COMMENTS TO AMR SEMINAR #56

CASE NO. 1 – CONTRIBUTED BY VOLKAN ADSAY:

Phil Allen: Invasive, poorly differentiated medullary-type carcinoma of the pancreatic head arising in the ampulla. A convincing case. I had never heard of it before.

Carlos Bacchi: In the slide I received, part of the tumor shows glandular lumens. Would that be fine for the diagnosis of medullary-like carcinoma? As we know, at least in the breast, the presence of ductal formation rules out the diagnosis of medullary carcinoma.

David Ben-Dor: Medullary carcinoma is one of those unicorns which I've never seen (at least in the breast). At a breast pathology update conference held fairly recently which I attended, I was informed (or thought I was informed) that medullary carcinoma in the breast is grouped with the triple negative tumors on immunohistochemical grounds, though the prognosis of the former is supposed to be better than for average breast carcinomas (as it is in the colon and pancreas, according to the submitted comments) while the latter are very aggressive. I never figured that one out. As for the histology in this case, in some places I think there are glandular features (if only vague).

Michele Bisceglia: Invasive poorly differentiated medullary-type carcinoma, arising in the ampulla. Nice case and very interesting observations. I have never seen one before. Two considerations: the first one is that – in consequence of the MSI pathway involvement –one would expect one such case be reported arising in the context of Muir-Torre syndrome; the other one is that *medullary-type* carcinoma expands the spectrum of carcinomas arising in the ampulla or periampullary region, aside the more common intestinal-type adenocarcinoma, signet-ring-cell carcinoma (Hepatogastroenterology. 2002; 49:561-3), large cell neuroendocrine carcinoma (J Clin Pathol. 2004; 57:1098-100), glandular-type carcinoid (somatostatinoma in von Recklinghausen patients), adenocarcinoid (Am Surg. 1998;64:355-9), and collision tumor of carcinoid and adenocarcinoma (Rev Esp Enferm Dig. 2007; 99:235-8).

Ira Bleiweiss: Interesting case. I've never heard of this. This is certainly carcinoma and has neuroendocrine features at least on H+E, but I personally don't really see the resemblance to medullary breast carcinoma, except for the inflammatory reaction.

Tom Colby: Agree with diagnosis; favored a poorly differentiated acinar cell carcinoma on the H & E. This is the first medullary carcinoma of the pancreas I have seen; there does appear to be some acinar/glandular-type differentiation.

Kum Cooper: Thank you. It was just a matter of time before the "mutator pathway" carcinomas are/were to be identified in the pancreas. I have only seen this morphology in the cecum!

Ivan Damjanov: Agree. Clinical and immunohistochemistry data support your diagnosis. Unusual location.

Otto Dietze: Convincing diagnosis, I did not see one in this region before.

Hugo Dominguez-Malagon: Medullary carcinoma of the ampulla, (or lymphoepithelial carcinoma?), interesting discussion, thank you.

Göran Elmberger: Nice case of recently described entity. It's interesting to note that tumors with similar activated molecular pathways (RER+) look similar in different organs. I guess it's a matter of time before we recognize rare variants of "medullary-type" carcinomas in most organs. By the way why not just "medullary carcinoma"?

Vincenzo Eusebi: To me, this case looks like poorly differentiated carcinoma with some lymphoid stroma. It has no features reminiscent of medullary carcinoma of the breast or of the basaloid carcinoma of pancreas.

Giovanni Falconieri: Great case, Volkan. My first idea was of a lymphoepithelioma or something like that. Yet, I have no experience with this topic. In any case, "medullary" carcinoma is appealing! Did you stain it for HLA-DR? By the way, thank you for taking the burden of organizing the next AMR seminar in Turkey next June. I look forward to the meeting.

Cyril Fisher: Medullary carcinoma of pancreas. I have not seen this before, most interesting - thank you.

Christopher Fletcher: Entirely convincing example of medullary-type carcinoma at an exceptional location which I have not personally encountered before – this is a most educational case.

Jerónimo Forteza Vila: I agree with the diagnosis. I guess that metastatic breast cancer should be considered.

Masaharu Fukunaga: I have never seen medullary carcinoma in this region. Thank you very much for the concise and clear-cut description, Volkan,

Allen Gown: Nice case, Volkan. I presume that loss of MSH6 accompanied MS2, which is almost always the case. I wonder if you looked for expression of GI tract markers such as CDX2; often in such tumors arising in the colon, there is marked reduction of CDX2 expression.

Thomas Krausz: Agree with diagnosis, but before reading the diagnosis/discussion, I was considering a poorly differentiated acinic cell carcinoma.

Janez Lamovec: We saw a number of such tumors in the stomach but called them lymphoepithelioma-like carcinoma. It is still unclear to me what is the difference between the latter and medullary carcinoma although certain histological distinctions have been pointed out; they do not appear so clearly defined to enable the easy distinction between the two.

Thomas Mentzel: Many thanks for sharing this example of a rare and newly described entity. Did the neoplastic cells express CDX-2?

Markku Miettinen: Solid, medullary carcinoma of pancreas.

Liz Montgomery: Volkan, this is a really pretty medullary carcinoma with tumor-infiltrating lymphocytes [TILs] to die for. Thanks.

Santiago Ramon y Cajal: It is interesting to see how this invasive carcinoma has pushing borders and seems to spare the pancreatic tissue. My first impression was of acinar carcinoma or neuroendocrine carcinoma.

Juan Rosai: Very nice case. I considered acinar cell carcinoma in my differential diagnosis, but apparently there were no zymogen granules by electron microscopy and the trypsin stain was negative. It would still be interesting to perform the new stain for BCL 10 recommended by Prof. Capella at the University of Varese, which he claims is very specific for acinar cells.

Dominic Spagnolo: Ampullary undifferentiated (medullary) carcinoma with loss of MSH2. Any evidence of Lynch syndrome? There is some discordance in the MLH1 and MSH2 status in the description vs comments sections. There was a nice series of ampullary carcinomas and MSI in AJSP of May this year. Most of the MSI-high cases showed loss of MLH1 or promoter methylation. Two cases showed both MSH2 and MSH6 loss. Thanks for the case.

James Strauchen: Poorly differentiated adenocarcinoma. I was unaware of medullary CA in the GI tract. Thank you!

Larry Weiss: Nice case. One always needs to think about genetic predilection in patients as young as this. Was the MSI analysis done?

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

Phil Allen: Lymphadenoma adherent to right parotid salivary gland. I think this corresponds pretty well with the three cases in John Chan's 2002 Histopathology paper. I have no previous experience with this

entity. Dr Svante Orell, the last author of that paper, worked here at Flinders full time for many years until moving part-time to Clinpath Laboratories. He has now completely retired but occasionally drops in. I'll show him this case the next time he is here.

Carlos Bacchi: Lymphoepithelial sialadenitis.

David Ben-Dor: I have to admit that I started looking at the slide and in the instant before I realized it was my case, I said to myself "this looks like carcinoma"! I'll be anxiously awaiting the considered judgments of the other members.

Michele Bisceglia: ?Metastasis from occult nasopharyngeal tumor or ?tumor of parotid or ?intraparotid lymph node or ?lymphoepithelial lesion (presenting as a nodular mass) or ?lymphadenoma (non sebaceous type). To be honest, I did not think of a malignant metastatic carcinoma, although after all your considerations I obviously would suggest to look into the rhinopharynx (due to some visible mitoses and mild atypias). However, I would favor lymphadenoma diagnosis either in the parotid or in a parotid lymph node (few minute duct lumina are seemingly noted). Parenthetically and rightly also in my case of 1998, some members I think expressed concern about metastatic carcinoma: however, the patient is currently ANED.

Ira Bleiweiss: I think this is benign and most consistent with benign lymphoepithelial lesion. Maybe it "fell out" of the parotid.

Tom Colby: Benign lymphoepithelial lesion in the generic sense/myoepithelial sialadenitis. I favor this lesion being benign but not a metastasis. I am not sure what the precise name is. Over 20 years ago, I wrote up 2 of these (and still have the slides in my files), but I can't remember what I called them and those files are long since discarded. Needless to say, the manuscript was rejected (can't remember which journal I sent it to), and I didn't pursue it. It was turned down because the reviewer thought that the cases were metastatic NPC's, despite the long clinical history prior to removal and relatively long follow-up for both cases following removal.

Kum Cooper: Thank you, David, for the great differential and discussion. I considered this to be an atypical MESA (myoepithelial sialadenitis). I would be more concerned with the potential evolution to marginal zone lymphoma. The role of heavy chain gene rearrangements has been recommended in the past with terms like "C-DUMP" being proposed (Quintana et al. Hum Pathol) in the presence of a clonal population; but ultimately it is the morphology which will clinch the diagnosis if it does evolve into a MALT lymphoma.

Ivan Damjanov: My gut feeling is that this is not malignant and would sign it out as lymphoepithelial lesion. Follow-up could teach us more.

Otto Dietze: The long duration is unusual for a metastasis and my first choice would be a lymphoepithelial lesion.

Hugo Dominguez-Malagon: It looks to me like a benign lymphoepithelial lesion, I am not sure if the lymphoid tissue is an intraparotideal lymph node. Another consideration would be a primary lymphoepithelial carcinoma of salivary gland (skimoma), but the epithelial component looks benign to me.

Göran Elmberger: I appreciate your diagnostic considerations and get some déjà vu feelings from my own old cases. Have no clear opinion on this. I really don't believe in metastasis from NPH ca or elsewhere. Too little atypia. However, an EBER test and an UAT endoscopy would not hurt. Ad 2. This is, in my experience, almost impossible to sort out. Have seen mucoepidermoid carcinomas in what was considered to be lymph node metastases when no primary tumor was found at parotidectomy twice... TALP reaction can almost perfectly imitate a lymph node... Since epithelial ectopic (?) SG tissue is often found within lymph nodes in parotid area emergence of SG tumors from these intranodal epithelial rests could be conceived. Fortunately this matter is probably of academic interest in a situation like this when an benign tumor is the most probable dx. Ad 3. Again hard question. LESA can be unilateral and focal. Only 50 % associated with systemic disease (Sjögren). The LEL is quite characteristic in the present case and that might swing me in this interpretative direction. Any evidence for myoepithelial differentiation on extended IHC? (SMMS1, Calponin, Actin etc). Non-sebaceous lymphadenoma very unusual and the few cases I have seen have not had the LESA morphology. Focal tumefactive LESA/LEL???

Vincenzo Eusebi: This case is very impressive. I would regard it as a benign so called lymphoepithelial lesion within a lymph node. In spite of the name no evidence of myoepithelium has ever been found.

Giovanni Falconieri: My slide is fine, David, yet I am not able to dispel further your doubts. I am a little bit more inclined toward a lymphoepithelial lesion of the salivary gland, however, it does not differ so much from the sebaceous lymphadenoma case that Michele submitted to the AMR 38 (case 4). I shall look forward to reading the Head & Neck experts' opinions.

Cyril Fisher: I am not convinced this represents metastatic carcinoma.

Christopher Fletcher: One can make an almost equally strong case for each of the three proposed diagnoses – a benign lymphoepithelial lesion, sebaceous lymphadenoma with minimal sebaceous differentiation or metastasis from a nasopharyngeal primary. Personally, I cannot think of an objective way to make this distinction and I look forward to being educated by the head and neck experts.

Jerónimo Forteza Vila: In my opinion it is a lymphoepithelial lesion.

Masaharu Fukunaga: Very difficult case. Thank you very much for the discussion. The lesion seems to be benign, epithelioid granulomatous lesion despite keratin positivity.

Allen Gown: From your description of the immunophenotype, with an 'incomplete' pattern of p63 expression, in this histologic context, I wonder if this is a malignant salivary gland tumor. I wonder if you looked for expression of some other salivary gland markers such as GCDFP-15.

Thomas Krausz: I favor benign lymphoepithelial lesion.

Janez Lamovec: I don't think that this is a metastatic nasopharyngeal carcinoma and would rather call it some kind of lymphadenoma. I could not find a single mitosis of the epithelial cell that shows some degree of immature squamous metaplasia.

Thomas Mentzel: I`m afraid that it will be very difficult or even impossible to distinguish reliably a rare and unusual lymphoepithelial lesion arising in a lymph node from diffusely distributed nodal metastatic deposits of an unknown primary tumour. Although the epithelioid cells look for me slightly atypical their distribution is very unusual for metastatic deposits. Please let us know if possible what happened to the patient to solve this diagnostic problem.

Michal Michal: I think that the tumor is not any type of lymphadenoma. In case the follow-up would confirm absence of metastasis from nasopharyngeal origin, I would diagnose it as a undifferentiated carcinoma of the parotid gland (sometimes called as "Eskimo tumor").

Markku Miettinen: Autoimmune sialadenitis, cannot rule out low-grade marginal zone lymphoma.

Liz Montgomery: Calling this lesion "lymphadenoma" seems perfect to a non-scholar in this area.

Santiago Ramon y Cajal: According to her medical history (the lesion has been there for years), and the fact that the atypia is focal and seems to be part of a continuum including clearly reactive epithelium, I would lean towards a benign process. I would call it a non-sebaceous lymphadenoma, probably with an important component of myoepithelial cells.

Juan Rosai: It seems to me that this lesion has lots of very florid but benign-looking so called epithelial-myoepithelial islands (a misnomer), and I would have, therefore, considered the possibility of Sjögren's disease as a manifestation of a MALT-type lymphoma.

Dominic Spagnolo: Fascinating case David. I had difficulty in deciding whether this is a node or not, in the end agree most likely is lymph node. That aside, it shows features consistent with lymphadenoma (in all respects otherwise looks like lymphoepithelial sialadenitis), ostensibly arising in a periparotid node. I don' think it is malignant morphologically and the history too would seem inappropriate for a metastatic NPC. Look forward to the opinions of the experts.

James Strauchen: Lymph node with florid proliferation of epimyoepithelial islands. This seems to be a lymph node with a well defined subcapsular sinus. I would not have favor lymphadenoma, sebaceous or

otherwise. The epimyoepithelial islands appear much better differentiated than in a lymphoepithelioma. I tend to agree with your original impression of a lymphoepithelial lesion arising in a lymph node!

Saul Suster: Looks like a standard benign lymphoepithelial lesion of Goodwin. The pattern of distribution is not that of a metastatic carcinoma to lymph node. The exact term applied to the lesion is not so important, so long as you do not make the mistake of calling it malignant.

Larry Weiss: I would like to see the immunostains, but I favor a low-grade MALToma, with benign lymphoepithelial islands. Kappa-lambda studies may be all you need to confirm it.

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

Phil Allen: Undiagnosed foamy cell lesion with lipoblast-like cells, left lung, Rosai-Dorfman disease to be excluded. I don't remember seeing another lesion just like this but it reminds me of Rosai-Dorfman disease. Has an S100 stain been performed?

Carlos Bacchi: Considering the presence of the spindle cell population and the findings of similar or identical morphological features throughout the lesion, I would think that this lesion is clonal (neoplastic). I believe I have seen one case of atypical fibroxanthoma in the skin with some areas very similar to this lesion but not a tumor/lesion exactly like this one. No idea about biological behavior.

David Ben-Dor: there is a biblical saying whose exact phrasing I forget, but goes something to the effect of "if the mighty cedars of Lebanon are smitten, what will the moss on the walls do?" (forgive any bowdlerizing). So if Drs. Fletcher and Colby are clueless what can I add? However, there are foci which look like they're infiltrated by neutrophils. Could this be a form of xanthomatous lobar pneumonia? I admit the immuno results would be against that. The nuclei of the large foamy cells are not uniformly pleomorphic- some are smaller and more regular. It would be very interesting to know how the boy is faring.

Michele Bisceglia: We could not render a definite diagnosis. I do not know what it is either, but I feel would have called this case as you did.

Ira Bleiweiss: I suspect this is benign and reactive, composed of xanthoma cells, although the peripheral spindle cell component is curious. Is there any history of inhaling anything (intentionally or unintentionally)?

Tom Colby: Still don't know what this is. Look forward to the thoughts of others.

Kum Cooper: Wow, if Fletcher and Colby have not seen such a case where does it leave mere mortals like myself? Sorry, I have no meaningful contribution!

Ivan Damjanov: My feeling is that this is an inflammatory pseudotumor. Any follow-up?

Otto Dietze: I did not see anything similar before; xanthomatous inflammatory pseudotumor seems to me a good diagnosis and believe that it is low-grade malignant.

Hugo Dominguez-Malagon: No idea. Before I read the discussion, I thought the tumor was a PEComa or perhaps a rhabdomyoma.

Göran Elmberger: Intriguing case. Unfortunately, I have not seen anything like that. Not sure whether reactive or neoplastic even if large size and focal presentation might indicate neoplasia. Unusual lipidized variant of pulmonary fibrous histiocytoma? Fibrous histiocytoma variant of inflammatory pseudotumor?? Reactive fibrohistiocytic tumor secondary to infection??? Remember unusual case of "benign metastatic fibrous histiocytoma" but that case had multiple lesions and a skin primary. Nothing else remarkable on skin or on metabolic screening? No hereditary or familial clues? Sorry for not being very helpful.

Giovanni Falconieri: What to say or comment after such accountable opinions rendered by three giants of surgical pathology? By the way this is an extraordinary and terrific case, and you may think of reporting it especially if you get adequate follow-up information.

Cyril Fisher: Not seen this before.

Christopher Fletcher: I am glad to hear that Tom Colby had the same difficulties as me with this case. Since the large polygonal/epithelioid cells are not histiocytic in nature (at least by our immunostains), I have difficulty in imagining that this lesion is anything other than neoplastic, although the biologic potential cannot be predicted reliably.

Jerónimo Forteza Vila: It does not look like a neoplastic lesion. Some molecular study should be performed to exclude monoclonality.

Masaharu Fukunaga: It is very interesting and I assume that it is benign or borderline tumor. I have never seen this type of lesion. A few 'lipoblast-like cells' are observed. Thank you very much for the contribution.

Allen Gown: Have never seen anything like this! I like Chris Fletcher's characterization as "unclassified epithelioid and spindle cell neoplasm with pseudoxanthomatous features".

Thomas Krausz: I think this is a neoplasm but I also have problem classifying it. I think the large cells represent lipidized forms of the spindle cells. I would suggest doing more immunohistochemistry to exclude a peculiar variant of a hibernoma and angiomyolipoma. Other crazy thoughts: lipidized spindle cell carcinoid/paraganglioma, undescribed lipidized variant of alveolar soft part sarcoma.

Janez Lamovec: I think that this is a neoplasm, possibly malignant but wouldn't dare to add anything else.

Thomas Mentzel: I`ve never seen a lesion like this, but given the morphological features of the spindled cells in the periphery I suspect that we are dealing with true neoplasm undergoing prominent xanthomatous (degenerative) changes.

Michal Michal: I think that the spindle cell component is neoplastic. Maybe the "inflammatory myofibroblastic tumor" would fit the best as the nature of the tumor.

Markku Miettinen: A balloon cell neoplasm with a spindle cell component, of uncertain, primitive mesenchymal cell histogenesis, potentially low-grade malignant.

Liz Montgomery: Goodness! This looks like it should be a neoplasm, and I suspect it is benign BUT not really sure so would have also suggested assurance of a complete excision.

Santiago Ramon y Cajal: I think it´s a neoplasia but I do not feel sure. In any case is a lesion of very low or undetermined biological potential, Moreover, the immunohistochemical profile is not clear.

Juan Rosai: I think that the cells of this pulmonary lesion cells are mainly of xanthomatous type, associated with others having a histiocytic (or fibrohistiocytic) appearance. I have seen a very similar intrabronchial lesion in the lung of a 52-year-old patient over 10 years ago that I called fibroxanthoma, and which I thought was unrelated to so-called inflammatory myofibroblastic tumor. As far as I know, the patient is still alive and well.

Dominic Spagnolo: I don't recognize this lesion. I think it is a neoplasm, and given the degree of pleomorphism and some mitotic activity would consider it of uncertain malignant potential. Given the reproducible EMA positivity in 2 labs, is the possibility of an ectopic xanthomatous atypical/malignant/anaplastic meningioma out of the question? Any EM done?

James Strauchen: I think this is convincingly a neoplasm. At first, I thought these cells were mucinous and without reading the history, considered an unusual mucinous adenocarcinoma. With the realization that they are xanthomatous and given the spindle cell component, I would have considered an unusually xanthomatized fibrous histiocytoma.

Saul Suster: I certainly don't know what this is either. At first I thought of a storage disorder (like Gaucher) but the cells are not histiocytic according to the markers. If this is a neoplasm, the closest match I can think of is a rhabdomyoma, but again, no support for this from the marker studies. In fact, the results of the markers don't make any sense at all. I guess this case is going to remain a mystery until we get the next one like this.

Larry Weiss: Although I have never seen anything like this, I favor a benign, reactive proliferation of histiocytes.

CASE NO. 4 – CONTRIBUTED BY GERALD BERRY:

Phil Allen: Anaplastic large cell lymphoma arising adjacent to a right breast implant. Bionic medicine is becoming more and more dangerous, what with prosthetic sarcomas, injection site angiosarcomas, desmoids at ventricular shunt sites and now, breast implant lymphomas.

Carlos Bacchi: Nice case. It seems that ALCL developing in the proximity of the breast implant is related to only one specific type of implant. I know there are some studies being performed in US in order to confirm this relationship.

David Ben-Dor: Will the concern about autoimmune disease developing in patients with breast implants be replaced with concern over lymphomas? To my probably untutored eye this doesn't look much different histologically than any other large diffuse B cell lymphoma. The two anaplastic large cell lymphomas that have crossed my path in recent years were also ALK negative- I wonder if this is anecdotal or if it's becoming more common as more and more cases accrue.

Michele Bisceglia: Interesting case. What was the EMA staining like? I do not know how many ALC lymphomas have been described in the breast so far outside the clinical setting of breast implant, however it seems of very low incidence (11 cases in The Netherlands in 17 years- De Jong et al JAMA 2008). Going through the literature after the 2 papers Gerry quoted, 3 other papers were published (2008-2009***) with 21 cases so far described (Miranda et al APLM 2009). ALCLs of the breast have been seen both in relation to silicone breast implant and in relation to saline filled breast implant (Bishara et al Diagn Pathol 2009). In conclusion, an association of ALCL of breast and breast implant has to be admitted. *** Additional refs from 2008-2009. Refs de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbé E, Casparie MK, van Leeuwen FE. Anaplastic large-cell lymphoma in women with breast implants. JAMA. 2008 Nov 5;300(17):2030-5. Newman MK, Zemmel NJ, Bandak AZ, Kaplan BJ. Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature. J Plast Reconstr Aesthet Surg. 2008 Jul;61(7):822-5. Epub 2007 May 16. Miranda RN, Lin L, Talwalkar SS, Manning JT, Medeiros LJ. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. Arch Pathol Lab Med. 2009 Sep;133(9):1383-90. Bishara MR, Ross C, Sur M. Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: an unusual case presentation. Diagn Pathol. 2009 Apr 2;4:11. Refs from before 2006 were brought to light as well: Sahoo S, Rosen PP, Feddersen RM, Viswanatha DS, Clark DA, Chadburn A. Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature. Arch Pathol Lab Med. 2003 Mar;127(3):e115-8. Gaudet G, Friedberg JW, Weng A, Pinkus GS, Freedman AS. Breast lymphoma associated with breast implants: two case-reports and a review of the literature. Leuk Lymphoma. 2002 Jan;43(1):115-9).

Ira Bleiweiss: Agree. I've seen this a couple of times. I doubt that there is any cause and effect.

Thomas Colby: Agree with diagnosis.

Kum Cooper: ALCL. Agree, and another more recent reference is in Arch Pathol 2009; 133(9): 1383, with 6 more cases documented.

Ivan Damjanov: Agree. I think that the link to the breast implant is just coincidental, despite your references. Follow- up would be appreciated.

Otto Dietze: I agree; quite unusual presentation.

Hugo Dominguez-Malagon: Beautiful case of anaplastic lymphoma, no experience with association to breast implants.

Göran Elmberger: Thanks for pointing out this to me - new potential coupling of ALCL and silicone implants. It is not the first thing that comes to mind but given the results of IHC it seems to be a reasonable diagnosis. From a strictly morphological point, I was considering also other types of lymphomas

and also lymphoepithelial carcinoma and possibly some variant of medullary carcinoma. I would probably have done more IHC stains and T-cell receptor rearrangement tests to substantiate the diagnosis of extranodal ALK negative ALCL given the large number of differential diagnoses and the unusual diagnostic setting.

Vincenzo Eusebi: Anaplastic large cell lymphoma.

Giovanni Falconieri: Great case. I have no experience with this. I must admit that my first impression was of a reactive condition.

Cyril Fisher: ALCL adjacent to breast implant, association unclear.

Christopher Fletcher: Convincing case. The association with an adjacent breast implant, as has been reported, is remarkable and difficult to understand. Are there other comparable examples of lymphoma (of any type) arising in association with presumed exposure to foreign material?

Jerónimo Forteza Vila: In the last WHO classification, they distinguish between ALK positive and negative anaplastic lymphomas. Based on practical criteria, only ALK positive should be named anaplastic lymphoma because its prognosis is better.

Masaharu Fukunaga: A nice case of anaplastic large cell lymphoma associated with a breast implant. Thank you.

Allen Gown: Interesting tumor, interesting site.

Thomas Krausz: I haven't seen anaplastic large cell lymphoma in this location before.

Janez Lamovec: Anaplastic large cell lymphoma. Had never heard of the association with breast implants.

Thomas Mentzel: A very interesting clinical setting for these rare anaplastic large cell lymphomas, many thanks.

Markku Miettinen: Anaplastic large cell lymphoma related to implant capsule. All published cases seem to be of the ALK-negative variety.

Liz Montgomery: The diagnosis of anaplastic large cell lymphoma seems reasonable based on the available immunolabeling information but tricky without knowing that. Another complication of implants for the group!

Santiago Ramon y Cajal: Very interesting. Thank you for this beautiful case! My differential was with a granulocytic sarcoma.

Juan Rosai: Great case of breast prosthesis-associated anaplastic large cell lymphoma. I saw two cases of this entity at Memorial Hospital in N.Y. several years before it was described, but I could not sell it to anybody because of the history and did not have the courage to publish it without the blessing of a hematopathologist. Big mistake!

Dominic Spagnolo: Nice case of breast periprosthetic ALCL. We saw a similar case about 2 years ago, T-phenotype, and as far as I am aware, she is doing well too. Thanks for the case.

James Strauchen: Anaplastic large cell lymphoma associated with a breast implant! I was unaware of this association but I seem to recall case reports of lymphoma in lymph nodes draining silicone implants.

Larry Weiss: Agreed. We are currently putting together a large series of these cases.

CASE NO. 5 – CONTRIBUTED BY MICHELE BISCEGLIA:

Phil Allen: Leiomyomatosis peritonealis. I regard this condition as one of the smooth muscle counterparts of endometriosis. Indeed, endometriosis sometimes occurs in the smooth muscle nodules of

leiomyomatosis. As expounded in the short lived Journal, "Surgical Pathology," I believe this group of conditions is more closely allied to endometriosis than to sarcomas (Surg. Pathol. 3:3-14, 1990). In 1948, the famous Australian pathologist, the late Rupert Willis, who was infamous for his disbelief in mesotheliomas and Ewing's sarcoma, diagnosed widespread metastatic leiomyosarcoma of the peritoneal cavity in a youngish woman. She went away to die while Rupert moved to England. In 1951, he developed obstructive jaundice. At operation, there was a hard mass in the head of pancreas and a single small nodule on the liver capsule. In those days, surgeons would not biopsy the pancreas, but they bypassed Willis' biliary obstruction and excised the liver nodule, which Willis himself confirmed as benign. Nevertheless, he believed he was about to die of carcinoma of the pancreas so he resigned his university appointment and moved to Penzance, Cornwall, where he continued his pathology studies for another 30 years until he eventually died of other causes, cured of his "cancer" in 1980 (Am J Surg Pathol 4: 511-516, 1980). Meanwhile, the patient with metastatic "leiomyosarcoma" lived on. Serial biopsies taken about 10 years apart during repairs of incisional hernias showed hyalinization and regression of the benign peritoneal metastases. For all I know, she could still be alive today, having survived the man who signed what he thought was her death warrant.

Carlos Bacchi: Great case, great discussion.

David Ben-Dor: Thanks for this masterful presentation. Are you planning to specialize in gynecology? I wonder whether some of the entities mentioned in the differential (such as "benign metastasizing leiomyoma") aren't different names for the same process- hormonally generated benign smooth muscle proliferations.

Michele Bisceglia: My case. Follow up of case 2 (the "pen"-case): in the meantime, I had the opportunity to look at some slides of some of the surgical specimens from one of the several interventions the patient underwent, and I think this also is a leiomyomatosis peritonealis disseminata. The patient also in the meantime let me know she experienced again (after a certain delay) a favorable response to medical treatment with antagonist of GnRH.

Ira Bleiweiss: Leiomyoma, of course.

Tom Colby: Agree with diagnosis.

Kum Cooper: Thank you, Michele. The first and last time I saw this entity was in the early 80''s!

Ivan Damjanov: Agree. Leiomyomatosis peritonealis disseminata is a strange disease and I learned more about the variety of clinical presentations from a colleague whose patient belongs to a LPD support exchanging notes about this disease. As usual Michele outdid himself with his write-up. Thanks. From what I have seen and heard the therapy is more or less hit or miss and the results are unpredictable.

Otto Dietze: Thank you for this excellent discussion, good teaching case.

Hugo Dominguez-Malagon: Agree with the diagnosis of leiomyomatosis peritonealis diseminata, thank you.

Göran Elmberger: Very illustrative and interesting case. The biology of this and other Mullerian smooth muscle tumors such as intravenous leiomyomatosis and "benign metastasizing leiomyomas" remains enigmatic to me. Your fortuitous section 5 B really gives one the impression of a local metaplastic process. The findings of clonality analysis cited (Quade et al) where the same parental X chromosome was non-randomly inactivated in all tumorlets has been interpreted as evidence for a metastatic allochthon unicentric process by some authors even if alternative interpretations are possible. A case with DPL developing after laparoscope assisted myomectomy also cast some doubt on pathogenesis.

Vincenzo Eusebi: Nice case of leiomyomatosis peritonealis disseminata.

Giovanni Falconieri: This is my first case of LPD, Michele. Thanks for this excellent contribution and your didactical discussion.

Cyril Fisher: Leiomyomatosis peritonealis disseminata. Thanks, Michele, for the thorough discussion.

Christopher Fletcher: I have seen several cases similar to this one and I remain uncertain as to whether 'leiomyomatosis peritonealis disseminata' is the most appropriate designation. As members of the AMR group well know, the overwhelming majority of patients with LPD develop innumerable small (typically

less than 1 cm) nodules, in contrast to patients such as this who have smaller numbers of larger nodules. It would be interesting to have cytogenetic data in cases such as this. Perhaps this might represent a peritoneal counterpart of so-called 'benign metastasizing leiomyoma'? Certainly, patients such as this, at least in my experience, have typically had a history of uterine fibroids.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: Very interesting case presentation, Michele. I have seen one case for consultation, which was reviewed by Dr. Fletcher. His diagnosis was leiomyomatosis peritonealis disseminata.

Allen Gown: Absolutely fascinating tumor and history; you were so very lucky to have been contacted by a second patient with this disease.

Thomas Krausz: Agree with diagnosis. I enjoyed reading the discussion.

Janez Lamovec: Most interesting case, Michele. Thank you.

Thomas Mentzel: Many thanks for the detailed description of a rare case of leiomyomatosis peritonealis disseminata.

Liz Montgomery: This is a beautiful case. You asked if there is something newer for treating these patients other than GnRH antagonists and aromatase inhibitors – my GYN colleagues had no better ideas.

Santiago Ramon y Cajal: Nice example of leiomyomatosis peritonealis disseminata.

Juan Rosai: Nice case. I guess the main differential diagnosis is with fibromatosis, being in the abdominal wall of a young female and having followed an operation in the abdominal cavity.

Elvio Silva: Michele, I agree with you. I am currently working on a group of smooth muscle tumors in the peritoneum in patients with uterine smooth muscle tumors. These cases were diagnosed as low grade leiomyosarcomas because of the "recurrence" in the peritoneum, but 60% of these patients are with no evidence of disease. I believe we need to expand the concept of leiomyomatosis peritonealis disseminata and include fewer and larger lesions, as expression of multicentricity.

Dominic Spagnolo: Quite a spectacular case of leiomyomatosis peritonealis disseminata. I agree with your comments relating to the last patient. Thanks Michele.

James Strauchen: I recognized this as smooth muscle but failed to recall the entity of leiomyomatosis peritonealis disseminata. Thank you for this reminder!

Larry Weiss: Beautiful case. I have no recommendations on therapy.

CASE NO. 6 – CONTRIBUTED BY THOMAS COLBY:

Phil Allen: Kimura's disease, right and left neck, in a black male. I had no trouble recognizing this one because of my experience in Hong Kong. I have seen one case in an Australian Caucasian and now this case in an American of presumed African descent.

Carlos Bacchi: Great case. I haven't seen a case of Kimura's disease with such chronicity.

David Ben-Dor: Looks like a florid reactive condition with numerous eosinophils. Is there any need to rule out a chronic parasitic condition? Has anyone figured out whether there is an immunogenic substance related to this (in the manner in which interleukin 6 is related to Castleman's disease)?

Michele Bisceglia: Have seen an almost identical case in a non-oriental young male patient with a long history of (and previously misdiagnosed) Kimura disease, and published it with clinical photos in G It

Dermatol Venereol 137 (Suppl. 2 al N. 1): 141-144, 2002 (La malattia di Kimura: osservazione di un caso occidentale).

Kum Cooper: Thank you, Tom. The lymph node picture appears to be somewhat "watered" down due perhaps to the chronicity. The big differential of course is angiolymphoid hyperplasia with eosinophilia (epithelioid hemangioma) particularly in the skin/subcutaneous tissue. I have seen a chronic case involving the skin/subcutaneous tissue of the thigh which also had masses of fibrosis.

Ivan Damjanov: Agree. I do not have much to add--most cases that I have seen were from slide seminars.

Otto Dietze: The few cases of Kimuras´s disease I have seen never showed this fibrotic reaction.

Hugo Dominguez-Malagon: Agree with the diagnosis, beautiful case of Kimura's, thank you.

Göran Elmberger: Thanks for sharing this impressing case with us. Never seen anything as dramatic in my practise. I guess careful clinical work-up as in this case is essential since histology in itself is not very specific?

Vincenzo Eusebi: Features consistent with Kimura's disease. The few cases I have seen were sent to me from friends from Far East.

Giovanni Falconieri: Great case, Tom. History and microscopic features point to a benign disease, yet I was not sure on the name. The nodular pattern imparted by fibrosclerotic tissue is dramatic.

Cyril Fisher: Kimura's disease, great case. Rarely see this.

Christopher Fletcher: The few cases of Kimura's disease which I have seen from patients in Asia have shown more prominent eosinophil microabscesses as well as more prominent folliculosis – but I would have difficulty in coming up with any alternative diagnosis in a case such as this. It is difficult to know whether examples of Kimura's disease arising in non-Asian patients are quite the same thing.

Jerónimo Forteza-Vila: I agree with the diagnosis.

Masaharu Fukunaga: Dr. Kimura was a professor of pathology in our university (Jikei University, Tokyo, Japan). Kimura's disease is not a lymph node lesion but a soft tissue lesion. Although I have seen many cases of Kimura's disease, I have never seen such a case with bilateral bulky masses with edema and fibrosis. Thank you very much, Thomas.

Allen Gown: Thank you for this wonderful example of Kimura's disease.

Thomas Krausz: Highly educational case.

Janez Lamovec: In contrast to epithelioid hemangioma which is one of the differential diagnosis in these cases among other differences, endothelial cells are not really epithelioid but swollen instead.

Thomas Mentzel: A very nice case of an entity we do not see usually in Europe. Do you know if they performed a skin biopsy as well?

Markku Miettinen: Kimura disease, focal collections of amorphous eosinophilic material in germinal centers noted.

Liz Montgomery: This Kimura's disease is really cool. My experience is based on 3-4 cases, which were mostly just sclerotic so I look forward to the remarks of those Asian colleagues who have broader experience.

Santiago Ramon y Cajal: What a remarkable case of Kimura´s disease.

Juan Rosai: Nice case of Kimura disease (not to be confused with angiolymphoid hyperplasia with eosinophilia, which many dermatologists and dermatopathologists keep doing). There are some funny-

looking cells in the stroma, raising for a second the alternative possibility of an inflammatory variant of atypical lipomatous tumor.

Dominic Spagnolo: Very nice case of chronic Kimura's disease. The progressive fibrosis is striking and typical.

James Strauchen: Kimura disease! Very nice example with eosinophilic folliculolysis and vascular proliferation. I do not recall seeing the extensive perinodal fibrosis before!

Saul Suster: I have seen previously 3 or 4 cases of Kimura's disease in non-Oriental patients, but they all showed eosinophilic microabscesses. Perhaps this is a feature that is no longer seen in longstanding, sclerotic lesions.

Larry Weiss: Thanks for sharing the case. The fibrosis is typical, and may be more extensive, but I have not seen such massive edema before.

CASE NO. 7 – CONTRIBUTED BY GORAN EMBERGER:

Phil Allen: Nasal seromucinous hamartoma with focal respiratory epithelial adenomatoid hamartoma-like features, right upper posterior nasal septum. I think this is benign and probably a reactive proliferation. However, the people who described it first called it a hamartoma and I wouldn't like to upset them. Moreover, I don't like aliases, which should be restricted to the criminal underworld. One could justify name changes for virtually every pathological lesion, but proliferating synonyms cause confusion and annoy the original discoverers, as in the case of targetoid hemosiderotic hemangioma. This must be why most stick with "synovial" sarcoma rather than bamboozling everyone with the more correct "carcinosarcoma of soft parts." I would also prefer to keep my nose out of the salivary glands, even if the acini are fundamentally similar.

Carlos Bacchi: Nasal seromucinous hamartoma seems fine to me.

David Ben-Dor: I have to be candid and admit that I didn't invest the requisite mental energy and attention to fully understand the argumentation. I admit that the small gland proliferation seems particularly florid in this case, more than there might be in classical REAH (as depicted in the images in Bruce Wenig's recently published atlas), but on an individual basis they look perfectly innocuous. But I would still think that this case and cases like it, even if given a specific name (seromucinous hamartoma), are probably related to REAH (in Bruce's book the latter is given as a synonym for the former). I think that the questions you raise illustrate the fact that we don't understand what changes lies at the basis of neoplasia – all we see are the histological manifestations. I agree with the basic intuition that this lesion exhibits a certain disarray beyond that expected in a regulated process such as hyperplasia but not reaching the full orderly development of an adenoma and without the aggressiveness of a malignant tumor. I agree with your point that the use of the term hamartoma should be cleaned up.

Michele Bisceglia: Actually, I could not imagine that all this (very helpful and interesting) dissertation could be derived from a deceptively and seemingly bland-looking nasal polypoid mixed fibroepithelial lesion. Thank you, Göran, for enlightening me and opening my horizon. Sorry; no input from my side.

Ira Bleiweiss: Interesting benign proliferation. The small glands remind me a bit of microglandular adenosis of the breast.

Thomas Colby: Given the choice between hamartoma and carcinoma, I favor the former. I will leave the issues of nomenclature to others. I guess I would consider this a minor salivary gland lesion.

Kum Cooper: Goran, I would have signed this out as REAH (and let you head/neck guys to resolve the terminology/origin issues). by the way there is a nice review of REAH by Jerry Berry in Ad Anat Path**:** 2007 Jan;14(1):11-6.

Ivan Damjanov: I think this is a low grade adenocarcinoma. Follow-up will teach us more, I guess. Nice discussion and differential diagnosis.

Otto Dietze: My experience with this lesion is limited and I remember only one case of a possible REAH in the past, lacking this small gland infiltrative pattern. I would favour LGSNAC.

Hugo Dominguez-Malagon: I see some preservation of gland lobular architecture, why not to call it a polyp with accessory salivary gland hyperplasia?

Göran Elmberger: My case. Guess small glandular proliferation getting less pronounced on deeper levels but hopefully enough remains to convince someone of the hamartoma diagnosis. I am studying this lesion now with molecular techniques such as CGH to see if there is any molecular evidence supporting neoplastic potential. Results are pending.

Vincenzo Eusebi: This lesion was proposed by Chuang and Lin as microglandular adenosis arising in chronic paranasal sinusitis (Histopathology 36:376-377, 2000). A similar case was sent to this slide seminar from Australia (Dominic Spagnolo) a few years ago.

Giovanni Falconieri: Interesting case. You have also raised some great questions, unfortunately I have no good answer. Sorry I can't be more help.

Cyril Fisher: Hamartomatous lesion.

Christopher Fletcher: Very impressive and educational case. It seems that many of the lesions which we have known as 'hamartomas' in the past are in fact truly neoplastic lesions, at least by any currently available criteria – although finding a satisfactory definition for a neoplasm is not straightforward either!

Jerónimo Forteza Vila: Very interesting case.

Masaharu Fukunaga: My initial impression was REAH. I appreciate the detailed discussion.

Thomas Krausz: Among all the options, I like the idea of microglandular adenosis.

Allen Gown: I would favor the diagnosis of a carcinoma, i.e., LGSNAC, for the reasons you have outlined as well as the immunophenotype, which shows an absence of p63 positive cells around the cell nests in question, as might be expected in a hamartoma.

Janez Lamovec: New to me. Thank you for your erudite discussion.

Thomas Mentzel: I do agree entirely that the term "hamartoma" does not reflect the nature of this lesion, and given the architecture and cytology I would prefer to label this lesion probably as a form of adenosis.

Markku Miettinen: Would have considered this respiratory epithelial adenomatoid hamartoma, out of ignorance for a better diagnosis.

Liz Montgomery: I can say that this looks benign with the assured confidence of someone who knows nothing about the topic. To this "salivary-naïve" reviewer, the haphazard arrangement seems lobulated and somewhat organized and composed of a mixed up version of what is found naturally in the locale. Doesn't that mean a "hamartoma"?

Santiago Ramon y Cajal: Would go with adenoma or hamartoma. I don´t think it is a carcinoma. Probably a good name for the entity would be microglandular adenosis.

Juan Rosai: Nice case of so called adenomatoid hamartoma, although I don't believe that this lesion is of hamartomatous nature. I would rather interpret it as a benign acquired hyperplastic process, analogous in some ways to microglandular adenosis (hyperplasia) of breast. I think that the term "hamartoma" is being widely abused.

Dominic Spagnolo: This seems identical to Case 16/Seminar #48, that I presented to the group, and as described in the recent Histopathology paper by Weinreb et al. I still think this is a benign proliferation, and am happy with the rubric of sero (mucinous) hamartoma. The relationship to REAH remains open at this stage for me.

James Strauchen: Thank you! The only other example of this I think I can recall was a previous AMR case!

Larry Weiss: Never heard of this. I am not qualified to opine on biology and nomenclature for this lesion, but that has never stopped me before: I think that it is benign, and hamartoma is as good a name as any.

CASE NO. 8 – CONTRIBUTED BY GIOVANNI FALCONIERI:

Phil Allen: Ameloblastoma of maxillary sinus. I understand that the maxilla is an acceptable site for ameloblastoma.

Carlos Bacchi: I agree with the diagnosis of sinonasal ameloblastoma.

David Ben-Dor: I agree that this is a beautiful example of an ameloblastic neoplasm. Didn't know that these can be native to the sinonasal tract. Is there any chance of a craniopharyngioma extending from the base of the skull? I once had glial tissue submitted as a sinus polyp.

Michele Bisceglia: Agree. Falco, have seen a similar case (in consultation).

Ira Bleiweiss: Agree.

Thomas Colby: I like sinonasal ameloblastoma.

Kum Cooper: Falco, I agree with you: ameloblastoma.

Ivan Damjanov: I think that your first thought was right, and I think that this is an ameloblastoma.

Otto Dietze: I agree with ameloblastoma.

Hugo Dominguez-Malagon: The tumor has the histological characteristics of ameloblastoma. However, due to its location in the nasal cavity, an obligate consideration would be craniopharyngioma (not necessarily connected with pituitary but from ectopic Rathke pouch remnants).

Göran Elmberger: Beautiful case of ameloblastoma. Radiological findings excluding gnathic origin as well as direct continuity with intact sinonasal surface mucosal epithelium in favor of primary sinonasal variant. The histology is very similar to what is seen in adamantinomatous craniopharyngiomas but this tumor usually presents as a sellar or sometimes nasopharyngeal process.

Vincenzo Eusebi: This case looks like ameloblastoma. Craniopharyngioma extending to the nasal sinuses should be excluded.

Cyril Fisher: Looks like ameloblastoma!

Christopher Fletcher: Indeed looks like a perfect ameloblastoma at a very uncommon location!

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: It seems to be ameloblastoma, but I have never seen it before. Thank you, Giovanni.

Allen Gown: Looks like it could well be an ameloblastoma to me.

Thomas Krausz: I agree that this is an ameloblastoma.

Janez Lamovec: I don't know if anything else than ameloblastoma could be considered in this case.

Thomas Mentzel: A very nice example of a rare peripheral ameloblastoma (adamantinoma).

Michal Michal: Peripheral ameloblastoma.

Markku Miettinen: Ameloblastoma, fully consistent with odontogenic epithelial origin.

Liz Montgomery: I have no better diagnosis than ameloblastoma but defer to the salivary-smart people.

Santiago Ramon y Cajal: Would go with adenoma or hamartoma. I don´t think it is a carcinoma. Probably a good name for the entity would be microglandular adenosis.

Juan Rosai: Beautiful case of ameloblastoma of the so-called peripheral (in this case sinonasal) type, which is said to be much more indolent than the classic type arising in the mandible or maxilla.

Dominic Spagnolo: Agree with extragnathic ameloblastoma, assuming the clinic radiological features are consistent with this. I saw an identical case in July last year, arising in the maxillary sinus of a 62 yo male.

James Strauchen: Sinonasal ameloblastoma with nice stellate reticulum. Didn't know they occurred there. Thank you!

Larry Weiss: Ameloblastoma seems good to me.

CASE NO. 9 – CONTRIBUTED BY MASAHARU FUKUNAGA:

Phil Allen: Comparatively well differentiated angiosarcoma of the kidney. I have seen similar angiosarcomas in other sites that killed patients within a few months, as in this case. I suspect, but cannot prove, that most angiosarcomas arise de novo and not from pre-existing benign hemangiomas. I think the fat around the edge of this tumour is normal perirenal fat which is being infiltrated by the tumour.

Carlos Bacchi: The fat tissue seems to be just infiltrated by the well-differentiated angiosarcoma.

David Ben-Dor: I wasn't aware of benign adipose tissue proliferation accompanying angiosarcoma (like the small fish that swim along with sharks?). How about angiosarcoma developing in angiomyolipoma with adipose predominance? Or the fat is simply a part of the perinephric fat (the simplest explanation)?

Michele Bisceglia: In my opinion the adipose tissue is part of the tumor (as in a mesenchymoma). We had another case of angiosarcoma of the kidney (Chris contributed it in Seminar 18) as part of a collision tumor with a RCC component.

Ira Bleiweiss: Agree. Angiosarcoma.

Thomas Colby: Angiosarcoma, relatively well differentiated. I am not convinced there is a pre-existing hemangioma. The fat is an interesting question and my initial reaction was that the fat was part of the lesion but one can see a pattern of infiltration at the edge from which one could conclude that the fat is simply being overrun by the tumor.

Kum Cooper: Thank you, Masa. Nice example of angiosarcoma. I have not seen it in the kidney before. Good to see you in Florence recently.

Ivan Damjanov: Angiosarcoma, but I do not believe that it originates from a pre-existing benign tumor.

Otto Dietze: a) I don't know a case of angiosarcoma arising from hemangioma. b) I also have seen adipocyte hyperplasia in association with vascular tumors, but except within the skeletal muscle, where this reflects fatty atrophy , I don't have an explanation.

Hugo Dominguez-Malagon: I agree with the diagnosis of angiosarcoma of the kidney. Beautiful case.

Göran Elmberger: Great case! The insidious infiltration of presumed capsular fat was tricky. I can clearly see how that could make one thing of other entities such as angiomyolipoma. Given the outcome of IHC, the grim clinical outcome and the fact that typical fat infiltration is seen at tumor periphery I am fully convinced.

Vincenzo Eusebi: Angiosarcoma dissecting adipose tissue.

Giovanni Falconieri: Agree with angiosarcoma, the tumor displays a fair polymorphism ranging from classic freely anastomosing vascular spaces to more solid, spindle, kaposiform area. Great case, Masa!

Cyril Fisher: Angiosarcoma of kidney, rare and striking example.

Christopher Fletcher: Based on the complex anastomosing growth pattern, focally striking endothelial atypia and more cellular spindle cell areas, I agree with the diagnosis of angiosarcoma at an exceptional location. Given that the tumour extended into perinephric/hilar adipose tissue, it is difficult to tell, at least from this one section, whether or not this fat is unusually prominent or increased in amount. I do not see convincing features of a pre-existing hemangioma, although some areas of the lesion are morphologically very low-grade, in a fashion quite reminiscent of angiosarcoma in the breast.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: My case. Other sections show multiple tiny clear cell carcinomas adjacent to the angiosarcoma Dr. Fletcher submitted renal angiosarcoma with renal cell carcinoma for an AMR seminar before according to the Archives.

Allen Gown: Lovely example of renal angiosarcoma.

Thomas Krausz: I also favor that the angiosarcoma arising either in association with a hemangioma/vascular malformation or even in an angiomyolipoma.

Janez Lamovec: The degree of vasoformation in this angiosarcoma is striking and the tumor doesn't appear very high grade type testifying to the fact that the morphology is not so much predictive as to biologic behavior in these tumors. I have never seen so prominent adipocytic stromal component in angiosarcomas elsewhere; however, we had no case of primary angiosarcoma of kidney here.

Thomas Mentzel: Histologically, I see a cellular vascular lesion with narrow and dilated vascular structures, papillary endothelial proliferations and areas of lipomatous metaplasia. Given that only slight endothelial atypia is present I`m not sure about the diagnosis of a rare renal angiosarcoma. Were neoplastic vascular structures surrounded by actin-positive cells ? Have you performed Ki-67 staining?

Markku Miettinen: Angiosarcoma, well-differentiated (although seemed to act fully malignant). Difficult to prove origin from hemangioma, unless you have a clear-cut benign element or time sequence available. The fat here could be explained by perinephric fat invasion. The tumor has some architectural resemblance to angiosarcomas of breast.

Liz Montgomery: Beautiful angiosarcoma. Suspect it is all malignant and some is just deceptively bland. The fat seems to be the fat found in the area anyway.

Santiago Ramon y Cajal: Very interesting case of angiosarcoma of the kidney.

Juan Rosai: Spectacular case of extremely well differentiated angiosarcoma of the kidney, very similar to those seen much more frequently in the breast. Actually, I thought I was looking at a breast until I found some glomeruli and tubules.

Dominic Spagnolo: Have not encountered primary renal angiosarcoma - agree with the diagnosis Masa - thanks for the case. I interpreted the adipose on my slide as being extrarenal.

James Strauchen: Angiosarcoma of ? retroperitoneum ? kidney. I think the hemangioma-like areas are just better differentiated angiosarcoma.

Saul Suster: I agree that this is pretty convincing for a well-differentiated angiosarcoma of the kidney. I think the fat is most likely perinephric fat that is being secondarily infiltrated by the tumor.

Larry Weiss: Holy cow, what a case. I do not see a benign hemangioma. The adipose tissue is probably normal tissue infiltrated by tumor.

CASE NO. 10 – CONTRIBUTED BY THOMAS KRAUSZ:

Phil Allen: Reticular perineurioma, left anterior tibialis muscle. This looks to me like a genuine histological entity but I have difficulties with a unifying concept of perineurioma that includes sclerosing digital perineurioma, intraneural perineurioma and sundry mongrels of doubtful lineage. I don't have much confidence in the specificity of the EMA stain and I am similarly cautious about some interpretations of electron microscopy.

Carlos Bacchi: Thanks Thomas for this great example of perineurioma with reticular features.

David Ben-Dor: Not recalling the previous examples of this entity submitted to the club, this slide knocked me for a loop when I first looked at it. Under low power, my first gut impression was an adipose tumor, especially with the hyperchromasia and atypia of some of the cells, after which I noticed what look like anastomosing channels as in a vascular tumor. Though not doubting Thomas' expertise in soft tissue tumor, I was surprised by the diagnosis finding it hard to believe that that a spindle cell proliferation could turn into something looking like this. But in fact this is what it is. Do these lesions really exist in the wild or are they found only in slide clubs and a few journal articles?

Michele Bisceglia: Reticular perineurioma. Indeed a difficult but convincing diagnosis. Thank you very much, Thomas.

Ira Bleiweiss: Don't know. I defer to the soft tissue gurus.

Thomas Colby: Agree with reticular perineurioma, although I probably would not have gotten there on my own.

Kum Cooper: This morphology is new to me, Thomas. Looks very much like a microcystic meningioma. It is only a matter of time (to me at least in my simplistic approach) before the perineurial fibroblasts and meningothelial cells merge! I recall a recent paper that also addressed this very same issue at the juncture of the spinal nerve roots.

Ivan Damjanov: Wow! Nothing to add. Agree.

Otto Dietze: Thank you for the reminder. I had already forgotten this entity.

Hugo Dominguez-Malagon: Reticular perineurioma. It looks like a microcystic meningioma (no wonder since perineurial cells are in continuity with arachnoidal cells).

Göran Elmberger: Thanks for sharing this rare case of perineurioma. Don’t see too many of those... Convincing IHC and molecular studies. The spectrum of morphological variants seems wide. Beside the dominating reticulated (microvacuolated?) component, there are also small areas with PASH-like sclerosing morphology

Vincenzo Eusebi: Reticular perineurioma. Thank you Thomas, I am sure I would have missed the diagnosis in this case.

Giovanni Falconieri: Thank you, Tom, for sharing with us another extraordinary example of soft tissue pathology. Nothing to add to your valuable comment

Cyril Fisher: A further nice case of reticular perineurioma with appropriate immunophenotype.

Christopher Fletcher: Convincing example of reticular perineurioma – I do not recollect seeing one of these which such prominent hyaline stromal collagen in the past.

Jerónimo Forteza Vila: The key is the immunohistochemistry study.

Masaharu Fukunaga: Thank you very much for the case, Thomas. It is very beautiful, and I will share this case with my friends.

Allen Gown: Thank you for submitting this interesting variation on reticular perineurioma, along with the IHC profile and molecular changes.

Janez Lamovec: Very difficult for me. I completely missed the diagnosis.

Thomas Mentzel: Many thanks for this unusual case of a reticular perineurioma with nuclear atypia and vacuolation of tumour cells that is mimicking at least focally a lipogenic neoplasm.

Markku Miettinen: Agree on reticular/retiform perineurioma, although not typical. Some areas show resemblance to "meningothelial hamartoma" of scalp.

Elizabeth Montgomery: This case is fascinating. Perineurioma seems the best interpretation – the "bubbly" appearance is very interesting.

Santiago Ramon y Cajal: Great case. Thank you. It is always worthy to se cases like this.

Juan Rosai: Spectacular case, beautifully documented immunohistochemically and by molecular biology. I might have missed it if I had the H&E slide alone.

Dominic Spagnolo: Spectacular case of reticular perineurioma - thanks for the case.

James Strauchen: I was unaware of this variant of perineurioma! Thank you!

Saul Suster: Pretty spectacular case! Thank you for having shared this with us. This case is not only convincing morphologically but also fits nicely by marker studies and EM. We recently saw a case here of a soft tissue mass in the neck with somewhat similar features but the marker studies were negative for everything – we still don't know what it is! I will contribute it for the next seminar if the surgeons resect the lesion (all we had was a small biopsy).

Larry Weiss: Terrific case. I have still never seen a case in "real life."

CASE NO. 11 – CONTRIBUTED BY THOMAS MENTZEL:

Phil Allen: Undiagnosed, histologically atypical, biphasic tumour, with EMA positive, CD34 positive and S100 negative elongated cells, and conversely staining plump cells, right thigh, tissue plane not stated. I don't know if this is benign or malignant. I would advise wider excision if it can be performed without causing undue morbidity.

Carlos Bacchi: Nice case.

David Ben-Dor: I had such a case which Chris Fletcher diagnosed and included in his paper on the topic published very recently in the AJSP. What's nice about this example is the fact that due to its hyperchromatic and enlarged nuclei (which is disconcerting at first look), the Schwann cell component is easily distinguished from the perineural component (in my case this separation was not so obvious, at least to me), giving the tumor a biphasic look.

Michele Bisceglia: Hybrid perineurioma and (ancient) schwannoma. Beautiful case, Thomas.

Ira Bleiweiss: Agree with benign nerve sheath origin.

Thomas Colby: Agree with diagnosis, and I appreciate seeing this hybrid case.

Kum Cooper: Wow! The wonder of soft tissue tumors. I have seen two hybrid tumors and neither looked like this. Thank you Thomas this is indeed a treat!

Ivan Damjanov: I called it a schwannoma with secondary changes, but then I read your comments and accept your arguments.

Otto Dietze: Like with the other lesion, I was not aware of this peculiar combination.

Hugo Dominguez-Malagon: Beautiful case. Besides the perineural component, in the center of the whorls there are structures that look to me like tiny nerves (they even have neurites). Why not to call it "hybrid perineurioma and neurofibroma"?

Göran Elmberger: Interesting and unique case. "Hybrid tumors" are now more commonly recognized in many organs not least H&N (ONB; SGT). This case challenges the old fashioned simplistic concept of monoclonal nonlineage neoplastic proliferations or at least highlights polyphenotypic differentiation and complex interrelationship between tumor-stroma-bystander cells. Thanks.

Vincenzo Eusebi: Very nice case. Thank you - the first one that I recognize of this kind.

Giovanni Falconieri: Another small gap of my big ignorance filled today! Thanks Thomas, for this excellent contribution.

Cyril Fisher: Intermingled hybrid benign peripheral nerve sheath tumor – it seems there is a wide range of patterns for these tumors.

Christopher Fletcher: This lesion probably belongs within the spectrum of hybrid schwannoma-perineurioma as we reported in *Am J Surg Pathol* 2009; 33:1554-1561 – however, at least in my experience, the two cell types are not usually so strikingly distinct as in this case.

Jerónimo Forteza Vila: Very interesting case.

Masaharu Fukunaga: Thank you very much for the excellent case, Thomas. It is very interesting and I have never seen or noticed it before.

Allen Gown: Thank you for this lovely case. I think you are very correct that these variants, hybrid and otherwise, of nerve sheath tumors emphasize that all these neoplasms are more closely related than previously recognized, and this can be seen in immunohistochemical evaluation of many tumors thought to be histologically composed of a single cell type which can demonstrate unsuspected subpopulations, e.g., of CD34-positive spindle or dendritic cells.

Thomas Krausz: Great case.

Janez Lamovec: I thought of some type of benign nerve sheath tumor and that was as far as I could go.

Markku Miettinen: Agree on nerve sheath tumor. No areas typical of schwannoma are present, no capsule either. Would favor neurofibroma with perineurial cell components.

Liz Montgomery: This is a very very cool nerve sheath tumor. Thanks so much for it, Thomas.

Santiago Ramon y Cajal: Very interesting case of mixed peripheral nerve sheath tumor.

Juan Rosai: Very nice case of a tumor which is becoming increasingly popular.

Dominic Spagnolo: Two wonderful cases (10 and 11) of nerve sheath tumors. Agree with hybrid perineurioma/ancient Schwannoma with epithelioid features. Are there axons in some of the whorled neuroid structures?

James Strauchen: I was unaware of this particular combination of peripheral nerve sheath tumors! Thank you!

Saul Suster: Never seen this before! Beautiful collector's item.

Larry Weiss: Simply an amazing case. And unbelievable that we are seeing two perineurioma back-to-back.

CASE NO. 12 – CONTRIBUTED BY ELIZABETH MONTGOMERY:

Phil Allen: Pyloric gland adenoma with high-grade dysplasia in a background of autoimmune metaplastic atrophic gastritis. Goodness knows how many of these I have missed in the past. Thanks for this very instructive case, Elizabeth.

Carlos Bacchi: Thanks for teaching me about this lesion.

David Ben-Dor: This was a bit of a challenge to figure out- I think I found the piece in question containing the lesional cells with pink cytoplasm. I wouldn't think these are severely dysplastic based on my own preconceptions but you say that these can turn into carcinoma (presumably without going through a phase showing more atypia?) (I think you deserve an "e for effort" for the previous case.)

Michele Bisceglia: Very instructive case. We have a large experience with autoimmune atrophic gastritis here, but never seen (or recognized) pyloric gland adenoma in this context. Thank you.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis of pyloric gland adenoma; had trouble finding high-grade dysplasia except possibly in one or two crypts.

Kum Cooper: Thank you, Liz, for sharing your recently published entity with us. My slide has none of the dysplastic areas. I wonder how many of these I have signed out as hyperplastic polyps. My ego will never know!

Ivan Damjanov: Agree. I probably missed a couple of them! Thanks for bringing it to my attention.

Otto Dietze: Due to Dr. Stolte´s lessons in the German IAP, I have learned about this tumor.

Hugo Dominguez-Malagon: Excellent example of pyloric adenoma, very illustrative, thank you.

Göran Elmberger: Educative case for me. Grading of dysplasias tough for one not very experienced in GI-pathology.

Giovanni Falconieri: I believe that the presentation and discussion are perfect! Thanks for submitting this instructive case.

Jerónimo Forteza Vila: I cannot see clearly the dysplasia.

Masaharu Fukunaga: Thank you very much for the great case. I have never or noticed this type of neoplasm although I am a Japanese pathologist. My initial impression is pyloric gland hyperplasia. Atypia or dysplasia seems to me
very mild.

Allen Gown: Thank you for this interesting case!

Thomas Krausz: Highly educational case. I enjoyed reading the discussion. I am not sure about the high grade dysplasia.

Thomas Mentzel: A very nice case indeed!

Michal Michal: Pyloric gland adenoma with dysplasia. Very similar case to the one we published (Michal M et al. Virchows Archiv 2003 Oct;443(4):589-90).

Santiago Ramon y Cajal: From the slide I received, could not distinguish clear cytological atypia and looks like hyperplastic and adenomatous lesion.

Juan Rosai: There was no high grade dysplasia in the section that I received. Actually, I had trouble finding dysplasia at all. Either there is a sampling problem or I forgot how to recognize dysplasia.

Dominic Spagnolo: I buy the pyloric gland adenoma, but I don't see dysplasia (inflammatory atypia focally for me; maybe I'm under calling it).

James Strauchen: Pyloric gland adenoma! I was unaware of this as a specific entity so I haven't caught up with the Europeans yet! Thank you!

Saul Suster: Was not aware of this condition – thank you for the education!

Larry Weiss: The dysplasia is too subtle for me. I am glad I did not get this case in my hospital.

CASE NO. 13 – CONTRIBUTED BY ELIZABETH MONTGOMERY:

Phil Allen: Mesenchymal hamartoma of the chest wall (alias chondromatous hamartoma, vascular and cartilaginous hamartoma of the ribs, vascular hamartoma of infancy). This looks to me like another variant of nodular fasciitis. I can't remember if we have seen one of these before in the club. Yet another very instructive case.

Carlos Bacchi: Thanks. First time I have seen one.

David Ben-Dor: I think you could cut the radiologists some slack; after all babies are small!

Michele Bisceglia: Interesting case, including the preoperative clinical imaging diagnosis. Chris Fletcher contributed one such case in Seminar 24.

Ira Bleiweiss: Wow.

Thomas Colby: Agree with diagnosis; have not seen one of these before.

Kum Cooper: Thank you (again) for a novel entity. I have read about these lesions but never seen one. I wonder what the present day soft tissue morphologists would call this? Some sort of periosteal myofibroblastic proliferative lesion?? The most important outcome is that it is benign.

Ivan Damjanov: I would have called it chondromatous hamartoma, but your diagnosis is more than appropriate.

Otto Dietze: Thank you for this contribution, I did not see a similar hamartoma before. It might be a diagnostic challenge especially if you get it in a frozen section.

Hugo Dominguez-Malagon: Agree with chest wall hamartoma, although not a typical one, bone formation with a myofibroblastic ("fasciitis-like") background predominates, there are chondroblastic areas but no cartilage.

Göran Elmberger: Great case. Note similarities to nasal chondromesenchymal hamartoma.

Giovanni Falconieri: I also believe that it is benign, but have no confidence with the name. Thank you for this extraordinary contribution.

Cyril Fisher: The appearances fit for this entity.

Christopher Fletcher: The few examples of chest wall hamartoma in neonates which I have seen have generally been dominated by the cellular cartilaginous component. How would we separate this lesion from something such as a solid aneurysmal bone cyst?

Jerónimo Forteza Vila: I do not have experience in these cases.

Masaharu Fukunaga: Thank you very much for the great case again. I have never seen it before. It looks like osteofibrous dysplasia.

Thomas Krausz: Great example.

Janez Lamovec: We saw one case of this lesion in the past but it was much more cartilaginous.

Thomas Mentzel: Many thanks for sharing this nice and rare case.

Santiago Ramon y Cajal: Thank you for this beautiful case of chest wall hamartoma.

Juan Rosai: Beautiful example of the entity described by Howard Dorfman's group many years ago (but is really a hamartoma?).

Dominic Spagnolo: Agree with mesenchymal hamartoma of chest wall - very nice example. Thanks.

James Strauchen: Chest wall hamartoma! I was unaware of this entity and thought it looked mostly like fibrous dysplasia. Thank you!

Saul Suster: Have no experience with this lesion (don't see pediatric pathology at all!) – thank you for contributing it.

Larry Weiss: Again, another lesion I have never heard of before. Thank you very much for showing us this case.

CASE NO. 14 – CONTRIBUTED BY GIUSEPPE PELOSI:

Phil Allen: In my experience, an angiofibromatous pattern is more commonly seen in intra-cavitary desmoids that in those arising in skeletal muscle. I can't remember ever seeing a mediastinal desmoid before but I have seen one or two large chest wall desmoids, one of which invaded the lung, the diaphragm and the liver. They are commonly confused with solitary fibrous tumors when they involve the pleura or lung.

Carlos Bacchi: Giuseppe, if you are interested, I have one case of fibromatosis in the lung and 2 cases involving the mediastinum.

David Ben-Dor: In section 14a, the lesion is well demarcated and presses against a thick fibrous layer overlying the lung while not penetrating into it- I assume that this is the visceral pleura which was not involved. I guess this process respects the boundaries of some structures but not others.

Michele Bisceglia: Very rare case. However Giuseppe and I spoke about another (inoperable/unresectable) case of mediastinal fibromatosis in a 19-year old female which subsequently was also seen in his institution (diagnosis confirmed).

Ira Bleiweiss: Agree. Fibromatosis.

Tom Colby: Agree with diagnosis; have 3 or 4 of these that have mimicked solitary fibrous tumor of the pleura.

Kum Cooper: Extra-abdominal fibromatosis.

Ivan Damjanov: Fibromatosis, agree.

Otto Dietze: I agree, especially with regard to the immunoprofile of the lesion.

Hugo Dominguez-Malagon: Fibromatosis. It is desirable to corroborate with beta catenin and/or electron microscopy (look for fibronexus). Mediastinal location of the tumor is unusual and is expected to behave in an aggressive manner. Treatment is still debatable and complete surgical excision is probably impossible. Radiotherapy has many secondary effects especially in that site, and chemotherapy is not standard. Oncologists in my institution treat cases of aggressive fibromatosis (musculo-aponeurotic, intraabdominal, retroperitoneal) with colchicine (1 mg a day for several months), with variable results but sometimes spectacular response (around 30%).

Göran Elmberger: Could not find any mediastinal-pleural case in our institutional files since 1990 at Karolinska. Thanks for contributing.

Vincenzo Eusebi: Very nice case.

Giovanni Falconieri: Great case, Giuseppe. I am not sure I have ever seen pulmonary desmoids, perhaps in the mediastinum when I was in Trieste many years ago. I will check my home computer where I have my personal case data base accessible (still in maintenance for a bad crash) and let you know if something is in the files, so I'll feel happy to contribute the case(s) for reporting.

Cyril Fisher: Agree with fibromatosis, unusual clinical picture with massive tumor.

Christopher Fletcher: Typical example of extra-abdominal desmoid fibromatosis. In my experience, while pleural/chest wall examples are not so uncommon, mediastinal involvement seems to be very rare.

Jerónimo Forteza Vila: The key diagnostic feature is the nuclear staining for B-catenin.

Masaharu Fukunaga: Beautiful case. I have rarely seen fibromatosis in this location.

Allen Gown: Thank you for this case, highlighting the problem of tumors occurring at unusual sites!

Thomas Krausz: Agree with diagnosis. I am so pleased to see one in this location.

Janez Lamovec: Agree. Desmoid-type fibromatosis.

Thomas Mentzel: What an unusual presentation of desmoid fibromatosis!

Markku Miettinen: Agree on desmoid fibromatosis.

Liz Montgomery: Nice classic desmoid/ fibromatosis. Nice that there is adjoining lung on the slides.

Santiago Ramon y Cajal: Remarkable case of extra-abdominal fibromatosis.

Juan Rosai: Typical case of extra-abdominal fibromatosis (desmoid tumor).

Dominic Spagnolo: Agree with desmoid chest wall - very stunning example. Low grade fibromyxoid sarcoma would be the main differential but the good nuclear beta-catenin strongly supports desmoid.

James Strauchen: Mediastinal fibromatosis! The encasement of the lymph nodes from without is interesting!

Saul Suster: Guiseppe, Cesar and I have seen 2 or 3 cases of fibromatosis in the mediastinum and we would be happy to contribute our cases to you for a publication. Perhaps we could join these cases with cases from the rest of the members of the club for a joint publication. This is a very rare occurrence in the mediastinum.

Larry Weiss: Nice case. I do not recall seeing a case of fibromatosis as such a massive lesion in this location.

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

Phil Allen: Infiltrating ductal carcinoma with mucin production, right breast. The pictures in Koenig and Tavassoli's article look very much like a mucinous cystadenocarcinoma of the ovary. While there is plentiful mucin production in my slide, it does not remind me of an ovarian tumor.

Carlos Bacchi: Great case, thanks.

David Ben-Dor: Mucinous tumors in elderly women can get very big and very bloody in my experience. The tumor cells have apocrine features characteristic of breast tumors which I'm not sure are typical for ovary (at least in my experience).

Michele Bisceglia: Primary mucinous cystadenocarcinoma of the breast. Agree, with a NOS-component. Carlos Bacchi contributed to the Club one such case soon after the entity was recognized (AMR Seminar 28). We personally saw one case (consultation case) which was presented at the at the 18th International Meeting of the Adriatic Society of Pathology held in Opicina-Trieste in 2004 (June 26-27) (S. Fiaccavento and M. Bisceglia. Mucinous cystadenocarcinoma of the breast: report of a case. - pag. 4 of the Abstract Book). Parenthetically the ASP was founded among others also by Janez and Vincenzo (and I have also to say that that 18th Meeting was the first and the only one of the Society I attended so far).

Ira Bleiweiss: While I agree that a portion of this lesion is the very rare mucinous cystadenocarcinoma of breast, it is admixed with invasive micropapillary carcinoma, a tumor which often has mucinous differentiation. Invasive micropapillary carcinoma invades lymphatics even at very small size, and the great majority of cases (either pure or mixed) are associated with positive lymph node(s). Thus mixed lesions typically behave according to the worst component, and I would not give this case the better prognosis usually ascribed to mucinous cystadenocarcinoma or pure low nuclear grade mucinous carcinoma. It may not matter as much in a 79 year old woman, but did she have a sentinel node biopsy? Also ER/PR negativity in the micropapillary carcinoma would be extremely unusual as they are typically ER/PR positive and Her2 is positive in 60% of cases.

Thomas Colby: Agree with diagnosis; I probably would have called this high-grade ductal carcinoma, perhaps with some apocrine differentiation and missed the significance of the mucin.

Kum Cooper: Thank you for sharing this case, Santiago. The key element (as you mention in your discussion) is the exclusion of metastases (ovary/colon/pancreas).

Ivan Damjanov: A variant of mucinous adenocarcinoma, but as you point out maybe it is worth separating them from other mucinous tumors.

Otto Dietze: The only case I remember was from a seminar with F. Tavassoli.

Hugo Dominguez-Malagon: Mucinous cystadenocarcinoma, although I would call it "mixed adenocarcinoma". I see areas with apocrine change and comedonecrosis; also, there is a micropapillary component.

Göran Elmberger: Thanks for sharing this highly unusual case with features of both mucinous cystadenocarcinoma and columnar cell mucinous carcinoma. From the prognostic perspective, I wonder if the small ductal infiltrative component should be interpreted as sign of combined mucinous and infiltrating ductal carcinoma indicating a more guarded prognosis.

Vincenzo Eusebi: Mucinous cystocarcinoma, primary. The frank invasive part looks apocrine or oncocytic.

Giovanni Falconieri: I am not questioning your interpretation, Santiago. Unfortunately, my slide has just areas of conventional ductal carcinoma in pools of mucins adjacent to foci of high grade DCIS. A few dilated spaces with neoplastic covering are represented but as long as I can see, they look more like conventional in-situ/clinging; perhaps images of intraductal mucinous carcinoma is the best approximation I could recognize.

Cyril Fisher: Mucinous adenocarcinoma of breast, very nice slide.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: Thank you very much for the beautiful case. I have never seen mucinous cystadenocarcinoma of the breast.

Allen Gown: Thank you for this interesting case. Highlights the heterogeneity of so-called "triple negative" breast cancers!

Thomas Krausz: The phenotype of the tumor cells also suggests apocrine differentiation.

Janez Lamovec: The first one I see. One should also consider mucoepidermoid carcinoma in such cases but there is of course no clear epidermoid component seen in this one.

Thomas Mentzel: I`ve never seen a case like this, many thanks.

Liz Montgomery: Thanks for an instructive rare breast lesion.

Juan Rosai: I guess that the term “primary mucinous cystadenocarcinoma of the breast” is as good as any to describe this peculiar tumor.

Dominic Spagnolo: On my section, I can't call this mucinous cystadenocarcinoma. It looks like invasive ductal CA with focal mucinous areas, surrounding high grade DCIS, and with remote intralymphatic tumor emboli.

James Strauchen: Mucinous cystadenocarcinoma of the breast! Thank you!

Saul Suster: My slide shows beautiful features of mucinous cystadenocarcinoma. Thank you for contributing this unusual case.

Larry Weis: I agree. These carcinomas are probably more common than the literature might suggest.

CASE NO. 16 – CONTRIBUTED BY JOSHUA SICKEL:

Phil Allen: If I have encountered one of these before, I'm afraid that I missed it. Thanks for showing it to me. I hope I don't miss the next one.

Carlos Bacchi: Great case, thanks.

David Ben-Dor: I was used to clear cell type of renal cell carcinomas undergoing sarcomatoid changes and behaving aggressively but didn't know that the chromophobe type (which I think usually has a better prognosis than the other types) could do the same thing. The osteogenic component is quite distinctive and well developed in this tumor.

Michele Bisceglia: De-differentiated chromophobe renal cell carcinoma with osteosarcomatous differentiation. Most interesting case.

Ira Bleiweiss: Agree. Osteosarcoma.

Thomas Colby: Agree with diagnosis. Chromophobe carcinoma with sarcomatoid differentiation and heterologous osteosarcomatous components. No, not seen in chromophobe before. Thank you. It seems (to me at least) that the term "dedifferentiated" has been "abused" in recent years with the application to salivary gland and endometrial tumors.

Ivan Damjanov: Agree. Must be very rare.

Hugo Dominguez-Malagon: Beautiful case of chromophobe renal cell carcinoma with osteosarcomatous component, although I would not call it “de-differentiated” since there is not a sharp separation of both components but a mixture of elements.

Göran Elmberger: Interesting case. Did not see any case here but I am suffering from increasing subspecialization. I believe this “dedifferentiation” is a quite common and more commonly recognized phenomenon in tumor biology and tumor histopathology today than before. Still the nomenclature is a bit problematic. When do we use dedifferentiated, divergent differentiation, high-grade transition, carcinoma ex, metaplastic carcinoma, carcinosarcoma, combined carcinoma, hybrid tumor and collision tumor to mention a few terms? Has tumor biology advanced far enough to let us agree on a consistent and logical classification terminology?

Vincenzo Eusebi: Renal cell carcinoma with bone differentiation.

Giovanni Falconieri: Wow, Josh! This is an impossible case, Thank you for sharing it with us.

Cyril Fisher: Dedifferentiated chromophobe carcinoma with osteosarcoma, great case.

Christopher Fletcher: Remarkable, very impressive and very rare case with entirely convincing features – I have not personally seen such a tumour before.

Jerónimo Forteza Vila: I agree with the diagnose that proves the potentiality of stem cells.

Masaharu Fukunaga: A wonderful case of dedifferentiated chromophobe renal cell carcinoma with osteosarcomatous differentiation. I thought it was a metaplastic carcinoma.

Allen Gown: Thank you so much for this extremely unusual case…I doubt I will see another one of them!

Thomas Krausz: Beautiful example.

Janez Lamovec: We saw a case of chromophobe renal cell carcinoma in association (in collision) with angiomyolipoma (AMR 43/11) but this is the first one with osteosarcomatous dedifferentiated component that we see. Thank you.

Thomas Mentzel: Many thanks for this interesting case! Can we call these neoplasms also chromophobe carcinoma with metaplastic osteosarcomatous changes?

Michal Michal: Nice case. We just saw a case of chromophobe renal cell carcinoma with liposarcomatous differentiation.

Markku Miettinen: Agree on chromophobic carcinoma with an osteosarcoma-like component.

Elizabeth Montgomery: RCC with osteosarcoma is very interesting. We have seen this as well. There is also another new case report: Quiroga-Garza G, Khurana H, Shen S, Ayala AG, Ro JY. Sarcomatoid chromophobe renal cell carcinoma with heterologous sarcomatoid elements. A case report and review of the literature. Arch Pathol Lab Med. 2009 Nov;133(11):1857-60.

Santiago Ramon y Cajal: The sharp transition in morphology among chromophobe renal cell carcinoma and osteosarcomatous differentiation is remarkable.

Juan Rosai: I agree completely with the diagnosis.

Dominic Spagnolo: Wow! Have certainly not seen this high grade osteosarcomatous dedifferentiation in a chromophobe carcinoma before. Thanks for the case!

James Strauchen: Chromophobe RCC with an osteosarcomatous sarcomatoid component. Does the osteosarcomatous component respond to chemotherapy for osteosarcoma?

Saul Suster: Great case Josh! Agree with the diagnosis. I have seen chromophobe carcinoma with spindle cell sarcomatous elements before but never one with osteosarcomatous differentiation.

Larry Weiss: I have seen chromophobe with sarcomatoid differentiation, but I do not recall specific osteosarcomatous differentiation.

CASE NO. 17 – CONTRIBUTED BY DOMINC SPAGNOLO:

Phil Allen: Florid marginal zone hyperplasia of the spleen. Without your erudite analysis, Dom, I would have had to consult the successor of the famous Florentine, Dr Guido Banti (1852-1925), who was the most eminent Italian pathologist of the early 20th century.

Carlos Bacchi: I would agree with the diagnosis of florid marginal zone hyperplasia as I don't see anything (clinically, morphologically, immunohistochemically and by molecular biology studies) definitive for lymphoma.

David Ben-Dor: I assumed it was lymphoma also until I read the erudite and convincing presentation. This goes to show that hematopathology is becoming more and more difficult, even for experts. Aside from

the molecular biology pointing to a benign condition, is the history of a persistent condition necessarily against low grade lymphoma?

Michele Bisceglia: Dom, I have seen a case recently, with an interesting clinical history. Splenomegaly with marginal zone hyperplasia with accompanying (in white pulp) histiocytic epithelioid microgranulomatous reaction, which I called (marginal zone hyperplasia – not lymphoma – on fragmented laparoscopic splenectomy specimen). Microgranulomatous epithelioid reaction had also been found in bone marrow on trephine biopsy. The patient was also affected by enlarged intraabdominal lymphadenopathies, which we suggested to biopsy. Around 1 year after the spleen diagnosis of MZ hyperplasia a perihepatic enlarged lymph node was excised. This lymph node also had MZ expansion but was not clear cut MZ lymphoma. Then I decided to submit all the previous samples along with the lymph node to Stefano Pileri: his molecularly-based final diagnosis was MZ lymphoma in the lymph node, but could not demonstrate clonal rearrangement in the spleen. Based on the lymph nodal finding he concluded that the spleen features are "suspicious" for liver involvement by MZ lymphoma.

Thomas Colby: Agree with your interpretation, Dom. As we all know, biology sometimes belies morphology. It is hard to get away from lymphoma on morphologic grounds but numerous ancillary studies failed to confirm lymphoma or a viral-related lymphoproliferation. I guess there is a good reason that hematopathology has a large armamentarium of ancillary supportive studies.

Kum Cooper: Dom, you are correct (as always) and you have considered everything; however, only the Aussies would follow a 19 cm spleen for 43 months!

Ivan Damjanov: I vote for benign hyperplastic changes. Do you have follow-up?

Otto Dietze: H&E morphology seems to me quite typically for splenic marginal zone lymphoma. However, according to the immunostaining I cannot offer another diagnosis than yours. I am interested to hear about the lymphoma experts' opinion.

Hugo Dominguez-Malagon: When I saw the slide it looked to me like a marginal zone lymphoma (although my experience is limited). It is difficult to trace (clinically and pathologically) the border between a reactive process and neoplastic transformation.

Göran Elmberger: Seems you have done a thorough work-up. From my non-hematologic perspective, nothing to add.

Giovanni Falconieri: Very difficult case, Dom. We are also challenged with some frequency by huge splenectomy specimen with borderline clinical and microscopic features. I went over and over the history and I have repeatedly looked at the features of your case. Needless to say that I am not sure about the diagnosis, however, I believe that the number of concerning features are too many for a reactive condition and I am afraid that I would entertain marginal lymphoma as the main possibility. I shall look to reading the opinions of the accounting heme-people members, as to get from you all a more solid back-up for cases that, I am confident, I'll get in the near future.

Cyril Fisher: Mantle zone hyperplasia. I do not see lymphomas outside the soft tissue but found the discussion very interesting. Thanks, Dom.

Christopher Fletcher: Have never personally encountered anything similar – a truly remarkable case in which your argument for a reactive/hyperplastic process is quite convincing.

Jerónimo Forteza Vila: Clinical data and morphology can not ruled out the diagnosis of lymphoma, even though polyclonality is seen. It is mandatory that the patient be followed-up.

Masaharu Fukunaga: My impression was marginal zone lymphoma. It is very unusual case clinically and pathologically. Thank you very much for the detailed analysis and discussion.

Thomas Krausz: I must say, that I also thought this was a lymphoma (but I am not a hematopathologist).

Janez Lamovec: I am sorry, Dominic, but I would diagnose this as a splenic marginal zone lymphoma as you did and I believe most of other pathologists would do. Splenic marginal zone hyperplasia – I don't know.

Thomas Mentzel: What an unusual case! Unfortunately, I have no sensitive answers to the questions.

Markku Miettinen: Difficult case. By histology, could go either way. Molecular evidence does not seem to point toward marginal zone lymphoma so that I agree with marginal zone hyperplasia. Follow-up might be advisable.

Liz Montgomery: I have no better dx though would have called it splenic MALT/marginal zone lymphoma based on the H&E but it seems like you tried to prove that and could not. The question remains – what is all this stuff reacting to! Your idea of an uncharacterized virus seems sensible.

Santiago Ramon y Cajal: ?????? Great clinical history and follow up. By microscopy, looks more consistent with a florid hyperplasia although should be important to rule out a marginal lymphoma by molecular biology.

Juan Rosai: I confess I would have called this lesion a marginal zone lymphoma, myself, on the basis of the H&E slide. Actually, I would not rule out that possibility entirely because of the negativity of the flow cytometry findings.

James Strauchen: Looks like SMZL to me! Both flow and molecular studies have false negatives!

Saul Suster: Dom, I will have to humbly accept your interpretation because I have been disconnected from hematopathology for quite a while already. Had I encountered this case 10 years ago, calling it lymphoma would have been a “no-brainer”.

Larry Weiss: While your workup seems to be complete, I have a hard time believing this is not lymphoma, if only because this case turns completely upside down my histologic notions of what constitutes a splenic lymphoma. There is too much expansion of the individual white pulp areas, there are too many white pulp areas, and there is too much infiltration into the red pulp. It just has to be a splenic marginal zone lymphoma, and no, I have never seen a case of splenic marginal zone hyperplasia that has come close to this. Now, I cannot explain the polyclonal results of your immunohistochemical, flow cytometry, and molecular genetic studies, and I do not doubt that you do them well. My only (and probably inadequate) suggestion is to do a CD138, and see if there is a population of non-immunoglobulin-bearing plasma cells. Other than that, I may have to just change my concept of the range of marginal zone hyperplasia can look like in the spleen.