wonder if these lesions belong within the spectrum of myopericytoma/myofibroma, particularly given the young age group involved.

Andrew Folpe - Fascinating case. Thank you for the nice write-up.

Jerónimo Forteza - It is very beautiful case. The broad irregular plates of mature cartilage, which were associated with airways, makes me think in the differential diagnosis of pleuropulmonary blastoma, solid type III or a hamartoma. Bronchopulmonary fibrosarcoma needs to be ruled out.

Masaharu Fukunaga - I have never seen congenital peribronchial myofibroblastic tumor (CPMT). It might be a hamartomatous lesion.

Thomas Krausz - Never seen this tumor type before. Highly educational case.

Janez Lamovec - The tumor appears quite uniform in composition; the cells are not so spindly that one would expect to see in myofibroblastic tumor; immuno results are not helpful. However, we have very little experience with congenital tumors.

Thomas Mentzel - Given the presence of rather immature plump spindled tumor cells with enlarged nuclei and a small rim of cytoplasm, the presence of mitoses and the growth of tumour cells around pre-existing structures, I found the case very difficult. What's the prognosis of these lesions?

Michal Michal - I cannot comment on the diagnosis, but I would not call this case as a myofibroblastic tumor.

Markku Miettinen - Previously unaware of this entity; would also have considered pleuropulmonary blastoma variant.

Fredrik Petersson - Never seen before. Looks a bit like (cellular) mesoblastic nephroma. Any info on the presence of t(12; 15)(p13;q25) - ETV6-NTRK3 fusion in these tumours ?

Juan Rosai - I have never heard of this entity before. Surely the myofibroblast has become the darling of surgical pathologists these days, the way the pericyte was some decades ago. Let's hope that it will not suffer the same fate.

Brian Rubin – Interesting – never heard of this lesion before.

Dominic Spagnolo - A new one for me Gerald. Was not aware of congenital peribronchial myofibroblastic tumour. Thanks for the case.

James A. Strauchen - Never heard of this one! Thank you!

Saul Suster – Great case – thank you Jerry for contributing it! First time I see this tumor.

Ady Yosepovich - thank you for this unusual case.

CASE NO. 5 – CONTRIBUTED BY THOMAS COLBY, M.D.:

Volkan Adsay - I was fooled. I thought the cytology and pattern was pretty good for granular cell tumor, with the exception of the lack of mega-mitochondria.

Abbas Agaimy - Beautiful case. Never heard of before! Seeing this wonderful teaching case, would never think of such a diagnosis. This underlines the importance of clinical history but also the necessity to know more about tumor capabilities for differentiation patterns.

Phil Allen - Multiple deposits of pulmonary metastatic chondrosarcoma with exclusively S100 negative granular cell features from a primary chondrosarcoma with minimal granular cell differentiation, right hip. I thought this was a histologically benign granular cell tumor that had metastasized to the lung. I have certainly never seen it before and doubt that I would ever have made the correct diagnosis.

David Ben-Dor - Fascinating case. I enjoyed the recapitulation of the steps leading to the diagnosis, including the "red herrings". At the end you couldn't rely just on immuno and needed to go back to old- fashioned histology in order to make the diagnosis- S100 wouldn't discriminate between chondrosarcoma, granular cell tumor, and schwannoma since they would all be positive! Without being able to refer back to the slides of the bone tumor I suppose you would have been lost. Fortunately you had access to that material.

Michele Bisceglia - Metastatic chondrosarcoma with exclusively granular cell features. Never seen or heard of this histological variant of chondrosarcoma. What is interesting here is also the immunonegativity for S100, which is not expected to be in a chondrosarcoma. However, even if it were positive, it would not be of great help, given the differential diagnosis (at least initially) with granular cell tumor which is also often S100 positive.

Ira Bleiweiss - Very granular with a capital G, but, as you say Tom, it's not quite right for granular cell tumor. Hard to believe it's malignant. And, no, I don't recall ever seeing a chondrosarcoma with granular cells.

Kumarasen Cooper - Not seen chondrosarcoma with granular cell change before; but have seen it in ameloblastoma, angiosarcoma and cervical leiomyosarcoma. Therefore even though I had metastatic granular cell tumor I did wonder about CS showing granular cell change since other tumors have been described with this phenomenon.

Otto Dietze - I was not aware of this entity, thank you.

Hugo Dominguez-Malagon - Beautiful case, I see bone tumors at my hospital but never seen a condrosarcoma with granular cell transformation.

Göran Elmberger - Sorry Tom, new for me. EM would have been nice. Wouldn't one expect S100 positivity even in the setting of metastatic chondrosarcoma as described focally in your cited paper by Cremonini? Collagen II, SOX9, HBME1, Podoplanin or Vimentin? I guess given clinical setting and comparative focus in original chondrosarcoma one have to accept and learn…

Vincenzo Eusebi - Incredible case. Never seen a granular cell chondrosarcoma.

Giovanni Falconieri - Well, Tom. What can I say? This is truly weird. I congratulate you for your sharp eye and astute differential. Always great to learn from you! Thank you for submitting this incredible case and for the comments.

Franco Fedeli - Metastatic chondrosarcoma with exclusively granular cell features. Incredible case. Although I previously heard of this histological variant reported for the first time by an Italian group. When I saw the lesion I thought of two differential diagnoses: a granular cell tumor and pecoma. I am sure I have never seen a case like this!

Cyril Fisher - Wow. Nothing to suggest chondrosarcoma here. Interesting that S100pr is lost.

Christopher D.M. Fletcher - I have never personally seen chondrosarcoma with granular cell change and I could never have imagined even thinking of this diagnosis. The appearances are truly remarkable. Negativity for S-100 protein would clearly help to argue against conventional granular cell tumour. This is an astonishing case but seems convincing since you have identified a morphologically similar focus in the primary bone tumor.

Andrew Folpe - I am still having a great deal of difficulty believing that this is metastatic chondrosarcoma. Too weird.

Jerónimo Forteza - I agree about a granular cell tumor metastasis. It is not that clear to me the relation with chondrosarcoma in granular cells. It is a complex case. Ultrastructual study would have been relevant for this case.

Masaharu Fukunaga - I thought that the tumor was a granular cell tumor. I have never seen chondrosarcoma with granular cell change. The case is very interesting.

Thomas Krausz - No, I haven't seen chondrosarcoma with granular cell features before. Looking at the section I also went through the same differential diagnostic considerations but metastatic chondrosarcoma was not on my list. Most chondrosarcomas express S100, it is interesting to know that this metastatic "chondrosarcoma with granular cell features" is negative.

Janez Lamovec - I have never seen such change in chondrosarcoma although I am aware of granular cell change in some sarcomas (e.g. leiomyosarcoma). I would never recognize these metastases to be chondrosarcomatous in origin.

Thomas Mentzel - That's a very impressive case and a great diagnosis. Does the granular cell phenotype represent a degenerative phenomenon?

Markku Miettinen - Looks like a granular cell tumor although not the usual one as an S100 negative tumor. I am unaware of this appearance in cartilage tumors. Maybe they can undergo differentiation similar to the "non-neural granular cell tumor".

Fredrik Petersson - No clue. Never seen. Surreal. First impression, ?? infection; atypical mycobacteria; Rhodococcus. But too "clean" histology. I guess the patient is not immunocompromised.

Juan Rosai - I like this case because it supports the notion that the cytoplasmic granular morphology is not exclusive of a cell type (supposedly the schwann cell) but rather a regressive change that can occur in a variety of cell types, including smooth muscle cells, epithelial cells (basal cell carcinoma), ameloblasts, and the cells we see here, i.e., cartilaginous cells. Ironically, and despite its original name (myoblasten Myoma), it almost never occurs in skeletal muscle cells. By the way, I think it would have been difficult to make a diagnosis of chondrosarcoma on the basis of this slide.

Brian Rubin – Weird! Seen lots of chondrosarcomas but never seen granular cell change in chondrosarcoma before. Why was it S-100 negative?

Dominic Spagnolo - Give me a break! Glad you had the frozen. On the blind I was thinking mycobacterial pseudotumour, Whipple's, etc, etc. Anything but granular cell chondrosarcoma! What a case.

James A. Strauchen - Granular cell chondrosarcoma. Never say never!

Saul Suster: Spectacular and very weird case! Have never seen anything like this before. The anatomic distribution (scattered small nodules) is wrong for granular cell tumor, which is usually single and peribronchial, and for that reason I would have looked further into the case. But metastatic granular cell chondrosarcoma???? I'm still having trouble accepting that interpretation and can't help but wonder whether there is something else to this case that's been missed. I'm still having trouble recognizing these nodules as malignant.

Ady Yosepovich - WOW!!! This is an unusual case – thank you for sharing.

CASE NO. 6 – CONTRIBUTED BY GORAN ELMBERGER, M.D.:

Volkan Adsay - Very nice example. In our experience also the majority of NECs of the GI tract are associated with an adenocarcinoma and an adenoma component. Anecdotally, we recommend platinum-based therapy for these even if the NEC component is small (although of course this is based on anecdotal observations).

Abbas Agaimy - Nice example of MANEC, fully agree with diagnosis.

Phil Allen - Mixed adeno-neuroendocrine carcinoma of the rectum (MANEC) with components of adenoma, adenocarcinoma and high-grade large cell neuroendocrine carcinoma. This is the best example I have seen. Thanks for the contribution.

David Ben-Dor - a differential diagnosis could include the "undifferentiated" or "medullary" type- what would be against these is the lack of lymphoid infiltrates. Though the adenocarcinoma and LCNEC components have the same genetic footprint, on this glass slide they seem separate- the former is related to the polypoid lesion while the latter seems to be standing on its own with no dysplastic precursor in the overlying mucosa.

Michele Bisceglia - Mixed adenoneuroendocrine carcinoma of the rectum. Very rare case. Beautiful documentation and explanation of the histogenesis of this complex tumors.

Ira Bleiweiss - Agree

Thomas Colby - Agree with diagnosis. Very well worked up and discussed case.

Kumarasen Cooper - Thank you Goran. Lovely example of MANEC with molecular p53 mutational analysis of clonality (composite tumor).

Otto Dietze - I recently have seen a well differentiated neuroendocrine tumor in a large tubulovillous adenoma, but I think that my case was a random "tumor in tumor" and not a neoplasm with a common stem cell.

Hugo Dominguez-Malagon - Nice case of MANEC, good discussion.

Vincenzo Eusebi - Interesting case of adenocarcinoma associated with poorly differentiated neuroendocrine carcinoma. For unknown reasons in the rectal-anal area it is not infrequent to observe tumours showing multiple lines of differentiation that might include poorly differentiated neuroendocrine carcinoma associated to adenocarcinoma. We have also seen a case showing rhabdomyoblastic differentiation (Am J Surg Pathol. 19: 217-223,1995.). The large cells of the present case need to be stained for desmin & myogenin as I feel there might be the great surprise of a rhabdomyoblastic line of differentiation.

Giovanni Falconieri - Needless to say, I completely agree with your assessment of this extraordinary polyphenotypic tumor. Thank you for this submission and the excellent discussion thereof.

Franco Fedeli - Mixed adenoneuroendocrine carcinoma of the rectum. Nice discussion. I will use your scheme on the differentiation lines of the epithelial simplex and mixed GI tumors for teaching purposes. Different pathogenesis between a composite tumor and a collision tumor well explains the different therapeutic response and requires to be differentiated correctly between the two types.

Christopher D.M. Fletcher -A beautiful example of mixed adenocarcinoma/neuroendocrine carcinoma. I Would have difficulty in believing that a lesion such as this was simply a random collision – instead, clonal evolution from a single precursor seems far more likely. This is a beautiful example and I have not personally seen such as case in the colon before.

Andrew Folpe - Agree. Very nice case.

Jerónimo Forteza - The first diagnosis with H&E is neuroendocrine carcinoma, it suggests a differential diagnosis with metastatic melanoma. I agree with the description of the case.

Masaharu Fukunaga - Thank you, Goran, for the interesting case and the discussion. I think the case is moderately differentiated adenocarcinoma with large cell neuroendocrine differentiation.

Thomas Krausz - Agree with diagnosis. Intriguing combination of features, I have seen a couple of similar

examples before.

Janez Lamovec - Carcinoma with many faces; thank you for the erudite discussion.

Thomas Mentzel - A nice case showing multiple lines of differentiation in a neoplasm!

Markku Miettinen - Agree on high-grade carcinoma with a prominent neuroendocrine differentiation. There is an overlying severely dysplastic adenoma. My slide had no definitive adenocarcinoma element.

Fredrik Petersson - Composite tumour. Roger.

Juan Rosai - Beautiful example of high grade large cell neuroendocrine carcinoma arising in a colorectal adenoma with a minor component of adenocarcinoma. The discussion by the contributor about the histogenesis of this tumor is very good, but I think that the fact that we are dealing with two different phenotypes of the same neoplasm has been convincingly shown by several authors (and supported in this case by the demonstration of the TP53G mutation).

Brian Rubin – Very interesting case and excellent discussion.

Dominic Spagnolo - Great example of a mixed adeno-neuroendocrine carcinoma of the rectum. Have seen this very rarely.

James A. Strauchen - Mixed adenocarcinoma/large cell neuroendocrine carcinoma arising in colonic adenoma.

Saul Suster - Beautiful example of a mixed adeno/neuroendocrine carcinoma of GIT. Interestingly, this was first reported by Cyril Toker from the Mount Sinai Hospital in New York (Toker C: Observations on the composition of certain colonic tumors. Cancer 24:256-260, 1969), who described three cases of composite adeno/neuroendocrine tumors of the colon and proposed, back then, and based solely on morphologic (H&E) observations, that the tumors were derived from a common progenitor cell.

Ady Yosepovich - agree - very nice case – very insightful presentation and discussion. Thank you.

CASE NO. 7 – CONTRIBUTED BY GIOVANNI FALCONIERI, M.D.:

Volkan Adsay - I wondered if the spindle cell areas were not an unusual example of the morule-predominant zone in a PTC. Looking forward to Dr. Rosai's comment on that. By the way, we recently had morule-predominant endometrial cancers in the ovary that were originally misdiagnosed as granulosa cell tumors. And the spindle cell proliferation in this case also had nuclear grooves. I wonder if they become like this in some exuberant examples. Perhaps a beta-catenin immunostain might prove interesting.

Abbas Agaimy - A nice example of biphasic follicular and spindle cell thyroid lesion. I am not convinced of PTC, but my slide might have missed typical areas. The problem of such lesions is the interpretation of the spindle cells and its relation to the follicular component. Similar lesions have been reported under different names: thyroid epithelial neoplasms (adenoma or PTC etc) + SFT or + spindle cell stroma. I do not think that the stromal component in this particular case represent reactive myofibroblastic cells as reported earlier by Rosai et al, as the cells are uniform and lack any reactive stromal and nuclear features. I would suggest and discuss three possibilities: 1. spindle cell mesenchymal metaplasia arising within a follicular nodule (adenoma). We recently have reported 2 such examples and reviewed the literature on 14 additional cases, one reported by Michal et al as meningioma-like tumor. Most showed CK expression and variable thyroid follicular markers (see Agaimy et al, Int J Clin Exp Pathol, 2012;5(2):143-51); 2. SFT (hemangiopericytoma) arising within the thyroid and entrapping follicles. Although I never have seen such a lesion in the thyroid, we have encountered rare parotid gland SFT/HPC entrapping ducts and acini and featuring similar biphasic histology. Your IHC (CD99+/CD34+) fits this. was bcl2 also +? I would suggest staining

this lesion for STAT6 using the protocol applied by Jason Hornick et al (Mod Pathol Epub 2013 Sep 13.); 3. Given the intimate admixture of the two lesions and patient's gender, testing steroid hormones (ER/PR) might be appropriate for the sake of completion. I am not aware of MEST as a thyroid lesion, Michal might comment on this?

Phil Allen - Undiagnosed, unilateral, 4.8 cm, atypical spindle cell proliferation, possibly malignant, associated with an atypical follicular lesion, thyroid, with uneventful follow-up. I have not seen one like this before. I am not sure that the follicular thyroid lesion is malignant and even the spindle cell component might be benign. Long-term follow-up would be of interest.

David Ben-Dor - this is a unique case that requires expertise in thyroid and soft tissue pathology. We already have the word of the expert of the former- it would be interesting to hear the opinions of any of those in the group who possess the latter. The cells themselves look bland but there is at some necrosis- not favorable. We try and understand lesions according to acquired knowledge but maybe a case such as this requires a conceptual breakthrough!! The question is why SFT- has this ever been reported as arising together with an epithelial neoplasm; and why necessarily malignant?

Michele Bisceglia - Papillary carcinoma of thyroid (follicular variant) associated with primary malignant spindle cell tumor consistent with solitary fibrous tumor of thyroid. Agree. BCL-2 is another helpful marker to confirm SFT.

Ira Bleiweiss - I don't have any better ideas but I also thought the carcinoma was anaplastic.

Thomas Colby - I would favor the process being related to all one tumor, i.e. papillary carcinoma gone spindle (isn't epithelial mesenchymal transformation in vogue?).

Kumarasen Cooper - I took the liberty of sharing this case with Dr LiVolsi who agrees that the spindle cell neoplasm is mesenchymal; however, she favored it being metastatic to the thyroid.

Otto Dietze - I can offer FVPTC with medullary and parathyroid carcinoma, but nothing similar like that.

Hugo Dominguez-Malagon - Interesting lesion. Synovial sarcoma and SETTLE are to be ruled out.

Göran Elmberger – Giovanni, unfortunately my knowledge of endocrine pathology is very limited. However, generally speaking I would, like yourself, prefer some kind of logical relationship between the two tumor components - either a dedifferentiation as suggested by yourself or an etiological one perhaps… I was thinking of an IMT arising in the background of the inflammatory response to the PTC. ALK??? Otherwise dedifferentiation processes are more easily proven utilizing more than a few markers. NGS holds great promise in these cases but we are just introducing it in much simpler circumstances – NSCLC predictive exome screening. All being said malignant SFT is not a bad suggestion regarding morphology and IHC… (GE)

Vincenzo Eusebi - Difficult case. If a PTC is present (I need to see more tissue from the rest of the lesion to be sure) I would favor a PTC associated to a sarcomatoid carcinoma. We regularly see these changes in sarcomatoid carcinomas from other organs simulating a malignant SFT.

Franco Fedeli - Papillary carcinoma of thyroid (follicular variant) associated with primary malignant solitary fibrous tumor of thyroid. Agree. Parenthetically Dr. Sobrinho Simoes was the senior author of the group that first reported SFT in the thyroid (Taccagni G, Sambade C, Nesland J, Terreni MR, Sobrinho-Simões M. Solitary fibrous tumour of the thyroid: clinicopathological, immunohistochemical and ultrastructural study of three cases. Virchows Arch A Pathol Anat Histopathol. 1993;422:491-7).

Cyril Fisher - Would have thought dedifferentiated PTC. In respect of solitary fibrous tumour, STAT6 immunostaining might be contributory.

Christopher D.M. Fletcher -To be honest, I do not think that this looks like solitary fibrous tumor – but we would be happy to stain the tumor for STAT6 if you'd like! I think that I would have assumed that

this was dedifferentiation/anaplastic carcinoma evolving from PTC, but I would not claim to be a thyroid expert.

Andrew Folpe - Being a simple rural soft tissue pathologist, I would tend to think of this as an anaplastic carcinoma arising within a PTC.

Jerónimo Forteza - It is a very complex tumour. I have never seen any case like this. I agree with your diagnosis. Thank you for the case.

Masaharu Fukunaga - Very interesting. I favor dedifferentiated papillary adenocarcinoma of the thyroid. The follicular variant of the thyroid and the spindle cell were intermingled and psammoma bodies were scattered.

Thomas Krausz - Very strange. I was considering papillary thyroid carcinoma with exuberant nodular fasciitis-like spindle cell proliferation, SETTLE or meningioma-like tumor, but none of them perfect, sorry…

Janez Lamovec - Falco, this is difficult. If your and Sobrinho's reasoning is correct this would be a collision tumor. However, I am not very much convinced of a SFT diagnosis for the spindle cell component and I wonder whether the loss of all immuno markers for epithelial/follicular epithelial cells could not be explained by some sort of dedifferentiation.

Thomas Mentzel - Another idea would be the diagnosis of metaplastic carcinoma with features of SFT (did spindle cells stain positively for STAT6?)

Michal Michal - Very nice case!!! It looks to me like a thyroid neoplasm (difficult to say whether benign or malignant) growing on the background of malignant solitary fibrous tumor.

Markku Miettinen - Agree on papillary thyroid carcinoma with anaplastic spindle cell transformation.

Fredrik Petersson - To me two tumours. Carcinoma with micropapillary and ?follicular features + (at least atypical) – malignant SFT. Carcinoma: MUC1/EMA with "inside-out"/reverse polarisation pattern ? (*Lino-Silva LS et al. Hum Pathol. 2012 Oct;43(10):1596-600.*), throughout the carcinoma or focal ??

Juan Rosai - Remarkable case of follicular variant of PTC associated with a spindle cell component. I suspect that - like in Case 6, we are dealing with a single tumor that has undergone a metaplastic change to become a spindle cell neoplasm. In a very general sense it is a differentiated tumor, but certainly doesn't look as malignant as the usual anaplastic thyroid carcinoma. Actually, it looks to me like the thyroid equivalent of Suster's metaplastic thymoma.

Brian Rubin –Doubt malignant SFT but you could exclude it with STAT6 IHC, which is uniformly positive in SFTs.

Dominic Spagnolo - Tough case Giovanni. I struggle to be sure this is papillary carcinoma rather than follicular, with oncocytic areas. But leaving that aside, I favor that this is dedifferentiated carcinoma. The spindle cell component is bland in some areas, akin to spindle cell metaplasia, but I agree overall this is a malignant spindle cell element, and the intimate admixture with the epithelial component suggests to me that this is all one lesion. But I do agree there is a SFT flavor to it! The negative BRAF findings don't really help in this scenario.

James A. Strauchen - Spindle cell anaplastic thyroid carcinoma/papillary thyroid carcinoma.

Saul Suster - Unfortunately, the slide I got contains only a minuscule amount of tissue (less than 0.5 cm across), precluding getting a better sense of the histology for this lesion. The small piece I received, however, shows scattered small follicles separated by a bland-appearing spindle cells admixed with small lymphocytes and numerous plasma cells. I don't know what this is but, from the small piece of tissue I've seen, I would not be able to: 1. Make a diagnosis of papillary carcinoma; 2. make a diagnosis of SFT, or 3. make a diagnosis of malignancy. I guess I would

need to see additional sections to get a better sense of the lesion. USCAP this year had dozens of posters about the new molecular translocation in SFT that is easily demonstrated with antibodies to STAT6. Perhaps that should be the start for this tumor, so that the theory of SFT can be laid aside.

Ady Yosepovich - could this be metastatic papillary carcinoma of breast origin?

CASE NO. 8 – CONTRIBUTED BY FRANCO FEDELI, M.D.:

Volkan Adsay - Great example. The squamoid corpuscles are truly squamoid for a change. In most examples the so-called squamoid corpuscles are more meningothelial or morular looking than the keratinizing-squamous appearance seen in this case.

Abbas Agaimy - Pretty case, thank you for sharing this rare tumor.

Phil Allen - Pancreatoblastoma, junction of body and tail of the pancreas. This is the first case that I have seen. The acinar formations in my section are minimal. I just hope I can remember it until I see another case.

David Ben-Dor - Pancreatoblastoma- for me the tip-off is the multiple squamous corpuscles. Wouldn't expect this in an adult.

Michele Bisceglia - Pancreatoblastoma in adult male patient. Nice and very rare case, of which 33 cases have been recorded in the literature according to a review article published in this month of December 2013, including the 3 personal cases of the authors (Salman B, et al. The diagnosis and surgical treatment of pancreatoblastoma in adults: a case series and review of the literature. J Gastrointest Surg. 2013;17:2153-61). It is amazing that we had the opportunity to see now 3 cases of pancreatoblastoma, two in adults (the case contributed by Noel Weidner in Seminar # 39, and the present one) and one in a stillborn female (contributed by John Chan in seminar # 22).

Ira Bleiweiss - Wow. Beautiful case.

Thomas Colby - Agree with diagnosis. Beautiful example.

Kumarasen Cooper - Thank you Franco for this beautiful example of pancreatoblastoma.

Otto Dietze - In the patients age my first idea was something like poorly differentiated mucoepidermoid carcinoma, but I am convinced by your diagnosis.

Hugo Dominguez-Malagon - Pancreatoblastoma. Very difficult diagnosis, I did not think of it.

Göran Elmberger - Great case. Initially I was struggling with adenosquamous carcinoma but given the acinar differentiation pancreatoblastoma is a better fit. Need for including trypsin and some orienting special stains in preparation of unusual cases. Thanks for sharing this highly unusual case.

Vincenzo Eusebi - Another difficult case. In the end I would need to ask a second opinion before accepting this case as pancreatoblastoma. This is not only for the age of the patient, but also for the squamous areas that to me are too large to be called "squamoid corpuscles". Finally I was not able to find a definite area containing a straightforward neoplastic acinic cell differentiation. I have the feeling that the so called acinic cell structures present in the slide could be entrapped residual glands. In conclusion I would have needed a second opinion if I had to report this case on my own.

Giovanni Falconieri - Great case of pancreatoblastoma, Franco, and nice discussion as well. The squamoid areas would suggest at a glance a metastatic SCC of lung.

Cyril Fisher - Pancreatoblastoma in adult, great rarity. Lovely slide.

Christopher D.M. Fletcher - At least to me, this lesion appears much more cytologically atypical than I would expect in pancreatoblastoma and, rather than squamous morules, large areas of this tumor seem to resemble conventional squamous carcinoma, admixed with a cytologically malignant acinar or glandular component. I think that I would have called this a poorly differentiated carcinoma with squamous differentiation. It will be interesting to hear what Volkan Adsay has to say about this interesting case.

Andrew Folpe - I thought the squamous and acinar component looked too high-grade, and was thinking of a combined acinic cell-squamous cell CA. Will be curious to hear the GI gurus on this one.

Jerónimo Forteza - This is an unusual case that can be diagnosed with H&E. Molecular findings given for the description of this case are very interesting.

Masaharu Fukunaga - It seemed to be adenosquamous carcinoma of the pancreas. It is very difficult to classify this tumor. Thank you for the interesting case, Franco.

Thomas Krausz - Very nice example.

Janez Lamovec - Most interesting case, Franco. I've seen only seminar cases of such a tumor.

Thomas Mentzel - An unusual neoplasm almost without a mesenchymal component arising in an elderly patient, many thanks.

Markku Miettinen - Difficult case – Extensive squamous differentiation is present in this carcinoma-like tumor but I could not find definitive acinar cell differentiation in the slide to fit pancreatoblastoma.

Fredrik Petersson - On H&E, I think a NUT-midline carcinoma is a differential diagnosis (at least from a H&N perspective).

Juan Rosai - I agree about the multidirectional features of this pancreatic tumor (ductal and acinar), but I would have regarded the prominent areas of squamous differentiation with cytoplasmic clearing as evidence of a prominent squamous component of the tumor (probably the ductal one) rather that the squamous eddies of a pancreatoblastoma.

Brian Rubin – Great case. It's been a while since I've seen one of these.

Dominic Spagnolo - In someone this age adenosquamous carcinoma would be a prime consideration, but I agree the features here are good for pancreatoblastoma. Thanks for the case.

James A. Strauchen - Pancreaticoblastoma. Very nice case!

Saul Suster – I would have thought of an adenosquamous carcinoma in this case rather than pancreatoblastoma. The largest series published by Klimstra and Rosai in AJSP showed cases that had a more definite acinar differentiation and the squamous foci resembled the morules in pulmonary blastomas rather than the extensive areas of well-differentiated squamous cell carcinoma seen here. Also not sure how specific or reliable the trypsin and chymotrypsin stains are here. But since I have very limited expertise with these tumors, I will gladly defer to the experts!

Ady Yosepovich - never seen this tumor before – thank you for sharing this beautiful case.

CASE NO. 9 – CONTRIBUTED BY JERONIMO FORTEZA VILA, M.D.:

Volkan Adsay - Very nice and challenging example.

Abbas Agaimy - Very unusual case, never seen this before. Something that might receive no good name in routine practice if one is not aware of the entity or does not consider the hematological background disease. Thanks for sharing this teaching case.

Phil Allen - Malignant extra-medullary myeloid tumor or myelosarcoma, left side of the abdomen in myelofibrosis. I'm not too hot on hematopathology but this entity seems to have also been called fibrous hematopoietic tumor arising in agnogenic myeloid metaplasia (Hum Pathol 13:804-810, 1982).

David Ben-Dor - it's nice to have a good history which helps in identifying those prominent large dysmorphic cells as megakaryocytes. I'm impressed by the photos as to how cleanly the autopsy was performed – when I do one it's much more messy.

Michele Bisceglia - Malignant extramedullary myeloid tumor or myelosarcoma in a patient with myelofibrosis, showing a macroscopic appearance mimicking "peritoneal carcinomatosis". Interesting case, thank you. Now we have the following cases of sclerosing extramedullary hematopoietic tumor (SEMHT) in the Club: the case of solitary SEMHT in the orbit contributed by John Chan in Seminar 33 (benign SEMHT associated with chronic myeloid leukemia), the case with multiple lesions in the abdomen in Seminar 55 by Carlos Bacchi (benign SEMHT with multiple nodules associated with chronic idiopathic myelofibrosis), and the present one (also intrabdominal, also with multiple nodules but malignant, arisen in the context of chronic myelofibrosis). [Not included here in the list of sclerosing tumors is the case of Janez Lamovec of tumor-forming myeloid metaplasia of the breast – which was not sclerosing and not a neoplasm – in a patient with idiopathic osteomyelosclerosis]. It is very interesting to be able to compare the benign and the malignant types of SEMHT. Query for Jeronimo: what was the bone marrow like in this patient in your postmortem histological examination? Did it show classic idiopathic myelofibrosis or was it also infiltrated by myeloid blasts?

Ira Bleiweiss - Couldn't figure this out (some kind of sarcoma).

Thomas Colby - Agree with diagnosis. Dramatic example.

Kumarasen Cooper - I thought this was the sclerosing extra-medullary hematopoietic tumor that Tony Nascimento described at the Mayo. I am sure we have seen a case at AMR too.

Otto Dietze - Never seen a similar case, however the atypical megakariopoesis and fibrosis was suggestive of an underlying myeloproliferative disease.

Hugo Dominguez-Malagon - A good case of myeloid sarcoma, thank you.

Göran Elmberger - Great case with unusual presentation. Clinical history and cytoplasmic granules helps. Molecular tests are also a very strong help.

Vincenzo Eusebi - Malignant myeloid extramedullary tumour. Instructive case.

Giovanni Falconieri - Very difficult. Extramedullary myelopoietic tumors are amongst the most challenging microscopic entities due to their objective rarity and subtle diagnostic features that would deceive the inexperienced pathologist, as for sure I am. Thank you for submitting this case and providing excellent discussion and outstanding illustrations.

Franco Fedeli - Malignant extramedullary myeloid tumor or myelosarcoma. Agree. This is a rare occurrence (malignant transformation) in a rare tumor, that is in the context of "sclerosing extramedullary hematopoietic tumor". Definitely in this case the scarcity of metamyelocytes and granulocytes suggests myeloid malignant transformation.

Cyril Fisher - Disseminated extramedullary myeloid deposits. Striking appearance

Christopher D.M. Fletcher - A lesion such as this could easily be confused with sclerosing extramedullary hematopoietic pseudotumour, particularly given the long history of myelofibrosis.

Andrew Folpe - To my eye this is a sclerosing extramedullary myeloid tumor. I don't see the "malignant".

Masaharu Fukunaga - Wonderful case. Is sclerosing extramedullary hematopoietic tumor the same as malignant extramedullary myeloid tumor or myelosarcoma?

Thomas Krausz - Highly educational case. Easily can be mistaken for other tumor types.

Janez Lamovec - We've seen a number of such cases; identification of megakaryocytes is most helpful on H&E.

Thomas Mentzel - A difficult case emphasizing that we have to think on these unusual neoplasms. Have you stained the lesion also for CD61, CD43 and CD34?

Markku Miettinen - Nice example of extramedullary myeloid tumor/sarcoma potentially simulating retroperitoneal liposarcoma.

Fredrik Petersson - Arising in Sclerosing extramedullary hematopoietic tumor?

Juan Rosai - If I had not known about the immunohistochemical and chromosomal studies findings in this case, I would thought of an inflammatory type of liposarcoma (or, in the past, the inflammatory variant of MFH) in a patient who happens to have myelofibrosis. Actually, even with that information I am reluctant to rule out this alternative out (here I am showing again my card-carrying morphologist card).

Brian Rubin – I haven't seen a lot of these although they are always in my differential diagnosis. I don't remember seeing one that presented with a carcinomatosis-type presentation.

Dominic Spagnolo - I would call this is a sclerosing extramedullary hemopoietic tumor arising in the context of chronic myelofibrosis. Very nice case.

James A. Strauchen - Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative disorder (Remstein ED, Kurtin PJ, Nascimento AG. Am J Surg Pathol. 2000 Jan;24(1):51-5).

Saul Suster – This looks more like the lesion described by Tony Nascimento as sclerosing extramedullary hematopoietic tumor than as a myelosarcoma. It is certainly unusual that there are so many of these studding the abdominal cavity, and that alone would be worthy of a case report – but the histology in my mind is not anywhere near the classical cases of myelosarcoma I've seen, which look very ugly, atypical, more cellular and ominous!

Ady Yosepovich - thank you for this beautiful case and presentation.

CASE NO. 10 – CONTRIBUTED BY MASAHARU FUKUNAGA, M.D.:

Volkan Adsay - I was worried about a peculiar angiosarcoma here, but was not sure how to classify this. Thanks for clarifying it.

Abbas Agaimy - Very peculiar case! Some of the features seen herein are sometimes encountered in some myxoid sarcomas. Mitoses are easily identifiable in perivascular cells and nuclei are pretty vesicular and large with some binucleation. This lesion does not fit into a clear entity and thus biology remains for me unsure. Atypical angioendotheliomatosis might be a possibility. Was there any history of previous radiation?

Phil Allen - Undiagnosed, single, 4 cm, mitotically active, atypical vascular proliferation somewhat resembling reactive angioendotheliomatosis surrounded by atypical, vascular fibromyxoid tissue, possibly neoplastic, in the subfascia of the left sartorius muscle with no recurrence at 18 months in a patient with colonic cancer resected four years previously. While parts of this lesion resemble atypical foci in reactive angioendotheliomatosis, this is a solitary deep-seated mass rather than a multifocal skin lesion resembling Kaposi's sarcoma. I don't recognize it as any of the

established vascular proliferations but I am worried by the atypia and mitotic activity. I would not yet write it off as benign, despite the 18 month follow-up. At least it does not seem to be a high-grade angiosarcoma.

David Ben-Dor - I thought that there were foci of vasculitis. This wouldn't explain the widespread proliferative changes which look benign to me and which I would have to interpret as reactive to that process.

Michele Bisceglia - Reactive atypical fibrovascular proliferation (reactive angioendotheliomatosis?). Honestly I personally believe this is an instance of proliferative fasciitis. Look forward to hearing what soft tissue experts say in this regard.

Ira Bleiweiss - Agree but scary.

Thomas Colby - Agree with diagnosis. This appears reactive to me. I have a somewhat similar case from the gut that I will be sharing in a future seminar.

Kumarasen Cooper - Masa, I agree with you that this is a reactive myofibroblastic proliferative fasciitis-type lesion. Defer your specific question to the soft tissue gurus.

Otto Dietze - The organizing pattern of the lesion in my opinion confirms the nature of a reactive and not of a neoplastic process.

Hugo Dominguez-Malagon - It certainly looks fasciitis-like as a reactive process, however the atypical mitosss concern me. Beautiful case.

Göran Elmberger - Masa I have not seen before. I am a bit worried that the vascular changes might be an epiphenomenon possibly of the type you suggest but that they might occur within a more significant neoplastic lesion possibly a lipomatous tumor such as pleomorphic (CD34) or atypical (mdm2) lipoma. Did you check these stains?

Vincenzo Eusebi - I would go for a benign process of epithelioid endothelial and stromal cells. Nevertheless I have no specific name for it.

Giovanni Falconieri - Very challenging, Masa, just impossible for me. I may comment by saying that the degree of cellularity and nuclear atypia would push me more toward a sarcomatous proliferation. But I am sure that this is a knee-jerk diagnosis rather than a critically and well-reasoned microscopic approach.

Franco Fedeli - Reactive atypical fibrovascular proliferation (reactive angioendotheliomatosis?). Despite the mitotic activity, including some atypical forms, I agree with the fact that this tumor is reactive and not a neoplasm. My first diagnostic option was a proliferative fasciitis with a prominent accompanying (reactive) vascular pattern.

Christopher D.M. Fletcher - This man's groin lesion is, at least to me, extremely unusual but I agree that the appearances would seem to fit best with some florid reactive fibrovascular proliferation of uncertain etiology. There is marked stromal edema and many areas have an almost tissue culture-like appearance. At least for me personally, I would not use the term 'reactive angioendotheliomatosis', since the latter to me is pretty much defined by the presence of diffuse or band-like dermal involvement and lacks the very prominent fibroblastic/myofibroblastic component which is evident in this unusual lesion.

Andrew Folpe - I would be concerned about a dedifferentiated liposarcoma here. This strikes me as being malignant, and the peripheral component has features of WDL.

Jerónimo Forteza - To complete this case comparative genomic in situ hybridization could be made. The lesion seems benign, but differential diagnosis between a reactive lesion and a true tumor is difficult in this case.

Thomas Krausz - I agree with your interpretation. I also favor reactive despite the brisk mitotic activity

and focally epithelioid phenotype of the endothelial cells. In my opinion reactive angioendotheliomatosis as described by Chris Fletcher and colleagues is the best diagnostic term for this case.

Janez Lamovec - I don't know if this could be called reactive angioendotheliomatosis but the tissue definitely appears reactive with very prominent vascular proliferation.

Thomas Mentzel - I think as well that the lesions represents a reactive fibrovascular process, however, the mentioned reactive angioendotheliomatosis is different in my opinion. Reactive angioendotheliomatosis represents a dermal intravascular endothelial proliferation with capillary tufts and fibrin thrombi and is seen in patients with cryoglobulinemia or infection. Diffuse dermal angiomatosis on the other hand is defined by the proliferation of newly formed narrow vascular structures probably as a result to ischemic conditions. No reactive granulation tissue and fibrous proliferation is seen in these two conditions.

Markku Miettinen - Although the tumor has reactive features such as those resembling proliferative fasciitis, the presence of atypia and atypical mitotic figures is worrisome so that I would consider it at least of uncertain malignant potential if not low-grade sarcoma – needs complete excision with negative margins and follow-up.

Fredrik Petersson - Vascular "Pseudosarcoma" to me. Awaiting the experts' opinion(s).

Juan Rosai - This mesenchymal lesion looks scary, particularly in the vascular component, but it seems to me that the overall appearance is more in keeping with a member of the reactive processes in the soft tissue family generically known as "reaction to injury", and which comprises nodular fasciitis, proliferative myositis, proliferative fasciitis, post-operative spindle cell pseudosarcomatous nodule, etc. I have sometimes wondered whether there is a malignant form of these processes. Has anybody else?

Brian Rubin – Looks scary but overall has reactive features - ? Proliferative fasciitis.

Dominic Spagnolo - I don't know what to call this. I'm uncomfortable with reactive angioendotheliomatosis because of the deep location and atypia, yet there are aspects which do look reactive. I would be concerned about a weird low grade dedifferentiation in a liposarcoma but can't prove it here.

James A. Strauchen - Reactive fibroplasia/organizing hematoma?

Saul Suster – I agree that this looks reactive and in some areas shows features of atypical granulation tissue. I would favor a descriptive diagnosis of "reactive fibrovascular process with atypia" rather than reactive angioendotheliomatosis, which should be reserved for the dermal lesions. The spindle cell proliferation surrounding the central "reactive" core of the lesion, however, looks different. This peripheral component shows a proliferation of stellate and dendritic spindle cells admixed with lipoblastic and floret-type cells. Abnormal mitoses are present here. I would run an MDM2 to evaluate this component of the lesion and forget about the central, traumatized portion of the lesion. I would want to rule out a dedifferentiated liposarcoma that happens to contain vascular reactive changes in the center of the tumor.

Ady Yosepovich - thank you for this unusual case. I was not aware of this entity.

CASE NO. 11 – CONTRIBUTED BY THOMAS KRAUSZ, M.D.:

Volkan Adsay - Those hyalinizing micronodules are indeed striking. Do not seem to be pre-existing silica nodules or anything of that sort either. Great case.

Abbas Agaimy - Thanks for this nice case of hyalinizing DMM.

Phil Allen - I have not seen the hyalinizing micro-nodules like this before and neither has Doug Henderson, our local mesothelioma expert. He agrees with Thomas that the hyalinizing micronodules are not osteoid and have probably been induced by the cisplatin/pemetrexed therapy.

David Ben-Dor - I think Thomas' observations and analysis are brilliant, as is usually the situation with the unique and challenging cases he submits to this forum or presents at the meetings. Fortunately there was a pre-treatment biopsy; otherwise these findings (the tumor, the talc crystals, the nodules) are so intertwined it would have made life more interesting and difficult.

Michele Bisceglia - Biphasic malignant mesothelioma with peculiar, probably therapy-induced, hyalinizing micronodules. Interesting case and (as usual) astute observations regarding the origin of these micronodules and their possible (eventually excluded) relationship with blood vessels.

Ira Bleiweiss - Agree. Strange hyalinizing nodules. Not sure what to make of them.

Thomas Colby - Agree with diagnosis of biphasic mesothelioma. I have not seen this many small rounded nodules as are present here before. In my opinion they may or may not be treatment related. Coincidentally, in our recent report of intrapulmonary mesothelioma (see AJSP 37:1555, 2013) we illustrated somewhat similar nodules in the lung in a patient who had had no prior therapy.

Kumarasen Cooper - Thank you Thomas for this nice example of biphasic malignant mesothelioma. I also wondered whether these were nodules of osteoid (i.e. heterologous differentiation).

Otto Dietze - I did not see this combination before, but I also don't know of a patient with a similar course of therapy.

Hugo Dominguez-Malagon - Biphasic mesothelioma. I have not seen the hyalinized nodules, perhaps they're related to the treatment.

Göran Elmberger - I guess I have no experience with treatment-induced changes in malignant mesothelioma. My first impression reviewing the slide blindly was epithelioid hemangioendothelioma, which can have this sort of characteristic hyaline intercellular substance. Further, I noted intracytoplasmic vacuoles that could represent vasoformation in epitheloid vasoformative tumors. Also MM could have IC neolumina/invaginations in that case outlined by slender microvilli containing hyaluronic acid precipitate. Even if some IHC overlap might be expected (CK, Vimentin and D2-40) other stains in panel might differentiate. Thomas you did not tell us about immunophenotype of this lesion. I am curious.

Vincenzo Eusebi - Nice case with never seen features in a biphasic mesothelioma.

Giovanni Falconieri - Another impossible case. Thank you Thomas, this is very instructive. Never seen before although we still see about 4-5 cases of mesothelioma per month in this area due to the large use of asbestos in the naval shipyards around the Venice and Trieste area.

Franco Fedeli - Biphasic malignant mesothelioma with peculiar, probably therapy-induced, hyalinizing micronodules. Of course I agree with both your diagnosis and your interpretation in regard to the neoplastic sclerosing micronodules. I think there are also some consequences of the use of talc.

Cyril Fisher - Biphasic mesothelioma with strange hyaline nodules, unexplained.

Christopher D.M. Fletcher - Agree that this multinodular pattern of hyalinization in this patient's mesothelioma is almost certainly treatment-related. In talking to our thoracic pathologists, they say they have rarely seen similar features, but so few mesotheliomas respond that this can't be a common finding. Most of our patients get chemo after surgery, not before, so we may be missing this!

Andrew Folpe - Agree with biphasic mesothelioma. The pulmonary fellow tells me that they've seen these nodules in untreated mesotheliomas.

Jerónimo Forteza - I have not seen before hyaline nodes with these characteristics, but it could be nodes caused by a previous lesion due to TB or sarcoidosis. However, since these nodes seem to be part of the tumor, it could be a meningiomatous differentiation.

Masaharu Fukunaga - Malignant mesothelioma. It shows biphasic pattern. Thank you, Thomas for the case and discussion.

Janez Lamovec - Very unusual change in mesothelioma, probably therapy related. Never seen anything like this.

Thomas Mentzel - Many thanks for this biphasic malignant mesothelioma showing unusual stromal changes.

Michal Michal - Mesothelioma with sarcomatoid component.

Markku Miettinen - Malignant mesothelioma with a major epithelioid and minor sarcomatoid component and foreign body material and reaction to talc pleurodesis. Perhaps the hyalinization is pleural plaque-like change here associated with mesothelioma.

Fredrik Petersson - Not seen before. The sclerotic collagen appears a bit "keloidal". The malignant cells appear "untouched" by the chemo.

Juan Rosai - Like Tom Krausz, I suspect that these peculiar hyaline nodules are secondary to the therapy for the mesothelioma, but I cannot go further. I don't remember having seen something quite like this before

Brian Rubin – I don't think I've ever seen a mesothelioma post-treatment. I'm not sure there isn't osteoid but it's subjective. It might be heterologous osteosarcomatous differentiation.

Dominic Spagnolo - I think these micronodules probably do represent early osseous metaplasia in a biphasic mesothelioma. They are stunningly prominent and I have not seen these before.

James A. Strauchen - Biphasic malignant mesothelioma with hyalinization (? therapy related).

Saul Suster – I saw at the AFIP several cases of mesothelioma with heterologous osteosarcomatous differentiation that had areas that looked like this, but they also had more convincing "osteoid" and clearly osteosarcomatous features. This one, although suggestive for this, does not quite make it. So I agree with you, Thomas, that perhaps it's related to therapy rather than this representing a tumor-secreted matrix. Really unusual example of mesothelioma – thanks for sharing it!

Ady Yosepovich - this is an outstanding observation. In continuance to your excellent presentation in the AMR symposium in Tel-Aviv the stroma (the soil of the tumor as you said) can give us a lot of information. It is my suggestion that the post treatment mesothelioma cells are producing and deposing this peculiar hyaline material and this is the reason for these peculiar micronodules. I don't know how this could be proved, this is only a suggestion.

CASE NO. 12 – CONTRIBUTED BY ALBERTO MARCHEVSKY, M.D.:

Volkan Adsay - I was strongly favoring a benign process but couldn't name it. It is good that I do not do dermpath anymore; it would have probably taken me hours to figure this out.

Abbas Agaimy - Agree with this nice case. It is really difficult to judge primary vs. metastatic in melanoma cases. Absence of other primary and disease free follow-up are good arguments for a primary pulmonary melanoma. This

implies stage IV vs. non-stage IV and thus treatment or not, very difficult clinical scenario. Thanks for sharing this case.

Phil Allen - Ulcerated primary malignant melanoma, right mainstem, middle and lower lobe bronchi. I agree that this is almost certainly a primary tumour because of its close relationship to the right main bronchus and the absence of other radiologically apparent intrapulmonary nodules.

David Ben-Dor - I had a case picked up on bronchoscopy. The lesion was pigmented which impressed the pulmonologist. It also helped in making the diagnosis. My initial assumption in this case would have been (prior to immunohistochemistry) sarcomatoid carcinoma although I don't know what a real "pro" would think about that.

Michele Bisceglia - Malignant melanoma of the lung; presumed lung primary in the absence of previous history of malignant melanoma and negative work-up for extrapulmonary lesions. Agree. Never seen a similar case as a primary in the lung. However a few years ago I saw a case which can elicit some analogies with your pulmonary case herein circulated. The case I refer to was a primary melanoma of the gallbladder in an old lady with long-lasting cholelythiasis. In that case there were accompanying areas of squamous metaplasia in the mucosa of the gallbladder and we could find a focus of atypical melanocytic proliferation on one side of an extensive ulceration of the mucosa.

Ira Bleiweiss - Wow. PRIMARY melanoma of the lung. Just when you think you've seen it all.....

Thomas Colby - Agree with the diagnosis and discussion. Proving primary melanoma at an odd site is always a problem, both practically and philosophically.

Kumarasen Cooper - Thank you Alberto. Reminded me of Falco's breast series.

Otto Dietze - I agree with the diagnosis and remember a similar case many years ago (autopsy case). Despite the fact that we did not find another primary lesion, we did not try to publish it because we could not rule out a regression of a melanoma before and the patient had never been seen by a dermatologist.

Hugo Dominguez-Malagon - Malignant melanoma primary of bronchus is a good possibility although it is a rare condition. The polypoid appearance, the uniqueness and the absence of skin or mucosal primary supports this possibility.

Göran Elmberger - Nice case. Primary versus metastatic - hard to tell. Does IHC reveal radial growth phase in bronchial mucosa? Problem similar to acceptance of squamous cell carcinoma in bronchogenic neck cyst – highly improbable. Criteria in that case 5 years follow-up without evidence for primary tumor!

Vincenzo Eusebi – Pigmented, negative HMB 45-positive malignant tumour. The lesion shows perivascular arrangement of neoplastic cells. I wonder how different this case would be from a malignant PECOMA or alternatively from the so called clear cell sarcoma.

Giovanni Falconieri - Great case Alberto! I have seen a weird case of lung melanoma years ago which was labelled initially with the most bizarre names from the tumor pathology catalog, including rhabdoid tumor of the lung (and other fancy diagnoses) till somebody ordered the only stain which should have been done since the beginning, e.g. S100 protein, that came up to be strongly positive. The patient was a nurse in this hospital and she later revealed that a mole had been resected from her leg 24 years (yes sirs! 24 years) previously which was an invasive melanoma, totally forgotten. And can you believe it? She is still alive and well 7 years after lobectomy. It seems that isolated metastases of melanoma to lung do not necessarily anticipate a bad clinical course.

Franco Fedeli - Malignant melanoma of the lung; presumed as a lung primary in the absence of previous history of malignant melanoma. Although the diagnosis is out of question, whether this tumor is a primary or a pulmonary metastasis is challenging.

Cyril Fisher - Consistent with melanoma. As no other primary and BRAF negative, FISH for EWSR1 rearrangement to exclude clear cell sarcoma might be of interest.

Christopher D.M. Fletcher - As in some cutaneous situations, the presence of surface ulceration makes it difficult to check for any junctional or pagetoid component but a solitary submucosal lesion such as this, in the absence of any evident melanoma elsewhere, would certainly seem to fit with a rare primary tumor at this site.

Andrew Folpe - Agree with melanoma.

Jerónimo Forteza - We must not forget differential diagnosis with melanoma. Despite being an unusual case, morphology showing big nuclei cells leads to think about it.

Masaharu Fukunaga - I have never seen melanoma of the lung. It is very difficult to make the diagnosis. My initial impression was myoepithelial carcinoma.

Thomas Krausz - Yes, I agree that in general it is difficult to diagnose primary melanoma of lung. However, I believe the presence of in situ melanoma in the adjacent bronchial mucosa (in the absence of primary melanoma elsewhere) is a strong evidence for bronchial primary site, similarly to other mucosal melanomas with in situ component. The presence of "melanocytic hyperplasia without significant atypia" in the basal layer of the bronchial mucosa can also be used as a softer criterion. In the submitted case I cannot see in situ melanoma but melanocytic markers might reveal a degree of melanocytic hyperplasia in the bronchial mucosa. I am fortunate enough to have the slides of a primary malignant melanoma of the bronchus from Dr. R. Salm's collection showing also an in situ component. As far as I know he was the first to describe a primary melanoma of the bronchus in J Pathol Bacteriol 1963; 85:121-126.

Janez Lamovec - I believe it is almost impossible to determine whether this is a primary or metastasis since the existence of spontaneous regression in primary melanoma is well known.

Thomas Mentzel - I think there is no doubt about the diagnosis, and morphological features also do not fit with clear cell sarcoma arising in an unusual setting. The only problem is with the exclusion of a regressing malignant melanoma in the past.

Markku Miettinen - Agree on malignant melanoma, rule out metastasis.

Fredrik Petersson - Malignant spindle cell tumour with IHC c/w melanoma. I assume no in-situ component was identified. Was IHC on (?) biopsies done – conclusive ?

Juan Rosai - This is a melanoma, all right, but if it is primary in the lung or metastatic I don't think anybody can say for sure on the basis of this specimen. The logical thing is for it to be metastatic, but lesions that were thought to be classic metastatic melanomas in the GI tract are now regarded as primary in that location because of the molecular findings. I would leave the question open. By the way, I'm showing my age again by being disappointed at not seeing a melanin stain among this sea of immunos. Let me also tell you about a similar case discussed by Dr. Raffaele Lattes at the Penrose Cancer Hospital Seminar in the fall of 1960, which was called by him metastatic malignant melanoma, with unknown primary. Delarue, from France, called it pigmented neuroid malignant tumor, and Purdy Stout called it a questionable melanotic malignant schwannoma. Dr. Ackerman, in his typical ironic style, commented "This is a metastatic malignant melanoma. It is too bad that the primary lesion, in the skin of the chest, in the eyes or meninges, was overlooked".

Brian Rubin - I'm always hesitant to diagnose primary melanomas in parenchymal organs but I do think it happens rarely.

Dominic Spagnolo - I agree with malignant melanoma, and primary bronchopulmonary until proven otherwise.

James A. Strauchen - Malignant melanoma. ? primary of lung ? regressed primary elsewhere.

Saul Suster – This is a very interesting case! Cesar Moran published the largest series on these tumors in Am J Surg Pathol (Wilson RW and Moran CA: Primary melanoma of the lung: a clinicopathologic and immunohistochemical study of 8 cases. Am J Surg Pathol 21:1196-1202, 1997). The problem involved in separating primary tumors from metastases was addressed in that paper. Short of demonstrating an in-situ component in the bronchial mucosa, all other arguments are debatable.

Ady Yosepovich - very nice case – thank you for sharing.

CASE NO. 13 – CONTRIBUTED BY THOMAS MENTZEL, M.D.:

Abbas Agaimy - A rare and very impressive difficult-to-diagnose case, probably often mistaken for some type of benign mesenchymal fibroblastic neoplasms, possibly perineuriomas and others. The neutrophils as a "clue" are helpful. A good example of "clinicopathologic diagnoses". Thanks for this teaching case.

Phil Allen - Tumor-like erythema elevatum diutinum, dermis of left heel. I thought this was a storiform collagenoma (plywood fibroma) until I read the history and the diagnosis. I memorized the name of this disease after reading about it in the textbooks about 50 years ago but was never shown a genuine case until now. Goodness knows how many I may have missed over the years. I can't see any vasculitis or eosinophils in this section. There is an illustration of a somewhat similar case on page 685 of the fourth edition of McKee's "Pathology of the Skin". Thanks very much for the contribution and the discussion.

David Ben-Dor - I thought that this was a keloid. The vasculitis is there if you look at the slide with required care. Very interesting and thought provoking.

Michele Bisceglia - Tumour-like erythema elevatum et diutinum. I looked at this case blind (as unknown) and I thought of a sort of extremely hypocellular sclerosing fibroma. Thank you, Thomas.

Ira Bleiweiss - ????? Too much Latin. I have always wondered why dermatopathologists love Latin so much (and I studied it for 5 years). Can any of the members explain this linguistic phenomenon?

Thomas Colby - Agree with diagnosis. A spectacular example of something that I will probably not recognize in the future.

Kumarasen Cooper - Thank you Thomas for this instructive case. I recall seeing the earlier lesions EEED (as a resident in Africa); but never realized that the late stage lesion could be so "tumoresque"!

Otto Dietze - Like many cases from Friedrichshafen, a "never seen before" lesion.

Hugo Dominguez-Malagon - Erythema elevatum diutinum, I had no idea.

Göran Elmberger - Very interesting and difficult. Several important concepts for a non-dermatopathologist– tumor like stage of inflammatory skin disorder and MPO as indicator of leukocytoclasis. Thanks.

Vincenzo Eusebi - Difficult case. Thank you, Thomas. After having looked at the slide several times, I think that your interpretation is the correct one.

Giovanni Falconieri - Impossible case Tom, that looked perineurioma or something spindle cell tumors of dermis exhibiting sclerosing qualities. I would never think about EED.

Franco Fedeli - Tumour-like erythema elevatum et diutinum. An incredible case: late stage erythema elevatum diutinum, in the absence of both vasculitis and granulocytes!

Cyril Fisher - Amazing fibrosis. Looks like sclerotic fibroma

Christopher D.M. Fletcher - I see one or two similar examples of erythema elevatum diutinum each year, because they are sent to me as some type of mesenchymal neoplasm. The focal, but usually readily recognized leukocytoclastic vasculitis as well as the multifocally prominent nuclear debris typically allow this distinction. The pathogenesis of this disorder still seems to be very obscure.

Andrew Folpe - From the "blind squirrel and acorn" file- we were thinking of a vasculitic process with sclerotic fibroma-like changes. That seems close enough!!!

Jerónimo Forteza - I did not know this entity. It is important to know it is one of the illnesses related to IgG-4.

Masaharu Fukunaga - Tumor-like erythema elevatum et diutinum. I have never seen or heard of it. It looks like a soft tissue tumor such as storiform collagenoma. Thank you for sharing the interesting case.

Thomas Krausz - This variant of erythema elevatum diutinum is new to me. Thank you very much Thomas for submitting and discussing this case.

Janez Lamovec - Thank you for teaching me something new.

Markku Miettinen - Being unfamiliar with this dermatologic entity I see features resembling sclerotic fibroma (sometimes associated with Cowden disease). Certainly this condition is at least "tumor-like".

Fredrik Petersson - Tumefactive vasculitis. The nuclear dust/karyorrhectic debris fairly obvious once you go high-power, an observation that, as you state, shifts the focus from a benign mesenchymal tumour ("sclerotic fibroma/ storiform collagenoma"). No identifiable vasculitis, but obvious vasculocentric neutrophilic infiltrate with swollen endothelium and extravasated RBCs in the periphery on my slide.

Juan Rosai - I would not have thought of erythema elevatum et diutinum in 100 years. Actually, I would like to ask a naive question, similar to the one I asked in connection with Case 9: why is this not a skin or soft tissue tumor in the fibroma family in a patient who happens to have erythema elevatum et diutinum. By the way, I would have liked to have at last ONE reference on EED to learn something about this mysterious disease.

Brian Rubin – Histologically looks like storiform collagenoma, which I regard as a non-specific pattern. Interesting that this pattern could be "end stage" erythema elevatum et diutinum.

Dominic Spagnolo - What a spectacular case! I'd like to say I picked it, but the diagnosis did not cross my conscious state. And I'm not having a scotch as I look at the cases. Thanks for the education.

Saul Suster – this is a new one for me! I thought it was another example of storiform collagenoma. Missed the vasculitis in my slide!

James A. Strauchen - Never heard of this one either! Thank you!

CASE NO. 14 – CONTRIBUTED BY ELIZABETH MONTGOMERY, M.D.:

Volkan Adsay - Believe it or not, all of our residents got the diagnosis on this one, because we had very recently shown a similar case in the gallbladder at our unknown conference. This example is so much more striking though. Thanks for a great example. The oncocytoid reactive epithelium is quite striking as well.

Abbas Agaimy - Very spectacular case, looks deceptively malignant, but the background argues against malignancy. More mitoses and more ugly-looking mitoses than expected for true neoplasia. Again a case for a telephone call. Thanks!

Phil Allen - Docetaxel associated mitotic arrest in gallbladder mucosa in a patient with widely disseminated metastatic prostatic carcinoma and ischaemic colitis. I assume that the surgeon somehow spotted the cholesterolosis, possibly with the assistance of a radiologist, and decided on a prophylactic cholecystectomy. I too recognised the cholesterolosis but missed everything else. I'll have to pay more attention to my gallbladders in the future.

David Ben-Dor - My admiration for those who looked carefully enough to observe the changes without prompting-chance favors the prepared observer! I think we've been given other examples of this phenomenon.

Michele Bisceglia - Taxane effect in cholecystectomy specimen. Interesting, especially if you couple this case with the other case (colchicine effect in a hyperplastic polyp) you contributed in Seminar #38.

Ira Bleiweiss - Wow. Bizarre. Thanks. I was unaware of this effect.

Thomas Colby - Agree with diagnosis. Beautiful case.

Kumarasen Cooper - Thank you Liz. I have seen colchicine effect in gastric biopsies; but this is phenomenal!

Otto Dietze - I do not remember having seen something similar.

Hugo Dominguez-Malagon - Taxane effect. The changes in the epithelium are spectacular, I also see similar changes (with ring mitoses) in stromal plump myofibroblasts, is it also a drug effect?

Göran Elmberger - Great case. Guess only clinical correlation and a high index of suspicion might save one from calling this lesion dysplastic. Mitoses without corresponding nuclear atypia and low N/C ratio…

Giovanni Falconieri - Another phenomenal and impossible case. Thank you for this extraordinary submission.

Franco Fedeli - Taxane effect in cholecystectomy specimen. Elizabeth I was so happy when I saw this slide. The diagnosis was immediate because it reminded me of a case you had shown in one of the courses organized by me in Tuscany.

Cyril Fisher - New to me, I would have missed the subtleties. Nice slide.

Christopher D.M. Fletcher - Very nice case – I had not seen changes such as this in the gallbladder before.

Andrew Folpe - I went down in flames ("high-grade dysplasia"). Very, very interesting case.

Jerónimo Forteza - It is interesting to know that taxane can cause epithelial dysplasia. In any case, the section shows inflammatory phenomena typical in gallstone cholecystitis. It must be difficult to differentiate between dysplasia caused by treatment and by cholecystitis.

Masaharu Fukunaga - I have never seen cases with taxane effect. Thank you very much for the interesting case and a nice concise discussion.

Thomas Krausz - Highly educational case.

Janez Lamovec - Another news for me. Thank you.

Thomas Mentzel - I`ve never seen (or ignored) these impressive morphological features.

Fredrik Petersson - Excellent case. Educational. Much more difficult than bladder biopsies with symptomatic (cystitis) patients on chemo. I guess a morphological clue to the diagnosis is, as you say, mitotic figures in the proliferative compartment in conjunction with maturation towards the surface. One wonders about the ischemic colitis - ?? *Taxane induced colitis. Colitis in patients with breast carcinoma treated with taxane-based chemotherapy. Li Z et al. Cancer. 2004 Oct 1;101(7):1508-13*

Juan Rosai - Spectacular case of taxane effect on the epithelium of the bladder mucosa. The number of mitotic figures, many of them atypical, is truly impressive. However, everything else, including the architecture, speaks of a benign process. So the lesson here is that mitoses do not mean necessarily cancer, even if there are many and even if they are atypical. I am reminded of a crack made by Malcolm MacGravan in the Skin chapter he wrote for an early edition of the Ackerman's Surgical Pathology book, in which he commented that *"the presence of mitotic figures, the favorite cytologic observation of neophytes, is of interest but rarely of diagnostic significance."*

Brian Rubin – Fascinating! Never heard of this before.

Dominic Spagnolo - Very stunning changes of Taxane effect on the gall bladder mucosa, which I have not seen before. I have only seen this in gut biopsies post-colchicine. Will see if my GI colleagues have seen this.

James A. Strauchen - Fascinating! Thank you!

Saul Suster – Spectacular case! Had never seen this and was not even aware of this association.

Ady Yosepovich - this is new for me, thank you for sharing this case and diagnosis.

CASE NO. 15 – CONTRIBUTED BY SANTIAGO RAMON Y CAJAL, M.D.:

Volkan Adsay - Thank you. Made us feel much better, after goofing badly with that granular cell tumor looking metastatic chondrosarcoma in the lung (case 5).

Abbas Agaimy - Nice and rare case of clear cell chondrosarcoma, agree, thanks.

Phil Allen - Clear cell chondrosarcoma, rib. This is the first case arising in a rib that I have seen.

David Ben-Dor - Nice case; never seen one before. Histologically looks pretty bad for what it is supposed to be, a relatively unaggressive lesion.

Michele Bisceglia - Clear cell chondrosarcoma. I agree with your diagnosis. Lots of reactive metaplastic bone (and focal reactive osteoid) which of course induces one to include chondroblastic osteosarcoma as a differential diagnosis.

Ira Bleiweiss - Agree. I haven't seen one of these in a very long time.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Santiago, I wondered what the radiology showed?

Otto Dietze - Convincing diagnosis, I know this tumor primarily from slide seminars.

Hugo Dominguez-Malagon - Clear cell chondrosarcoma, agree with the diagnosis.

Göran Elmberger - Interesting diagnostic points in differential against chondroblastic osteosarcoma.

Vincenzo Eusebi - I think there are too many osteoid areas to exclude a chondroblastic osteosarcoma.

Giovanni Falconieri - I do not have so much experience with bone tumors but I think I have recognized the diagnostic clues. Thank you, Santiago, for this submission.

Franco Fedeli - Clear cell chondrosarcoma. A rare tumor in an extremely uncommon location. I used to think of clear cell chondrosarcoma as a tumor of the proximal femur or humerus. On the contrary, after a quick search in the published literature I became aware of the other ten cases involving the ribs which have been described so far.

Cyril Fisher - Clear cell chondrosarcoma, lovely example. The bone formation would worry me.

Christopher D.M. Fletcher - Clear cell chondrosarcoma – the appearances of the associated osteoid are always somewhat unnerving !

Andrew Folpe - Agree. Very nice case- thanks.

Jerónimo Forteza - Some areas make me think about the possibility of a previous lesion or associated type of chondroblastoma or solid variant of ABC.

Masaharu Fukunaga - A beautiful case of clear cell chondrosarcoma. Thank you for sharing the case.

Thomas Krausz - Very nice example.

Janez Lamovec - Classical case of clear cell chondrosarcoma. We've seen some cases before; I contributed a case for AMR seminar No 4.

Thomas Mentzel - Many thanks for sharing this rare neoplasm!

Fredrik Petersson - Only read about so far. Great to see a case.

Juan Rosai - Very nice case of clear cell chondrosarcoma. This complements nicely case 5, in the sense that it is another demonstration of a cartilaginous tumor showing secondary change (granular cell in one and clear cell in the other) that are not the prerogative of a specific cell type but which may induce diagnostic misinterpretations when developing in unexpected places.

Brian Rubin – Gorgeous example of something I've actually seen before. Thanks!

Dominic Spagnolo - Agree with clear cell chondrosarcoma.

James A. Strauchen - Clear cell chondrosarcoma versus chondroblastic osteosarcoma.

Saul Suster – Beautiful example of clear cell chondrosarcoma! Many thanks for having shared it with us.

Ady Yosepovich - thank you for sharing this illustrative case.

CASE NO. 16 – CONTRIBUTED BY BRIAN RUBIN, M.D.:

Abbas Agaimy - Impressive and probably very rare case! As per my email, now I have a name for one case I received some months ago, for which I didn't have a ready name at that time except for calling it benign smooth muscle tumor with epithelioid/some plexiform and sex-cord like features. Both your and my cases were HMB45 and sex cord markers negative. Thanks Brian for this excellent contribution.

Phil Allen - Intravenous leiomyomatosis with plexiform tumorlet morphology. I understand that plexiform tumorlets of the uterus are histological variants of benign smooth muscle tumors. There is a good deal of vascular invasion in my slide.

David Ben-Dor - this entity was also discussed as a subset of epithelioid leiomyomas in the classical reference by Hendrickson and Kempson, volume 12 of the "Major Problems in Pathology" series. Anybody remember that? Much like refrigerators and TV sets, they don't make books like that anymore, in the sense of giving exhaustive treatment to histological details (similar to Azzopardi's book). That reference implies that these plexiform tumorlets form tumors or at least appear in the context of a leiomyoma; here the larger collections can be considered as tumorous. According to Hendrickson and Kempson, these are "typically located" at the endometrial-myometrial junction. Very nice case- thanks.

Michele Bisceglia - Multiple plexiform tumorlets of the uterus. Agree. Interesting. By instinct (dictated by the architectural pattern of this special type of multiple tumorlets) one might include in the differential diagnosis even low grade endometrial stromal sarcoma.

Ira Bleiweiss - Unique to me too.

Thomas Colby - Agree with diagnosis.

Kumarasen Cooper - Thank you Brian. Would you believe I just saw a case last week here at UPenn. I also saw one other case in the early 2000's in VT.

Otto Dietze - I agree, this is a unique case!

Hugo Dominguez-Malagon - Plexiform tumorlets, a collector slide, thanks.

Göran Elmberger - Intriguing pattern of distribution as you remark.

Vincenzo Eusebi - Multiple plexiform tumorlets of the uterus.

Giovanni Falconieri - This is unique, and impossible in my experience as well. Congratulations to your sharp eye. My pleasure to meet you in Tel Aviv last summer!

Franco Fedeli - Multiple plexiform tumorlets of the uterus. Beautiful case. Never seen the multiple variant of this tumor. Some authors include it in the spectrum of the uterine tumors resembling ovarian sex cord tumors. Since 1993 only six cases have been described (Seidman JD, Thomas RM: Multiple plexiform tumorlets of the uterus. Arch Pathol Lab Med 1993 Dec; 117:1255-6)

Cyril Fisher - Multiple plexiform tumorlets. Great slide.

Christopher D.M. Fletcher - The appearances indeed fit very well with multiple small epithelioid leiomyomas ('leiomyomatosis'). I find some of the more arcane terminology in our specialty difficult to understand or explain to residents.

Andrew Folpe - Plexiform tumorlets- nice example. Thanks.

Jerónimo Forteza - I did not know this entity. This is a very interesting case. Immunohistochemical study is necessary to characterize the nature of the cells and be able to address the case.

Masaharu Fukunaga - A beautiful case of multiple plexiform tumorlets of the uterus. My impression without immunostainings was low grade endometrial stroma sarcoma with ovarian sex-cord like features or uterine tumor resembling ovarian sex-cord tumor.

Ondrej Hes - This is fantastic case, I haven´t seen one similar. Just one question...is it possible to expect HMB45 positivity? In my eyes this case reminds me of epithelioid angiomyolipoma or PECOma.

Thomas Krausz - Extraordinary case. On H&E I was also considering low grade endometrial stromal sarcoma; provided CD10 is negative, I agree with the diagnosis. Some of the "nodules" appear intravascular. If intravascular is proven then "multiple plexiform tumorlet" might be considered within the spectrum of intravenous leiomyomatosis.

Thomas Mentzel – What a case, Brian, many thanks and I`ve never seen this before.

Fredrik Petersson - May apparently show vascular invasion: *Bucella D et al. Multiple epitheloid plexiform tumourlet leiomyoma of the uterus with focal vascular invasion. Eur J Gynaecol Oncol. 2010;31(4):443-5.* Given the growth pattern in the actual case, a DDX would perhaps be the epitheioid variant of intravascular leiomyomatosis ? - Clement PB, Young RH, Scully RE. Intravenous leiomyomatosis of the uterus. A clinicopathological analysis of 16 cases with unusual histologic features. Am J Surg Pathol. 1988 Dec;12(12):932-45.

Juan Rosai - Are these really multiple tumorlets of the uterus or is this a case of UTROSTCT? I would go for the latter because of the extent of the disease. Actually, I suspect that the uterine tumorlet is the "bonsai" form (to paraphrase Sobrinho Simoes) of a UTROSTCT, just as a <1cm thyroid micropapillary carcinoma is a bonsai form of a grown up papillary carcinoma, and a pulmonary tumorlet is a bonsai form of a neuroendocrine tumor in the carcinoid family.

Dominic Spagnolo - Beautiful example of multiple uterine plexiform tumorlets.

James A. Strauchen -? stromal nodules with sex cord differentiation.

Saul Suster – This is a beautiful slide to look at – striking plexiform pattern! Have no opinion regarding histo-pathogenesis in this case (merely out of ignorance – my interest/expertise in GYN pathology continues to decrease as I age….).

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

CASE NO. 17 – CONTRIBUTED BY DOMINIC SPAGNOLO, M.D.:

Volkan Adsay - Great case. Our residents were very impressed when I came up with the first 2 diagnoses quite rapidly (thanks to the consult cases I had seen with Dr. Rosai during my fellowship). But then I spent 10 minutes trying to figure out the third component whether it was some sort of low-grade malignant lymphoma associated with it, for which I think "infiltrate of immature thymic T cells" is a great diagnosis. What a case.

Phil Allen - Recurrent follicular dendritic cell sarcoma infiltrated by immature thymic T-cells and arising in hyaline vascular Castleman's disease, right parapharyngeal region. If the late Ben Castleman could only see this case and the discussion, I have no doubt he would ask permission to slip it into the New England Journal of Medicine as a case from the records of the Massachusetts General Hospital.

Abbas Agaimy - A further documentation of FDCS in HV Castleman disease with immature thymic T-cells, quite challenging findings, thanks for this beautiful case.

David Ben-Dor - Great case Dominic- thanks for sharing it. The presence of immature thymic lymphocytes in Castleman disease- didn't know this. Another example of data which is available due to modern technologies (i.e. immunohistochemistry) but which we don't have any idea what their significance is.

Michele Bisceglia - Follicular dendritic cell sarcoma, recurrent, arising in hyaline-vascular Castleman disease and containing an infiltrate of immature thymic T cells. Thank you very much, Dominic, for this detailed description. I looked at this case as a teaching case contributed by a real expert in hematopathology and I could recognize every component of the tumor and indeed I learned a lot!

Thomas Colby - Agree with diagnosis. Complicated case. There is a good reason that they don't let me do hematopathology anymore.

Kumarasen Cooper - FDC sarcomas also express EGFR; hence the potential role for cetuximab as targeted therapy is being investigated (Clin Cancer Res. 2013 Sep 15;19(18):5027-38).

Otto Dietze - A perfect teaching case, case history, discussion and slide.

Hugo Dominguez-Malagon - FDCS, beautiful case and discussion.

Göran Elmberger - Great with a haematological case in the seminar. Interesting disguise.

Vincenzo Eusebi - I agree on principle on whatever Dominic states. Nevertheless, I would have never made the diagnosis of follicular dendritic cell sarcoma in hyaline vascular Castleman's disease without seeing the latter features that are not well represented in my slide.

Giovanni Falconieri - Very difficult case Dom. I cannot comment, never seen before. And whenever I have seen it, I have for surely not recognized!

Franco Fedeli - Follicular dendritic cell sarcoma, recurrent, arising in hyaline-vascular Castleman disease and containing an infiltrate of immature thymic T cells. Nice description, complemented by helpful and demonstrative illustrations. Very interesting.

Cyril Fisher - FDCS in Castleman's fantastic case, thanks Dom

Christopher D.M. Fletcher - This is indeed a weird and remarkable case. The cytomorphology and illustrated immunophenotype are certainly convincing for FDC sarcoma, but I have not personally encountered such a case in the past with such a massive T cell infiltrate. Given the lack of any clear biologic reason for such an occurrence, I agree that one would always want to exclude the possibility of some kind of T cell lymphoma before making this final diagnosis. This is a very educational case, at least for me.

Andrew Folpe - Fascinating case and great write-up.

Jerónimo Forteza - We must not forget that Castleman is also an illness of dendritic cells. This explains the spectrum between Castleman illness and dendritic cells in follicular lymphoma.

Masaharu Fukunaga - An extraordinary case!!. It is very tough case. Initially it seemed to represent reactive changes. Thank you very much for the wonderful case and grade discussions, Dominic.

Thomas Krausz - I agree, this is an extraordinary example of follicular dendritic cell sarcoma. Thank you very much for the highly educational discussion.

Janez Lamovec - A very complex lymphoproliferative lesion demanding a lot of expertise. Thank you for this case and comment.

Thomas Mentzel - Great case, many thanks!

Markku Miettinen Agree on dendritic reticulum cell sarcoma. Castleman is no longer so obvious as the dendritic cell proliferation is taking over.

Fredrik Petersson - Very good case. Nice work-up and discussion!

Juan Rosai - Spectacular demonstration of a reticular/dendritic cell tumor arising in Castleman disease. To me, the most interesting aspect of the case is the "in situ" or "dysplastic" component of the tumor, represented by the isolated reticular/dendritic cells within the Castleman nodules.

Brian Rubin - Fantastic case.

James A. Strauchen - FDCT in hyaline-vascular CD. Very nice case!

Saul Suster – Spectacular case! Agree with FDCT; I wish we could have received the sections in which the Castleman disease is convincingly demonstrated! This case illustrates why the Creator created hematopathologists – without the fancy immunophenotyping, who would have thought there were immature thymic T-cells in this node?

CASE NO. 18 – CONTRIBUTED BY PAUL WAKELY, JR., M.D.:

Volkan Adsay - Great case.

Abbas Agaimy - Very unusual and misleading histology at uncommon location, thanks much for contributing this nice teaching case.

Phil Allen - Epithelioid variant of pleomorphic liposarcoma, mesentery and pelvic retroperitoneum. I had no trouble spotting the lipoblasts but from time to time, I have seen histologically identical "lipoblasts" in hepatocellular and adrenocortical carcinomas. In my opinion, the lack of a primary in any other site but the mesentery and retroperitoneum is of more help than the immunohistochemistry. Will the molecular or genetic studies of this tumour established that it is nothing more than a dedifferentiated retroperitoneal lipoma-like liposarcoma?

David Ben-Dor - Yes there are fat cells and a few tumor cells containing fat droplets. My problem is in deciding whether they're part of the tumor or adipose cells with degenerative changes secondary to the tumor infiltrating into fat from the outside. The crux of the issue is "thinking of the diagnostic possibility" in the first place- the key to success.

Michele Bisceglia - Pleomorphic liposarcoma, epithelioid variant. Paul, I am pleased to hear that nobody diagnosed this case of yours when you presented it as unknown in an "evening seminar". In fact in 2007/2008 you also presented this case in Udine (Italy) in a different context (it was an "afternoon slide seminar" there), but the results were the same: nobody made the correct diagnosis, and I personally proposed from the audience the possible and similarly wrong diagnosis of adrenocortical carcinoma.

Ira Bleiweiss - I thought it could be adrenal carcinoma.

Thomas Colby - Agree with diagnosis. I hope that I would think of this the next time I run into this histology.

Kumarasen Cooper - Thanks Paul. I saw an example in the mediastinum here at UPenn in a patient with a history of radiation for thyroid carcinoma.

Otto Dietze - I agree that the identification of lipoblasts is the only way to get this correct diagnosis, as the staining to my opinion is not very helpful.

Hugo Dominguez-Malagon - Epithelioid pleomorphic liposarcoma. Completely agree with the diagnosis, the cases I have seen are also positive for CK8 and CK18.

Göran Elmberger - Not the first diagnosis one thinks of but as you say, lipoblasts are there. Unusual variant. Thanks for reminding.

Vincenzo Eusebi - Thank you very much for this pleomorphic liposarcoma, epithelioid variant. Fortunately, at the edge of my slide there were atypical looking lipoblasts.

Giovanni Falconieri - Nice case Paul. Reminds me of a similar case that Saul presented at the AMR in Istanbul in 2010. By the way, thank you again for coming to Italy last week. You have done a great job and your handout on thyroid cytopathology is now on each fellows' desk at my department. An essential and valuable source of practical information!

Franco Fedeli - Pleomorphic liposarcoma, epithelioid variant. Surely this case is epithelioid.
Since I read your description, I have been hunting for lipoblasts and I succeeded in finding a few of them though very focally.

Cyril Fisher - Excellent diagnosis. This is really difficult especially given the rare intracavitary location.

Christopher D.M. Fletcher - Beautiful example of the epithelioid variant of pleomorphic liposarcoma. Indeed, at least in my experience, these lesions are most often mistaken for metastasis from an adrenocortical or renal cell carcinoma. The morphologic overlap is very striking.

Andrew Folpe - Lovely example.

Jerónimo Forteza - This is a difficult case to diagnose since morphology is confusing and lipoblasts cannot be easily seen.

Masaharu Fukunaga - Pleomorphic liposarcoma, epithelioid variant. A beautiful case; thank you, Paul.

Thomas Krausz - Yes, this is virtually always a diagnostic challenge and most pathologists usually consider carcinoma first. Also, in my opinion, it is not easy to distinguish lipoblasts from lipid containing vacuolated cells of an adrenocortical carcinoma.

Janez Lamovec - Well, Paul, this appears quite fancy to me. We see quite a number of liposarcomas here but have never encountered a case like this!

Thomas Mentzel - Many thanks for this wonderful example of a rare variant of pleomorphic liposarcoma mimicking features of carcinoma.

Markku Miettinen: I also like this for an epithelioid variant of pleomorphic liposarcoma. An interesting (? unanswered) question is whether this could be related to dedifferentiated liposarcoma so that MDM2 studies would be of interest.

Fredrik Petersson - Same thought process here. Initially adrenocortical carcinoma. Pleomorphic epithelioid sarcoma 2nd. Immunowise (ppp) = potential painful PITFALL. Patchy CK-positivity (and EMA - *Fukunaga M, Nomura K. Pathol Res Pract. 2004; 200(7-8):545-9*).

Found one case with FUS-CHOP transcript. (*De Cecco L et al. Gene expression profile identifies a rare epithelioid variant case of pleomorphic liposarcoma carrying FUS-CHOP transcript Histopathology. 2005 Mar;46(3):334-41*). Any more genetic info on this entity ??

Juan Rosai - Another spectacular case of clear cell change, which complements nicely the clear cell osteosarcoma of case 5.

Brian Rubin - Really interesting case. Fits well with the epithelioid variant of pleomorphic LPS.

Dominic Spagnolo - Can never see too many of these epithelioid pleomorphic liposarcomas, as the potential for misdiagnosis is so great. Thanks for the case.

James A. Strauchen - Would have missed this! Thank you!

Saul Suster – Wonderful example – thank you Paul for this contribution. The cases I've seen previously did show, at least focally, nuclear positivity for MDM2 by IHC. Fortunately, in the cases I've seen before, cytokeratins were negative, forcing us to rethink the differential diagnosis and consider other possibilities. We owe the recognition of this entity to our good friend and colleague, Markku Miettinen, who was the first to describe this tumor together with Dr. Enzinger (Mod Pathol 12:722-728, 1999), and all this without the aid of molecular pathology! Kudos!

Ady Yosepovich - very illustrative case – thank you for sharing.