COMMENTS TO AMR SEMINAR #62

CASE NO. 1 – CONTRIBUTED BY VOLKAN ADSAY:

Phil Allen: Rosai-Dorfman disease, sigmoid colon, serosa and mesentery.

David Ben-Dor: Obviously necrotizing granulomas. Otherwise no clue. I'm sure it's something unusual and fascinating and that there is some clue buried in the histology that I'm too benighted to pick up.
(Revised comment: maybe this is cheating but after looking at Ofer's case I do see some punctate matter in the cytoplasm- is this also malakoplakia? A double header? - not the first time in my club experience).

Michele Bisceglia: A soft tissue mass involving the wall of sigmoid colon. I suspect several possibilities of totally different etiology: from ameboma (but would need PAS stain) to Rosai-Dorfman disease (but would need immunostains) to other conditions.

Ira Bleiweiss: Reactive and histiocytic lesion. Sclerosing mesenteritis? Malalkoplakia?

Thomas Colby: I am stumped on this one; have considered histiocytic/inflammatory proliferations such as Rosai-Dorfman disease, Erdheim-Chester disease; of course, IgG4 disease is always at the tip of one's tongue these days; some of the cells might contain crystals and a crystal-producing lymphoma post-chemotherapy might look like this; could not really decide if there was necrosis or some peculiar degenerative change; peculiar granular cell tumor/granular degeneration in some other tumor. Look forward to knowing what it really is.

Kum Cooper: Rosai-Dorfman disease. Areas of granulomatous inflammation and necrosis: R/O mycobacterial infection. I have seen two cases with both diseases in the same sections.

Otto Dietze: Histiocytic disease (Rosai Dorfman Disease vs . Erdheim-Chester disease).

Goran Elmberger: Non-neoplastic? Inflammatory-infectious? IgG4? Malakoplakia? Storage disease? Rosai-Dprfman disease? Subserosal location? Stains and clinical correlations needed! Looking forward to solution.

Vincenzo Eusebi: I think it is Rosai-Dorfman's disease if S-100 is positive.

Giovanni Falconieri: Sorry, no idea; just guessing: ? Inflammatory pseudotumor ? IgG4 disease.

Franco Fedeli: A soft tissue mass involving the wall of sigmoid colon. The slide shows fibrosis and dense infiltrate composed of large histiocytes, lymphocytes and plasma cells. The presence of emperipolesis, or the engulfment of lymphocytes and erythrocytes by histiocytes could be suggestive of Rosai-Dorfman disease. Another possibility could be an infectious process (Amebic pseudotumor of the colon?).

Christopher Fletcher: This looks suspiciously like crystal-storing histiocytosis associated with a B cell/ plasma cell neoplasm.

Andrew Folpe: Rosai Dorfman disease.

Allen Gown: Could this be a FDC Tumor?

Masaharu Fukunaga: Thank you very much for the very interesting case. Inflammatory myofibroblastic tumor, low grade, is considered.

Thomas Krausz: Favor Rosai-Dorfman disease; (Pecoma is less likely).

Janez Lamovec: Rosai-Dorfman-Destombes disease.

Thomas Mentzel: Plasma-cell rich, sclerosing inflammatory pseudotumour with focal necrosis.

Michal Michal: Rosai-Dorfman disease.

Markku Miettinen: Rosai-Dorfman disease.

Elizabeth Montgomery: Rosai-Dorfman disease.

Cesar Moran: At first glance I thought about the possibility of inflammatory myofibroblastic tumor but I see lots of larger cells that may be histiocytes containing some sort of material in their cytoplasm. At the end I am not sure.

Juan Rosai: It looks inflammatory rather than neoplastic. Maybe I am imagining, but I think there is emperipolesis. I would love to see an S100 protein stain.

Brian Rubin: I don't think it's neoplastic – looks more inflammatory. The histiocytes are very large and I thought I could see crystals in some of them. Could this be a crystal storing histiocytosis? I've only see a couple of cases before. Otherwise, I'd guess it would turn into an inflammatory myofibroblastic tumor or IgG4 sclerosing disease.

Dominic Spagnolo: Looks like Rosai-Dorfman disease with spindle cell pseudotumor and granulomas. Has atypical mycobacterial infection been ruled out? The two may coexist (Kum Cooper wrote about this in the late 90's).

James Strauchen: Extranodal Rosai-Dorfman disease involving the colon. Some of the plump histiocytes demonstrate emperipolesis!

Bruce Wenig: Epithelioid and spindle shaped histiocytic appearing cellular proliferation with admixed mature plasma cells and lymphocytes within the depth of the colonic wall. There is emperipolesis. In areas, the cytoplasm of these cells appears fibrillar and possibly contains crystalline material. My diagnostic considerations include crystal storing histiocytosis, extranodal Rosai-Dorfman, mycobacterial spindle cell pseudotumor and rhabdomyoma or variant thereof. I would do appropriate staining to rule in/rule out these considerations. I would also wonder if the patient has known lymphoplasmacytic neoplasm (e.g., multiple myeloma, other) and/or monoclonal gammopathy. I look forward to learning what this lesion represents.

Ady Yosepovich: Plenty of plasma cells, fibrosis, my differential infection vs. inflammatory. There are large bizarre looking cells, some of them show emperipolesis or maybe ameba like cells. PAS stain? S-100 – Rosai-Dorfman? IgG4 related disease? GIST? Inflammatory pseudotumor?

Volkan Adsay: My case. S100 protein immunostain confirmed that the histiocytic type cells with large nuclei, vesicular/washed-off chromatin and single prominent nucleoli are indeed positive for this antibody, making us conclude that this is Rosai-Dorfman disease (SHML). There were also foci with emperipolesis further supporting this diagnosis. Interesting finding in this case was that the IHC also showed the abundance of IgG4 plasma cells. Whether this can then be regarded as an "IgG4-related sclerosing disorder (I4SD) " (associated with Rosai-Dorfman in this case) or not, I am not sure, and would like to hear everyone's opinion on this. My inclination is to think that the IgG4-positive plasma cells are an epiphenomenon, a result of the immune derangement as a secondary result of the Rosai-Dorfman in this patient. I suspect the cases being reported in the literature recently also represent this phenomenon. Of note, most of these reports are by Asian authors (whether a sign of higher incidence in Asia or the current publication boom by Asian authors, hard to tell). Because of my interest in the pancreas, I cannot help but follow the ongoing hype in IgG4 plasma cells rather closely. Despite the general impression (or mis-impression), immunologists agree that, even in classical I4SD lesions, IgG4 plasma cells are actually a product but not necessarily the primary process nor the underlying mechanism of I4SD. Along these lines, since I have been paying attention (and have been wasting money doing IgG4 IHC fairly commonly), I have been seeing IgG4 plasma cells increased in various tissues as a part of the routine inflammation. An increase has been also noted in pilonidal sinus cases, for example. We also recently performed the IgG4 immunostain in 150+ gallbladders with plasma cell infiltrates and found IgG4 plasma cells to be increased in not too insignificant number of ordinary cholecystitis cases, in many cases, > 50/HPF (the current cut-off being advocated, which is thankfully increased from "10" that used to be a couple of years ago). Interestingly, many of these "unexpected" IgG4 high cholecystitis cases also had diabetes mellitus. Therefore, I am beginning to think that IgG4 plasma cell infiltrate is a pattern (epiphenomenon) of certain types of injury, and I4SD is simply one of those. In a way, this can be likened to the organizing pneumonitis and BOOP relationship. And Rosai-Dorfman (SHML) may very well be yet another disease with capability to recruit IgG4 plasma cells in abundance. I remember seeing multiple cases of Langerhans cell histiocytosis associated with Rosai-Dorfman with Dr. Rosai in his consultation material. This (IgG4-rich fibroinflammatory reaction) may be another

example of how RD-SHML cells may lead to other immune proliferations. Any follow-up comments will be greatly appreciated.

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

Phil Allen: Clear cell Hurthle tumor (2.2 cm in diameter) right lobe of thyroid, male aged 75. Thanks for the discussion on the clear cells. I could not see the extracapsular vascular invasion, without which I am reluctant to make a diagnosis of thyroid carcinoma. Hurthle cell carcinomas of the elderly frequently exhibit extensive extracapsular vascular invasion which is apparent to the surgeon at operation. I would not be surprised if this patient eventually dies from something other than a thyroid carcinoma.

David Ben-Dor: Nice case if I say so myself. Hope everyone else finds it worthy of his/her attention.

Michele Bisceglia: Encapsulated Hurthle cell carcinoma of the thyroid with extensive cytoplasmic clear cell changes. Very nice case description and discussion. Agree with that diagnosis, even including the oncocytic variant (with clear cell changes) of papillary carcinoma. Immunohistochemistry with antibody mES-13 to mitochondrial antigen would definitely prove the oncocytic nature.

Ira Bleiweiss: Agree but this reminds me why I hate thyroid.

Thomas Colby: Agree with diagnosis. It is clear that the issue of clearing has been cleared up, but with some granularity.

Otto Dietze: Good case and discussion. Despite I am in an endemic goitre area, I did not see this peculiar differentiation before.

Kum Cooper: Thanks David. Nice example of Hurtle cells with clear cell change. I have not seen this in the thyroid before.

Goran Elmberger: Nice case and discussion on thyroid clear cell tumors. Agree on classification even if I must admit I rarely get to see these kinds of cases here at Karolinska where Lars Grimelius and Anders Höög sign out and guard their area well. Seems to be aggressive towards capsule with suspected vascular capsular invasion at one point in my section.

Vincenzo Eusebi: I agree with the diagnosis of Hurtle cell carcinoma showing clear cell changes. Very nice case. Oncocytes when undergoing degranulation of their cytoplasm become clear.

Giovanni Falconieri: Difficult case, never seen this pattern before. I shall look forward to reading the thyroid gurus' opinion. Thank you for submitting this valuable case.

Franco Fedeli: Encapsulated Hurthle cell carcinoma of the thyroid with extensive cytoplasmic clear cell changes. Thanks, David for your exhaustive discussion. In the old literature we found an article "Papillary carcinoma of the thyroid, oxyphil (Hurtle) cell type, "clear cell" variant (Am J Surg Pathol 4:501-509, 1980). In your case there are very small foci of tumor composed of typical papillary thyroid carcinoma; the most part of this tumor shows columnar cells with clear apical portions, oxyphilic basal zone, and mid-placed nuclei.

Christopher Fletcher: Convincing example of Hürthle cell carcinoma with clear cell change. The presence of residual brightly eosinophilic cytoplasm in a significant subset of the lesional cells would argue against spread from a renal cell carcinoma.

Cyril Fisher: Angioinvasive Hurthle cell tumor with clear cell change.

Andrew Folpe: Agree with some type of unusual follicular neoplasm with clear cell change. I might have considered a metastatic neuroendocrine tumor too, and done chromogranin/synaptophysin.

Thomas Krausz: Agree with diagnosis. Thank you for the thorough discussion.

Masaharu Fukunaga: My impression is Hurtle cell follicular carcinoma and some areas seem to be papillary carcinoma. Nice description of clear cell changes of the thyroid.

Allen Gown: Never use thyroglobulin to distinguish metastatic renal cell CA to thyroid from thyroid carcinoma! The combination of PAX8 and TTF1 positivity is diagnostic of thyroid.

Janez Lamovec: Hurthle cell carcinoma with extensive clear cell change. We've seen this change occasionally in benign thyroid nodules as well as in different types of carcinoma, often very focally.

homas Mentzel: A very nice case of follicular carcinoma with prominent clear cell changes, many thanks.

Markku Miettinen: Agree on follicular carcinoma with clear cell features. Vascular invasion is present in the capsular region.

Elizabeth Montgomery: This is terrifying. I only thought of it because Pete Argani likes to fool us with these.

Cesar Moran: Interesting case, in my slides the clear cells make the bulk of the tumor. Why not clear cell carcinoma.

Juan Rosai: Dr. Ben-Dor summarized so well the section on "clear cell features" of thyroid tumors in our AFIP fascicle that he left nothing for me to say. By the way, the 4th series of this fascicle is essentially complete.

Brian Rubin: Didn't have a slide for this one. Sounds like an interesting case though.

Dominic Spagnolo: It is "spectacular" David! Agree with your diagnosis of oncocytic carcinoma with prominent cytoplasmic clearing.

James Strauchen: Oncocytic follicular thyroid carcinoma with striking clear cell change. Supports the concept that clear cell change (like oncocytic change) is a secondary phenomenon seen in a variety of thyroid lesions!

Saul Suster: Follicular carcinoma with clear cell features and focal oncocytic features. My slide shows a focus of unequivocal vascular invasion in the capsule.

Bruce Wenig: There are many controversial issues in thyroid pathology, including but not limited to what constitutes invasive growth (capsular and lymph-vascular). Certainly this is a large encapsulated thyroid follicular cell neoplasm characterized by cells with prominent oncocytic cytoplasmic changes (so-called Hürthle cells) and clear cells lacking nuclear features diagnostic for papillary carcinoma. There are reactive and degenerative changes in this lesion consistent with alterations secondary to the previous FNAB. In areas such reactive/degenerative changes obscure the periphery of the lesion. In my slide I see no convincing evidence of capsular invasion and there is a grouping of blood vessels that may or may not be outside the confines of the lesion proper. Based on the slide I reviewed I would be reluctant to diagnose this case as a follicular carcinoma given the equivocal presence of invasive growth. However, I would not be surprised if this lesion were invasive in other slides and/or in other sections of the neoplasm. Nice discussion on the issue of cytoplasmic clearing a feature that can be seen in oncocytic dominant lesions of the thyroid gland (as well as salivary glands).

Ady Yosepovich: A very nice case, I would also consider in the differential oncocytic variant of medullary carcinoma (adding calcitonin, congo-red, thyroglobulin stains; would also stain for PTH).

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

Phil Allen: Malakoplakia in colo-rectal adenomas in a renal transplant patient. I thought I could always spot malakoplakia, having found a couple in prostatic core biopsies, but I missed this one. Thanks very much for the very instructive discussion.

David Ben-Dor: This is quite an eye opening case. I wish I could say that I was able to get the diagnosis on my own. There are punctate inclusions in the cytoplasm of the macrophages but I didn't know what to make of them. Unfortunately the slides become faded by the time I get to them; I'm not sure to what extent the inclusions are

laminated in the picturesque manner demonstrated by the beautiful photo of this entity in Jonathan Epstein's bladder biopsy book (p. 189 2004 edition). On second thought I'm going to revisit Volkan's case.

Michele Bisceglia: Malakoplakia in colorectal adenomas. Very interesting and informative discussion. Thank you, Ofer. Have seen 2-3 personal cases in the pelvis, all in association with genitourinary pathologic processes. Indeed PAS, and stains for calcium and iron do highlight Michaelis- Gutmann bodies.

Ira Bleiweiss: Malakoplakia, the real thing. I haven't seen one in a real long time.

Thomas Colby: Agree with diagnosis. Once one sees one M-G body then they start jumping out.

Otto Dietze: Hitherto I have seen cases of MAP only in the urogenital tract.

Kum Cooper: Great example of Malakoplakia. Thank you for the great write-up. I have seen malakoplakia associated with schistosomiasis in the urinary bladder (Africa).

Goran Elmberger: Great case. Got it after struggling with Volkans quiz case. Read in Cecilia Fenoglia-Preiser's excellent textbook on GI Pathology; Atlas and text; 3'd ed; Lippincott; table 13.24 p.852 of various malakoplakia associated diseases including carcinomas and immune deficiency. Any positive identification of organism in this case? Our microbiologists are starting to play around with Malditoff for cases like this... Our molecular biologist is trying out ribosomal RNA subtyping... Quite amazing even if it probably does not make a big difference in care for the patient in every case...On the other hand the Michaelis-Gutmann bodies can be quite difficult to spot and last time I tried our von Kossa in histochemistry it did not perform too well...Times are changing! Thanks.

Vincenzo Eusebi: Very good example of malakoplakia.

Giovanni Falconieri: Amazing case. Thank you for the thorough case discussion.

Franco Fedeli: Malakoplakia in colorectal adenoma. Very educational case. I think also that we have to open mind about the different histological diagnosis on biopsy between malakoplakia and Whipple disease (I know that usually clinically these diseases have little in common!). Foci of malakoplakia in the lamina propria show histiocytes disclosing numerous typical Michaelis-Gutmann bodies. In the Whipple disease accumulation of foamy macrophages (containing the intracellular pathogen) usually appear as a diffuse infiltration in the lamina propria of the small intestine, although a more localized and even polypoid appearance has been noted. Whipple's disease of the colon is absolutely rare.

Cyril Fisher: Malakoplakia, nice case. Thanks for images of 'special' stains.

Christopher Fletcher: Indeed convincing malakoplakia – I am sure that the association with an adenoma is coincidental and, instead, the history of renal transplantation may be more significant in this regard.

Andrew Folpe: Cool- I've never seen malakoplakia in this location before. Thanks.

Masaharu Fukunaga: Malakoplakia with adenocarcinoma in adenoma of the rectum. Beautiful case of malakoplakia! I have never seen malakoplakia of GIT.

Allen Gown: Thank you for this fascinating case of malakoplakia.

Thomas Krausz: Beautiful example.

Janez Lamovec: Spectacular case of malakoplakia in colorectal adenoma!.

Thomas Mentzel: A nice example of "always think twice", and to be honest I`ve missed the associated, specific inflammation.

Markku Miettinen: Agree on malakoplakia although parasite/infection was in the differential, in fact it probably is a product of E. coli infection.

Elizabeth Montgomery: Glorious case of malakoplakia. Thanks so much.

Cesar Moran: Nice case.

Juan Rosai: You have to look hard for the Michaelis Guttman bodies, but the search is very rewarding. They are as typical as they can be.

Brian Rubin: Haven't seen a case of malakoplakia in a long time. Nice case and discussion. I didn't realize it was associated with immunosuppression.

Dominic Spagnolo: Beautiful case of malakoplakia of the colon in an immunosuppressed patient, and involving an adenoma. Can't ask for more!

James Strauchen: Adenoma with malakoplakia! Never seen it in a polyp! Thank you for this informative case!

Saul Suster: Nice case of intestinal malakoplakia. Dr. Rywlin wrote a paper about this topic (Rywlin AM et al. Malakoplakia of the colon. Am J Dig Dis 14:491-499, 1969).

Bruce Wenig: I have seen a few cases of malakoplakia of various sites but not one in the colon. Nice case.

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

CASE NO. 4 – CONTRIBUTED BY GERALD BERRY:

Phil Allen: Pleuropulmonary blastoma, type 3. I never see any children's lung pathology. Thanks for showing this case.

David Ben-Dor: Immature hypercellular mesenchyme and somewhat more mature looking but still hypercellular cartilage consistent with provided diagnosis.

Michele Bisceglia: Pleuropulmonary blastoma, Type III. This is the first such a case in the AMR seminars. Very appreciated. A few years ago we had a case of lung metastasis from a teratoid nephroblastoma in a child and we had hard time in differentiating it from a primary PPB-type III, also considering the familial and intraindividual association of the two tumors* you referred to in the discussion to case 5. (*Ref. Boman F, et al. Familial association of pleuropulmonary blastoma with cystic nephroma and other renal tumors: a report from the International Pleuropulmonary Blastoma Registry. J Pediatr. 2006;149:850-854).

Thomas Colby: Agree with diagnosis; lovely case.

Kum Cooper: See comments on case 5.

Otto Dietze: The few cases I have seen were mainly of the type 2.

Goran Elmberger: Great and fairly classical case although obviously rare. Malignant appearing cartilage with fibrosarcoma-like blastematous areas. Focal pleomorphic areas possibly representing rhabdomyoblastic differentiation with atypical mitoses. Peculiar tendency to develop fibrin thrombi with resulting tumor necrosis. Minor entrapped benign epithelial component without any atypia.

Giovanni Falconieri: Our experience with oncologic pediatric specimens is quite limited, hence I cannot comment. Yet, this looks a great case. Thank you for submitting this challenging lesion and the superb images.

Franco Fedeli: Pleuropulmonary Blastoma, Type III. I am particularly grateful for this fantastic pulmonary pediatric pathology subspecialty case.

Cyril Fisher: Pleuropulmonary blastoma, very interesting to see these two types together.

Christopher Fletcher: Pleuropulmonary blastoma, type III.

Andrew Folpe: Very nice and very timely. I have a case on my desk right now where the clinicians were wondering about this diagnosis. Unfortunately, it turns out just to be an undifferentiated high-grade sarcoma.

Masaharu Fukunaga: Pleuropulmonary blastoma, agree. Some areas seem to show rhabdomyoblastic and bone differentiation. Thank you very much for the beautiful case.

Allen Gown: Curious to know the immunophenotype of this tumor; e.g., is it TTF-1 positive?

Thomas Krausz: Agree with diagnosis. I have seen only few examples before.

Janez Lamovec: Pleuropulmonary blastoma, type III. A solid tumor with biphasic morphology and primitive mesenchymal component. Most instructing case.

Thomas Mentzel: Many thanks for sharing this clinically aggressive neoplasm. Is there an association of the morphology (extent of immature blastematous and/or sarcomatous tissue) with the prognosis in PPB Type III?

Markku Miettinen: Agree that the features match with those of type III pulmonary blastoma, but I have very little personal experience of this.

Elizabeth Montgomery: Stunning case of variant of pulmonary blastoma.

Cesar Moran: Great case.

Juan Rosai: Nice example of the tumor that prior to Pepper Dehner's description was usually called malignant teratoma.

Brian Rubin: Interesting case. It's been a while since I've seen a type I PPB.

Dominic Spagnolo: Nice to see this Type III pleuropulmonary blastoma, (and case 5) as I don't routinely see pediatric cases.

James Strauchen: Pleuropulmonary blastoma!

Bruce Wenig: Incredible case. I never get to see such lesion types so thank you for sharing.

Ady Yosepovich: Never seen one, thank you.

CASE NO. 5 – CONTRIBUTED BY GERALD BERRY:

Phil Allen: Regressed pleuropulmonary blastoma, type I. This makes an excellent companion for case 4.

David Ben-Dor: This is obviously no flash in the pan diagnosis but requires very careful clinico-pathological correlation and experience with pediatric pulmonary pathology. Not for the unwary or the inexperienced.

Michele Bisceglia: Pleuropulmonary Blastoma, Type I, regressed. Thank you, Gerry. This case is complimentary to the previous (florid) one contributed by John Chan a few years ago.

Thomas Colby: Histologically benign cyst, not otherwise specified. I am not sure I buy the diagnosis of regressed PPB. I am not sure I was aware of these undergoing spontaneous regression. Surely I was not aware that regression is "common" and short of having serial biopsies it would seem to be difficult to prove. It will be interesting to know if chemotherapy affects the other cysts in this patient. If they look like the current cyst, I doubt chemo would do anything and the clinicians may still be left with having to biopsy those to know what they are. I also think it is also unusual for type 1 PPB to present as multiple lesions. I would include other cystic lesions in the D/D.

Kum Cooper: Thank you Gerry for this treatise on PPB. I remembered JKCC's case and assumed that the Type I stroma was always rhabdomyoblastic; which you have now corrected with immature cartilage too. Also I was not aware that they can regress.

Otto Dietze: I agree, the other side of the spectrum of PPM.

Goran Elmberger: Only fibrotic cyst/pseudocyst wall and hemosiderin containing macrophages in my sections. Interesting phenomenon with regression of these lesions. I guess clinico-radiological correlations were important in this case but chemo without any morphological confirmation… Is radiology that characteristic?

Giovanni Falconieri: I am missing the point: without adequate clinical information it looks just normal lung. Very good images, congratulations! Thank you for circulating this impossible case.

Franco Fedeli: Pleuropulmonary Blastoma, Type I, regressed. Honestly I must admit not to know that pleuropulmonary blastoma can commonly undergo regression.

Cyril Fisher: This is very hard to diagnose in the absence of typical histologic features and the imaging findings seem contributory here.

Christopher Fletcher: I am sure that I would have missed the diagnosis of regressed pleuropulmonary blastoma in this case – I find cystic lesions in the lungs of children often to be very difficult and always defer to the pediatric experts.

Andrew Folpe: I'm not seeing much on my slides. I'll take your word for it.

Masaharu Fukunaga: It is very difficult to make a diagnosis histologically. It is beyond my understanding.

Thomas Krausz: This is difficult as it deviates from the classic. I do not have enough experience with this type of lesion, so if I get one in the future I will send it to you for expert opinion. Thank you for sharing pleuropulmonary blastoma cases with us.

Janez Lamovec: Without clinical data, this cystic lesion would be very hard to diagnose properly.

Thomas Mentzel: This is an "impossible" case for me.

Markku Miettinen: Agree that the features match with those of type III pulmonary blastoma, but I have very little personal experience of this.

Elizabeth Montgomery: This regressed pulmonary blastoma is apparently so regressed that I could not see it. I just see hemosiderin and scattered enlarged cells that I cannot recognize!

Cesar Moran: Interesting case as I do not see any mesenchymal component. I wonder how many of these cases one can miss by not having the classical mesenchymal component.

Juan Rosai: Nice demonstration of the wide spectrum that this tumor can exhibit.

Brian Rubin: Interesting that a PPB could undergo total regression. Kind of shocked that they would have given chemo but that's pediatric oncology for you.

Dominic Spagnolo: Edifying example of regressed type I PPB.

James Strauchen Another pleuropulmonary blastoma, this one sans blastoma! Didn't know they could regress!

Saul Suster: Could find no tumor in my slide. I guess this is not a diagnosis that can be made on histology alone and that requires clinical and radiographic correlation.

Bruce Wenig: Incredible case. I never get to see such lesion types so thank you for sharing.

CASE NO. 6 – CONTRIBUTED BY THOMAS COLBY:

Phil Allen: Intrapulmonary silicone emboli in a patient with a ruptured breast implant. The small intravascular vacuoles looked just like fat emboli but some residual silicone is still just visible in a few of the foreign body giant cells.

David Ben-Dor: Didn't see anything first time around. After reading the description I saw what I missed. Of course it's nice to be able to have the diagnosis confirmed with advanced technology (if you have access to it). The question is given the clinical history and the axillary lymph node, couldn't the pulmonary findings have been assumed without taking the trouble to do a biopsy? . (addendum: I found the answer to the question in the continuation of the handout. But if not silicone then what else? An occult tumor somewhere? I assume she was already worked up for tumor elsewhere (a likely culprit would be breast) with no diagnostic finding).

Michele Bisceglia: Silicone lung embolization from ruptured breast implant. A new entry in our seminars for silicone-induced pathology. We previously had a case of foreign body reaction to silicone in the breast (Sem. # 8 / case 2 by dr. M. Hurt) and two cases of non-Hodgkin lymphomas of the breast arising adjacent to silicone breast implant (Sem. # 57/ case 4 and Sem. 61 / case 19, contributed by G. Berry and J. Strauchen, respectively).

Ira Bleiweiss: "Metastatic" silicone. This case reminds me of a story... A number of years ago, when the lawyers were going after Dow Corning, et al in the silicone breast implant/autoimmune disease era, I was asked to look at some slides by one of the New York City Medical Examiners. I assumed it would be to classify some rare breast tumor, but instead she wanted me to look at lung and kidney slides (from an autopsy of course) since I had a lot of experience identifying silicone in capsules surrounding breast implants. Sure enough there was silicone in vessels in the lung and in the kidneys. The autopsied individual had been a man who had undergone a sex change and in so doing had direct silicone injections to create breasts. This was apparently preformed outside of the United States, being illegal here (although I'm told there is a black market). After a few years, he apparently developed progressive renal and pulmonary failure and expired. I told the Medical Examiner she should rule the death a homicide, although there would never be a way to track down the killer.

Kum Cooper: Thank you for sharing this unusual manifestation of silicone implants. I last saw a fat emboli that JKCC shared with us many years ago.

Otto Dietze: Well documented case (if you have the possibility to perform energy dispersive EM).

Goran Elmberger: Great case Tom. New to me but at least I spotted the minor deviations present in the slides. Inert substance giving rise to no tissue reaction but hemodynamic consequences.

Vincenzo Eusebi: Thank you very much for showing this instructive case of diffuse embolic process consequent to silicone.

Giovanni Falconieri: Tough to catch! Fantastic case, Tom. Thank you for supplementing illustrative images as well. It looks like just a minimal change disease of lung. The degree of difficulty is comparable to the case of acute fat embolism seen after hip replacement surgery which had been submitted by John Chan years ago (see AMR 26-4).

Franco Fedeli: Silicone lung embolization from ruptured breast implant. Yes, Thomas, you are correct. I think that this case encourages pathologists to consider injected silicone in the differential diagnosis of optically empty spaces within the pulmonary vasculature, even if the typical light microscopic features of residual silicone are not seen (Detection of silicone in Lung Tissue. Arch Pathol Lab Med-Vol 136, October 2012). After reading your text, I can only congratulate on your brilliant diagnosis and sophisticated atomic analysis with energy-dispersive X-ray spectroscopy.

Cyril Fisher: Silicone emboli, subtle appearances as you say.

Christopher Fletcher: Very convincing silicone embolus – I think that the multinucleate giant cells are the most obvious clue. I had no idea that such emboli were a potential complication of breast implants.

Andrew Folpe: Silicone embolism - very nice.

Masaharu Fukunaga: I have never seen this educational case, Thank you very much, Tom.

Allen Gown: Changes are subtle on my slide, although with that history and some persistence, I can see then. Thanks for the case.

Thomas Krausz: It is fascinating to see so many silicon containing macrophages in the alveolar wall/capillaries without attracting other inflammatory cells, or causing fibrosis or thrombosis.

Janez Lamovec: Another foreign material embolism submitted to AMR seminars. We've seen some other causes for this phenomenon before in the seminars (34-3; 52-6). Thank you for this most instructive case.

Thomas Mentzel: An interesting case that is easily missed, many thanks!

Markku Miettinen: Agree on silicone material although it was difficult to see bi-refringent material in the vacuoles (still focally present at least subpleurally). Obviously your spectroscopy finding is convincing.

Elizabeth Montgomery: Very very sneaky example of silicone lesion from breast implants. Another reason to be happy with what one was given.

Cesar Moran: Great case.

Juan Rosai: I guess this is a form of exogenous lipoid pneumonia (the vanity type).

Brian Rubin: No slide. Very interesting case – did not realize that silicone could embolize to the lungs.

Dominic Spagnolo: Dramatic example of embolic silicone pneumonitis.

James Strauchen Silicone emboli! Very pretty case!

Saul Suster: Never seen this before, Tom. Pretty spectacular – thanks for sharing it!

Bruce Wenig: Another incredible case. The vacuoles are quite distinctive. I have seen untoward events in the neck secondary to teflon injection (i.e., teflon granulomas) for paralyzed vocal cords but those injections were more or less a medical necessity. Esthetic enhancements carry risks but I would never have expected embolic silicone.

Ady Yosepovich: Fascinating case, thank you.

CASE NO. 7 – CONTRIBUTED BY THOMAS COLBY:

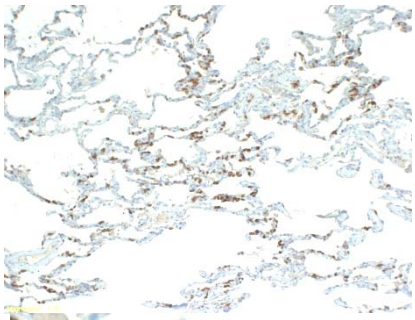
Phil Allen: Don't know.

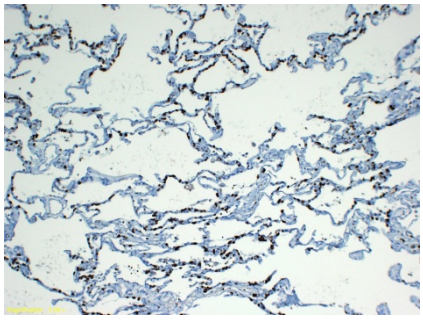
David Ben-Dor: I'm waiting to be amazed.

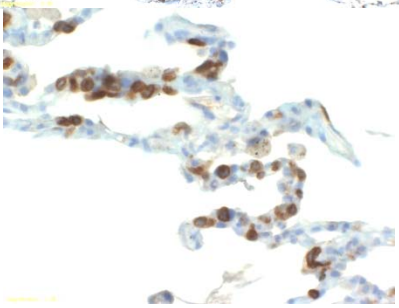
Michele Bisceglia: A 61-year-old man had dyspnea, diffuse pulmonary infiltrates and a history of deep vein thrombosis. Maybe the capillary lumina are filled with neoplastic cells (if so would immunostain also for hematologic/myeloid malignancy).

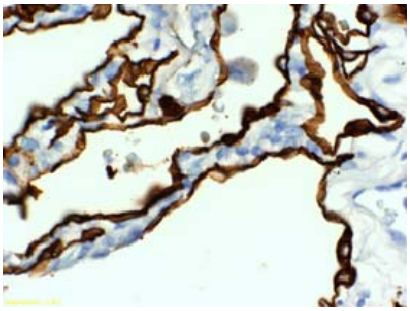
Thomas Colby: Careful examination of the H & E shows a population of atypical intermediate-sized cells within the capillaries associated with very mild foci of hemorrhage and alveolar septal widening. Immunohistochemically one is amazed at how many of these atypical cells are present. They stain positively with CD20 and CD79a and the diagnosis in this case was intravascular large B-cell lymphoma. CD31 highlights the intravascular presence of the cells. Cytokeratin highlights the presence of these cells within the alveolar septa. Ki-67 shows a high proliferation rate and again a very large number of cells compared to what is apparent on initial inspection of the H & E slide.

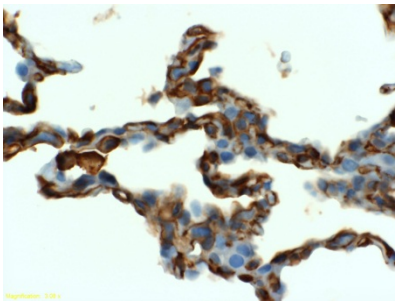
Images below in order are: CD79a, CD79a, CK, CD31, Ki-67, Ki 67.

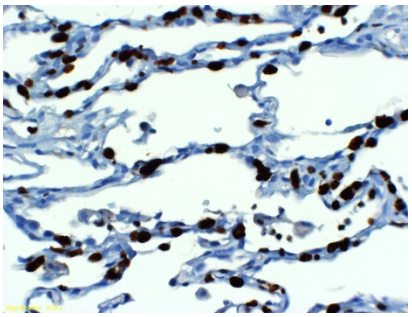












Kum Cooper: Large atypical cells in the interstitial capillaries? megakaryocytes.

Otto Dietze: Hematologic disease e.g. PV ?

Giovanni Falconieri: I would order congo red for amyloid, but the truth is that I have no clue, Tom!

Goran Elmberger: Subtle findings. Minor clinical info. Association deep vein thrombosis and cancer... Still knowing Tom has a surprise for us alveolar septae looks a bit busy. These anatomical structures contain pneumocytes, capillaries with endothelium and cellular content and some minor interstitial cellular constituents. I would like to penetrate with special stains which of these components is responsible for the busy look. I do see some atypical cells and some cells with cytoplasmic granulations and vesiculations. My guess is we may be dealing with tumor embolism

in the wide sense and the approach could be like the one we use for carcinomas of unknown origin. High on my list of differentials would be haematological disorders such as leukaemia –phenomenon called leukostasis but many other things could possibly explain these subtle findings. Infection-parasites intracellular?

Vincenzo Eusebi: There are cells with pleomorphic hyperchromatic nuclei in the septa. Whether they are megakaryocytes or neoplastic cells or something else I wait for the answer.

Franco Fedeli: A 61-year-old man had dyspnea, diffuse pulmonary infiltrates and a history of deep vein thrombosis lung biopsy was performed for diagnosis. I see in the septa cells with irregular nuclei. I am not sure about its nature. Is might be any link between the tumor (giving rise to embolism) and the vein thrombosis?

Christopher Fletcher: Some of the alveolar septa appear to be widened by a population of rounded or ovoid histiocytoid cells with finely microvacuolated cytoplasm. Focally, it appears possible that these cells may be present within the lumina of alveolar capillaries. The cytology reminds me of peripheral hemangioblastoma but the clinical presentation would seem quite ridiculous in that regard and therefore I look forward to being educated by Tom.

Andrew Folpe: I'm not seeing anything. This is going to be very embarrassing. OK Tom- what is it?

Masaharu Fukunaga: There are some fluid material in the veins and scattered cell with large hyperchromatic nuclei.

Allen Gown: There appear to be tumor cells within the alveolar walls, favor hematolymphoid. I have seen a lobular breast cancer infiltrate the alveolar walls this way, too.

Thomas Krausz: What am I missing? I can hardly wait for the answer. The only possibly abnormality I can see/imagine an increased number of "mononuclear cells" in the alveolar wall/capillaries. Perhaps I would also do an amyloid stain.

Janez Lamovec: I don't know what this is, we even thought of some strange type of plasma cell dyscrasia.

Thomas Mentzel: I´m looking forward to the results of immunostainings and the comments – unfortunately, I have no sensitive diagnosis.

Markku Miettinen: Not sure. Was trying to find platelet thrombi, immunostain for CD31 would be of interest. Also some flocculent material is present in alveoli (would immunostain pneumocystis). Otherwise, findings looked lean.

Elizabeth Montgomery: Clueless. Saw scattered enlarged nuclei but had no idea what they were.

Cesar Moran: Not sure what is in here but I think it may be capillaritis.

Brian Rubin: I didn't have a slide – looking forward to being amazed by Tom's immunostains and discussion.

Dominic Spagnolo: Either extramedullary hematopoiesis with an exquisitely alveolar septal distribution (which I probably favor) or intravascular lymphoma with the same distribution. The stains should be interesting!

James Strauchen Fibrosis around small vessels somewhat resembling "diffuse pulmonary lymphatic disease presenting as interstitial lung disease in adulthood" (AJSP 2012; 36:1548). Ready to be amazed!

Saul Suster: This is extremely subtle and I completely missed it! I noticed the atypical cells in the alveolar septae but had no clue as to what they could be.

Bruce Wenig: Either whatever is supposed to be pathologic in this case is not on my slide or more likely I have no idea what I am supposed to be looking for. I await your diagnosis with bated breath.

Ady Yosepovich: Sorry, just don't know.

CASE NO. 8 – CONTRIBUTED BY JONATHAN EPSTEIN:

Phil Allen: Renal oncocytoma with marked diffuse degenerative atypia. There is a good chance that I would have called this malignant. A most instructive case.

David Ben-Dor: Looking at the slide as is, without looking at any of the written material, this looked like a breast carcinoma at first glance. The atypia is very impressive and I agree that it is degenerative in type.

Michele Bisceglia: Oncocytoma with marked diffuse degenerative atypia. Never seen this kind of ancient degenerative atypia, despite having seen fairly numerous renal oncocytomas. Thank you.

Ira Bleiweiss: Agree. Oncocytoma.

Thomas Colby: Agree with diagnosis. Subtracting the atypia, the features are otherwise typical of oncocytoma.

Otto Dietze: I agree, I remember a few cases with a similar degree of atypia.

Kum Cooper: I have seen this degree of nuclear atypia only focally in oncocytomas but never this diffuse. Thank you for sharing this case. Thank you again Jon for presenting at the AMR in South Africa.

Otto Dietze: I agree, I remember a few cases with a similar degree of atypia.

Goran Elmberger: Impressing but degenerative atypia. I find the multinucleation fairly typical of these processes. With regards to the growth pattern, including relation to perirenal fat and vessels, it seems like a cousin of salivary gland pleomorphic adenoma. Any cases of benign metastasizing oncocytomas?

Vincenzo Eusebi: This is an oncocytic tumor (oncocytoma) with bizarre non-malignant nuclei. Some follicle-like structures are observed at the periphery of the nodule which makes again some neoplastic lesions of the kidney structurally and cytologically similar to thyroid lesions. Very nice case with appropriate discussion on the biology of the tumour.

Giovanni Falconieri: Of course, agree with oncocytoma. Never seen such a degree of bizarre nuclei.

Franco Fedeli: Oncocytoma with marked diffuse degenerative atypia. This is a new addition to the list of tumors with degenerative atypias. I think this is a paradigmatic example of this histological lesion.

Cyril Fisher: Remarkably atypical oncocytoma. Fortunately other features are present to aid diagnosis.

Christopher Fletcher: Oncocytoma with extensive degenerative nuclear atypia. I agree that immunostains seem to be quite unreliable in the distinction from chromophobe renal cell carcinoma.

Andrew Folpe: Oncocytoma with degenerative atypia. These can be tricky on FS.

Allen Gown: Thanks for the interesting case!

Thomas Krausz: I find it diagnostically challenging. Highly educational case; thank you very much for the diagnostically helpful tips.

Masaharu Fukunaga: Thank you for the great case and the concise comments. My impression was oxyphilic papillary carcinoma of the thyroid gland, follicular variant.

Janez Lamovec: In thyroid oncocytomas, we often see quite extensive foci of atypical cells of this type but I don't remember seeing them so diffusely. We don't have much experience with kidney lesions of this type.

Thomas Mentzel: A wonderful case of renal oncocytoma with prominent degenerative atypia. Probably the stromal changes are of help as well for the diagnosis.

Michal Michal: Degenerative oncocytoma. As proof of the diagnosis there is a component of small cell oncocytoma (Hes O. et al Human Pathol 201; 42:1751-1760).

Markku Miettinen: Agree on oncocytoid neoplasm with atypia (apparently people have followed these and found them benign?).

Elizabeth Montgomery: Lovely oncocytoma with degenerative atypia.

Cesar Moran: Nice case.

Juan Rosai: Great case of renal oncocytoma. The problem I have with this entity is that I cannot buy the idea that they are all benign.

Brian Rubin: Impressive case. I do find it scary when "degenerative atypia" is so diffuse. It's comforting that there were other areas of more typical oncocytoma.

Dominic Spagnolo: Impressive degenerative atypia in a renal oncocytoma.

James Strauchen: Oncocytoma with a remarkable degree of cytologic atypia!

Saul Suster: I've seen this type of atypia previously in renal oncocytoma – very scary but in the absence of mitotic activity should not prompt a diagnosis of carcinoma. A situation analogous to paragangliomas.

Bruce Wenig: Without looking at the history I thought I was seeing a thyroid lesion (no renal parenchyma on my slide); had it been the thyroid I would have diagnosed it as a follicular adenoma, oncocytic, with endocrine atypia and degenerative changes. But, it is kidney which makes me refer back to David Ben Dor's write up of his case in which he refers to thyroid-like renal lesions. In any event, I agree with oncocytoma. Nice case.

Ady Yosepovich: Thank you for sharing this nice case

CASE NO. 9 – CONTRIBUTED BY GIOVANNI FALCONIERI:

Phil Allen: High-grade pleomorphic sarcoma metastatic to the left lung, probably from the previously excised breast phyllodes tumour. Despite the anaplastic histology, I agree that this probably came from the breast phyllodes tumour.

David Ben-Dor: Is it possible to tell at this point? Did the original breast lesion show this severe atypia to any extent (even if focally)? At this point the question may have only speculative or theoretical value. Given the clinical history the tumor would seem to be very rapidly progressive.

Michele Bisceglia: Pleomorphic sarcoma, NOS in the lung – probably metastasis from malignant phyllodes tumor of the breast. I think this tumor is from the primary in the breast.

Ira Bleiweiss: Probably metastatic phyllodes, but no way you tell unless you get the original slides.

Thomas Colby: No additional suggestions. Obvious pleomorphic sarcomatoid malignancy. This is somewhat of a peculiar appearance for a lung sarcoma and common sense would tell me metastatic phylloides tumor would make the most sense. Was the prior breast lesion on the same (left) side? In any case I think the patient was appropriately managed.

Kum Cooper: Metastatic malignant phyllodes tumor. Thank you, Falco for coming to the IAP/AMR meeting in South Africa.

Otto Dietze: I don't believe that it is another malignancy.

Goran Elmberger: Falco, you need to be a detective or hire one to dig out previous breast tumor for comparison. I find those simple things as resampling and review of previous material more and more rewarding the more experienced I get. Hope it was positive for vimentin at least. Just wanted to mention that this tumor shows this bizarre degree of atypia that reminds a bit of the degenerative type seen in the previous case. However, mitoses are plentiful and partly atypical this time. The small "base-line" tumor cells are not very atypical. These cells are producing something as seen by eosinophilic intracytoplasmic matter. Or possibly eating... Myoepithelial, rhabdo and

angio markers... On which side was the phyllodes tumor? Any post-op radiation therapy? It's a bit strange if metastases are only left-sided. One would assume a hematogenous mechanism of metastasis...Any luck with nuclear transcription factors such as TTF1?

Vincenzo Eusebi: I think that the diagnosis of pleomorphic sarcoma is correct. Malignant phyllodes tumours can show pleomorphic sarcomatous features. It is true that the total involvement of the left lung is unusual, but at the end, in absence of any other tumour, a metastasis from the breast is plausible. Giovanni, you should retrace the original lesion.

Giovanni Falconieri: My case; still do not know what this is, I am confident that the club members will shed light on the case.

Franco Fedeli: Pleomorphic sarcoma, NOS in the lung – probably metastasis from malignant phyllodes tumor of the breast. Given the clinical history the first choice diagnosis would favor metastasis from malignant phyllodes tumor of the breast. In fact the malignant subtypes of fibroepithelial neoplasm of the breast show high incidence of hematogenous (20%) and lymphogenous (10%) dissemination (Arch Gynecol Obstet (2011) 283: 591-596) and the commonest sites of metastasis are lung (70-80%), pleura (60-70%), and bone (20-30%). The risk of metastatic spread seems not to be influenced by the extent of initial surgery, but to be predetermined by tumor biology. And also a giant metastatic phyllodes tumor has been described in the lung and another giant phyllodes pleural metastasis (Ann Thorac Surg 2007;84:1750-2). I do not find it surprising that cancer cells lose their immunophenotype in metastasis.

Cyril Fisher: Looks like myxofibrosarcoma. The history suggests metastasis from malignant phyllodes tumor though comparison with previous material not possible.

Christopher Fletcher: Undifferentiated pleomorphic sarcoma. Given the history of malignant phyllodes tumor, this could indeed be metastasis (albeit the latter is really quite infrequent in tumors of this type) and, therefore, it would have been most useful to compare the morphology with the primary neoplasm in order to check for morphologic similarities.

Andrew Folpe: Undifferentiated sarcoma, consistent with metastasis from phyllodes tumor of the breast.

Masaharu Fukunaga: I agree, Falco. Metastatic malignant phyllodes tumor. Metastatic lesion composed of only malignant mesenchymal element is seen very often. This lesion is very similar to high grade myxofibrosarcoma.

Allen Gown: Might suggest mdm2 FISH to see if this may not be a dedifferentiated liposarcoma.

Thomas Krausz: I agree, metastatic malignant phyllodes tumor is the most likely option. It is unfortunate that the slides from the previous breast tumor are not available for review.

Janez Lamovec: Pleomorphic sarcoma, probably from malignant PT. With a known malignant phyllodes tumor, I would first think of its metastasis using Ockham'r razor reasoning.

Thomas Mentzel: Histologically, a pleomorphic sarcoma with myxoid stromal changes is seen, and given the clinical history, metastatic phyllodes tumour is the best diagnosis.

Markku Miettinen: Sarcoma which could be consistent with metastatic phyllodes sarcoma.

Elizabeth Montgomery: Certainly makes good sense for metastatic phyllodes.

Cesar Moran: Agree with your opinion and cannot add anything more.

Juan Rosai: Metastatic phyllodes tumor is probably right, although I would have included sarcomatoid carcinoma in the differential diagnosis.

Brian Rubin: I think it's a metastatic phyllodes tumor. Without the history you'd be stuck at undifferentiated pleomorphic sarcoma.

Dominic Spagnolo: I can't distinguish between pulmonary sarcoma or metastatic phyllodes.

James Strauchen Metastatic phyllodes tumor.

Saul Suster: Given the history, I agree that the best assumption is that this is a metastasis from the phyllodes tumor.

Bruce Wenig: I guess it's anybody's guess whether this is a primary malignancy of the lung or a metastasis. Given the apparent history of malignant phyllodes tumor I would favor a metastasis (even in the absence of CD10 staining) rather than a primary pulmonary pleomorphic sarcoma. Certainly it would be helpful to review the slides from the malignant phyllodes tumor to compare the histology to the lung lesion and better determine if this is a metastasis. Quickly checking the literature a majority of metastatic malignant phyllodes tumors (stated to be 66% per T. Tavassoli's textbook) go to the lung

Ady Yosepovich: I agree with metastatic phyllodes tumor.

CASE NO. 10 – CONTRIBUTED BY FRANCO FEDELI:

Phil Allen: Probable signet ring stromal tumour, right testis. I agree that this seems to be the most likely diagnosis. Incidentally, I was shocked by the poor quality of the H and E photomicrographs in the Human Pathology paper (2009, 40: page 585). I am surprised that the reviewers accepted the paper with such illustrations.

David Ben-Dor: Very interesting case with a thorough differential diagnosis. The histology appears fairly polymorphous while the telegraphic description of ovarian signet ring cell tumors in the AFIP fascicle on the ovary is less so. Morphologically I would go for an endothelial tumor but the immunos don't support it. I would think that sclerosing stromal and signet ring cell tumors of the ovary would be related.

Michele Bisceglia: Signet-ring stromal tumor of the testis versus solid pseudopapillary tumor (pancreatic type) of the testis. Do not know what this case is and look forward to others' opinions, mostly to Michal's and Epstein's on this case.

Ira Bleiweiss: Not sure. I was thinking about endodermal sinus tumor. Was AFP performed?

Thomas Colby: Can't add to the excellent discussion and not sure I would have gotten as far as Franco did but I think the differential has been well addressed.

Otto Dietze: I remember one case of the ovary but did not see it in the testis before.

Kum Cooper: Franco, I wondered about yolk sac tumor. Would a SALL-4, Glypican-3 and AFP help?

Goran Elmberger: Very prominent signet-ring cell morphology for sure. To me seems to be a decently good fit with described entity of signet-ring stromal tumor. Awaiting Michals response.

Giovanni Falconieri: Great case, Franco. I am not a urologic pathologist, as you know, so my opinion is not accountable at all. With that serious limitation in mind, I would favor SRC merely because this pattern has been described in the testis; in addition, the nuclear pleomorphism does not fit very well with the pancreatic papillary type tumor, and the papillary tumor of pancreas may stain for keratins. Let's wait for the experts' opinion.

Cyril Fisher: Signet ring stromal tumour seems reasonable once the other differential diagnoses are excluded**.**

Christopher Fletcher: Appreciate the education here – I have no personal experience with signet-ring stromal tumors.

Andrew Folpe: Strikes me as being an unusual sex cord stromal tumor, in areas resembling microcystic Leydig cell tumor.

Masaharu Fukunaga: A wonderful case, Franco, I did not see this type of tumor in the testis before. I think it is solid cystic tumor which occurs usually in the pancreas. Very nice differential diagnosis.

Allen Gown: Any hormones positive? Positive synaptophysin makes me worry about a NE tumor, perhaps one arising in the context of a germ cell tumor.

Thomas Krausz: I am not sure. Something "lipidized". ? lipidized Leydig cell/stromal tumor. Not proliferative enough for epithelioid variant of pleomorphic liposarcoma. Not keen on the "pancreatic" idea.

Janez Lamovec: I have never seen such a tumor in the testis but idea of signet ring cell stromal tumor of testis seems to me a good diagnosis. Let's wait for experts' opinion.

Thomas Mentzel: Given the prominent vacuolation of tumour cells, areas of bleeding and anastomosing channels in the periphery of the neoplasm I was thinking on a malignant vascular neoplasm as well, however, the results of immunohistochemical staining does not support this hypothesis.

Michal Michal: Signet ring cell stromal tumor. Since the time we published it first in 2005 (Michal et al. Virchows Arch 2005:2005:447:107-110), we have seen other cases. They often have non-signet ring cell component looking like epithelial neoplasm, which is cytokeratins negative, like in this case!

Markku Miettinen: Based on morphology would consider this a combination of Sertoli cell and lipid cell/steroid cell tumor.

Elizabeth Montgomery: Hmmmm. The nuclei are different from those usually seen in pancreatic solid pseudopapillary tumor – I do not know how to diagnose genital tract signet ring stromal tumor.

Cesar Moran: Interesting and difficult case. To me this looks like an adenomatoid tumor or Stromal tumor but I do not have any experience with pancreatic type solid/papillary tumor of the testis.

Juan Rosai: Signet-ring stromal tumor of the testis sounds right.

Brian Rubin: The vacuoles are incredible but I don't have a better idea of what it is. You excluded my various hallucinations by your IHC results. Great discussion of the differential dx.

Dominic Spagnolo: I like it for signet ring stromal tumor of the testis morphologically. It is yolk-sac like in some areas. But I agree the immunos are like solid/pseudopapillary neoplasm of pancreas.

James Strauchen No idea!

Saul Suster: Have no prior experience with signet-ring stromal tumor. This reminded me of yolk sac tumor with signet ring cells and massive amounts of hyaline globules. Were stains for YST done?

Bruce Wenig: Beats me what this tumor is but in my ignorance I considered a possible mixed germ cell tumor with yolk sac and teratomatous (carcinoid/neuroendocrine) elements. Staining for Sall-4, Oct3/4 and glypican 3 might be helpful.

Ady Yosepovich: Agree, looks like a peculiar sex cord stromal tumor.

CASE NO. 11 – SUBMITTED BY MASAHARU FUKUNAGA:

Phil Allen: Canalicular adenoma, left hard palate. I don't see much oral pathology and am very glad to have seen such a textbook case.

David Ben-Dor: Yes - nice case.

Michele Bisceglia: Canalicular adenoma of minor salivary glands. Agree with your diagnosis, Masa. The 3-4 such examples I have seen, mostly of tubular pattern, all involved the lips.

Ira Bleiweiss: Never seen this before. With such an infiltrative look, it's hard to believe it's benign.

Thomas Colby: Agree with diagnosis.

Kum Cooper: Great call Masa! I started with benign and then crept into the low grade papillary carcinoma. Thanks for the lesson.

Otto Dietze: Like from the textbook.

Goran Elmberger: Important case due to possibility of misdiagnosis as malignant salivary gland tumor. The differential to me would be PLGA and CAT but I agree with your diagnosis. I am not sure about bone infiltration in slide. Could be superficially located metaplastic bone since it very superficially located, at least in my slide. Compare with nearby benign salivary glands. Even the radiological impression of bone destruction is a bit unusual. The radiologists need to try to differentiate from bony erosion caused by long term expansile forces.

Vincenzo Eusebi: Monomorphic adenoma, canalicular type. It is true that in spite of the name this lesion can be locally aggressive.

Giovanni Falconieri: Great case, Masahara, head and neck pathologists would love it.

Franco Fedeli: Canalicular adenoma of minor salivary glands. A beautiful example of this sort of adenoma, mostly arising from minor salivary glands. The morphological beauty of this case is confirmed by the fact that Dr. Rosai has chosen this image for the cover of the first volume of the ninth edition of his book!

Cyril Fisher: Canalicular adenoma with a range of patterns.

Christopher Fletcher: At least to me, the degree of cytologic atypia, as well as the remarkably infiltrative growth pattern, would seem quite unusual for canalicular adenoma.

Andrew Folpe: Fascinating. I don't think I have seen a salivary gland tumor quite like that before.

Allen Gown: Lovely case, thank you.

Thomas Krausz: Agree with diagnosis. Very nice example. Absence of myoepithelial participation is new to me.

Janez Lamovec: Classic appearance of canalicular adenoma.

Thomas Mentzel: Thanks for this case of a canalicular adenoma with bone invasion (in my slide areas of haemorrhage and necrosis/necrobiosis were present).

Markku Miettinen: Not enough experience on the entity, though it is more atypical than the more common canalicular adenomas (could not rule out a low-grade process).

Elizabeth Montgomery: Stunning case.

Cesar Moran: Nice case.

Juan Rosai: Too large and complex to be a canalicular adenoma. What about polymorphous low-grade carcinoma?

Brian Rubin: Agree with canalicular adenoma. Nice example.

Dominic Spagnolo: Very nice canalicular adenoma. The destructive growth is very disquieting for a supposedly benign lesion.

James Strauchen: Canalicular adenoma! Very nice case!

Saul Suster: Difficult case, Goran. The monotony, primitive nuclear histology and invasive features made me think of a carcinoma.

Bruce Wenig: Very interesting case. I can certainly understand the diagnosis of a canalicular adenoma given focal areas showing a canalicular pattern with columnar appearing cells and sharp demarcation from an edematous appearing stroma. There are some findings that give me pause in diagnosing this case as a canalicular adenoma. First, the clinical history of an infiltrative lesion with bone destruction and invasion into the maxilla are not findings associated with any intraoral benign minor salivary gland neoplasm. The histology in the majority of the neoplasm is complex with papillary architecture, back-to-back glands and solid nests representing features that are typically not seen in canalicular adenomas. In my slide I find no evidence of osseous invasion but the indication in the description that there was histologic evidence of osseous invasion would be another feature that should not be seen in any intraoral benign minor salivary gland neoplasm, including canalicular adenoma. In my experience, all intraoral benign minor salivary gland neoplasms are circumscribed (although not encapsulated) and the lesion seen in the slide I received appears to lack circumscription in its depth. Admittedly, the lesion is transected in its depth so I cannot see whether it is or is not circumscribed so perhaps it is non-infiltrative but given the clinical scenario I suspect it may be infiltrative in its depth. So, if this is not a canalicular adenoma what is it? Given the fact that I believe it is malignant I would consider a diagnosis of a papillary variant of polymorphous low-grade adenocarcinoma (PLGA) or an adenocarcinoma, low-grade, not otherwise specified. It is not an adenoid cystic carcinoma or mucoepidermoid carcinoma representing some of the more common types (other than PLGA) of intraoral malignant minor salivary gland neoplasms.

Ady Yosepovich: Agree, very nice case.

CASE NO. 12 – CONTRIBUTED BY THOMAS KRAUSZ:

Phil Allen: Chronic granulomatous disease presenting as Aspergillus fumigatus pneumonia in a male aged 6 weeks. Goodness knows how many of these I have missed in the past. Thanks for the discussion.

David Ben-Dor: I agree that this case requires thinking "outside the box". It could be easily banalized by someone less thoughtful as an acute bronchopneumonia. Though obviously there are eosinophilic infiltrates and scattered granulomas, in many fields the acute inflammation is paramount which would lead to misdiagnosis via the "anchoring" mechanism. Thus the slide needs to be carefully examined before the final conclusion is reached.

Michele Bisceglia: Chronic granulomatous disease presenting as fungal pneumonia. Have never seen a case. Many thanks, Thomas. Excellent discussion.

Thomas Colby: Agree with diagnosis. It all fits and I only can hope I would have thought about CGD. Nevertheless there is a necrotizing granulomatous process that includes appreciable numbers of eosinophils and all of these features one can encounter in necrotizing aspergillus pneumonia in CGD.

Kum Cooper: Thank you, Thomas, for sharing this great teaching case. My differential lay between LCH and pneumocystis. I recently saw a forensic autopsy in a young man with acute myocarditis and granulomas in his abdominal lymph nodes and liver (with scattered eosinophils). I suggested the possibility of CGD to the forensic pathologist but I don't think they took this very seriously. My reasoning was the same as yours. Why should a young man die of acute (possibly viral) myocarditis and have granulomas in his abdomen? Clearly the patient's family has to be screened since this is an inherited disorder.

Otto Dietze: Thank you, I have not seen something similar before.

Goran Elmberger: Interesting manifestation of a rare disease. Histopathology is indeed somewhat non-specific to me and you need a very high index of suspicion to make this diagnosis. Congratulations!

Vincenzo Eusebi: I would have gone as far as suppurative granulomatous fungal pneumonitis. Thank you very much for the discussion that has led to the diagnosis of chronic granulomatous disease presenting as fungal pneumonia.

Giovanni Falconieri: Impossible case, Tom. Thank you for this terrific contribution.

Franco Fedeli: Chronic granulomatous disease presenting as fungal pneumonia. I have seen only another very terrible case of this entity.

Cyril Fisher: Very unusual case and useful discussion - thank you, Thomas.

Christopher Fletcher: Amazing case Thomas – I have never seen the like and would again consult with pediatric experts.

Andrew Folpe: Pneumonia. Very interesting clinical history. What is this, “pediatric pulmonary pathology month”?

Masaharu Fukunaga: Very educational case, thank you Tom. I have never seen this lesion before. The discussion is very informative.

Thomas Mentzel: Many thanks for this impressive case, and I hope that I did not miss it until now in the skin!

Markku Miettinen: Pneumonia with eosinophils, agree that chronic granulomatous disease in an excellent consideration, seems to be confirmed. Another possibility is auto-inflammatory diseases. Both are well represented here.

Elizabeth Montgomery: This is fascinating. I found it difficult since the pigment is not there.

Cesar Moran: I had not seen one of these before.

Juan Rosai: Nice case, beautifully documented.

Brian Rubin: Interesting and educational. I had completely forgotten about CGD. Thank for the reminder.

Dominic Spagnolo: If I have ever had a case of chronic granulomatous disease, I’ve missed it. Thanks for the update on the pathogenesis. The pathological changes are striking and the fungus is clearly there on the H&E.

James Strauchen: CGD presenting as fungal pneumonia! I have not seen this before! Thank you for this informative case!

Bruce Wenig: This must be the pediatric lung seminar! In a few hours I have seen more pediatric lung pathology than all my years of practice. Incredible case and one that I am likely never going to see again but if I do I will now know what it is (or at least I hope I will recognize it). Thank you!

Ady Yosepovich: Thank you for this enlightening case.

CASE NO. 13 – CONTRIBUTED BY ALBERTO MARCHEVSKY:

Phil Allen: I can't make a diagnosis on this honeycomb lung. The opinions have to be returned by today so I have no time to do a proper literature search. I will be interested in the final diagnosis.

David Ben-Dor: Looks like honeycomb lung but there must be something else. I didn't know that Langerhans cell histiocytosis of the lung could progress to end stage lung (if this is what the diagnosis is). Guess I'll have to patiently wait out the next few months until the solution is made available.

Michele Bisceglia: Bilateral lung transplant in a patient previously diagnosed with Langerhans cell histiocytosis. Unquestionably a cystic disease/change of the lung: have not a precise name.

Thomas Colby: Honeycomb change with probable background emphysematous lung. Could be the late phase of PLCH. Would wonder what the pituitary lesion was and whether there was a cause for the blindness.

Kum Cooper: Lung cysts associated with vHL (similar to the case TC showed previously 48/5).

Otto Dietze: UIP (pattern)?

Goran Elmberger: Not easy. I find rather non-specific looking cystically dilated bronchiolar structures. The medical history sounds intriguing. The list of cystic pulmonary diseases is growing longer. One would expect LCH with

respect to smoking history and distribution of lesion but I see no microscopic evidence for this disease. The constellation of clinical findings could fit with hydatid cysts but again I see no specific findings in my sections. Serological work-out. ACTH producing pituitary tumor associated with pulmonary and renal cysts has been described once by Pullman 1994 but in an infant. Diffuse cystic disease with coexistent SAD has been described but merely in non-smokers. Looking forward to your diagnosis.

Giovanni Falconieri: Very difficult, cannot say more than cystic/pseudocystic lung disease not otherwise specifiable. Don't know if LCH may present with such extensive cystic changes.

Franco Fedeli: Bilateral lung transplant in a patient previously diagnosed with Langerhans cell histiocytosis. Not sure. Can it be in the spectrum of any bilateral cystic malformation of the airways?

Christopher Fletcher: No comment.

Andrew Folpe: Looks like an end-stage lung with emphysematous changes.

Thomas Krausz: This is one of the most advanced/dramatic example of Langerhans cell histiocytosis of lung I have ever seen.

Janez Lamovec: ?Cystic adenomatous malformation in adult.

Alberto Marchevsky: My quiz case; in my opinion, this represents cystic bronchiectases.

Elizabeth Montgomery: I cannot see any Langerhans' cell histiocytosis but cystic medical lung(?) is over my head. I do not know what is going on.

Cesar Moran: I do not see LCH here, but would like to know what the imaging shows.

Juan Rosai: Isn't this what Liebow called honeycomb lung and regarded as an end-stage of a variety of inflammatory lung conditions, including Langerhans cell histiocytosis?

Brian Rubin: There are some eos and histiocytes focally but this doesn't look like LCH to me. The lungs are obviously emphesematous at this point but I have no idea what the underlying disease is. Could it be some longstanding eosinophilic pneumonitis that completely destroyed his lungs?

Dominic Spagnolo: This looks like end-stage honeycomb lung to me, cause unknown, but could be due to pulmonary LCH.

James Strauchen: End stage something!

Saul Suster: This looks like end-stage interstitial fibrosis with honeycombing and smooth muscle proliferation indistinguishable from end-stage UIP. This could easily be the end result of advanced Langerhans cell histiocytosis. I would have to imagine that the LCH must have been fairly advanced and non-responsive to conventional treatment to prompt a lung transplant.

Bruce Wenig: Egads, non-neoplastic lung disease. There is fibrosis and emphysematous change but I am sure, Alberto, these findings are not the reason prompting you to share this case.

Ady Yosepovich: Very interesting case, did the patient had pituitary germ cell tumor? Could this be metastatic teratoma?

CASE NO. 14 – CONTRIBUTED BY THOMAS MENTZEL:

Phil Allen: Granulomatous slack skin/granulomatous mycosis fungoides. At least I recognized it as a lymphoma. Thanks for the contribution.

David Ben-Dor: Yes - very nice and educational case. The degree of lymphocytosis in the epidermis in the absence of spongiosis should at least raise the possibility of MF.

Michele Bisceglia: Granulomatous mycosis fungoides of the skin. Thank you, Thomas. We previously had in the seminars 2 cases of granulomatous slack skin lymphoma (in Sem. #12 / case 5 and Sem. 38 / case 1, contributed by Dr. N. Cartagena and C. Bacchi, respectively), but we missed granulomatous mycosis fungoides of the skin. Now the gap is filled in.

Thomas Colby: Can certainly agree with the diagnosis. In this day and age of sub-specialization, I have completely lost touch with MF but don't recall ever seeing a case quite like this.

Kum Cooper: Thank you Thomas. I thought it inflammatory with neutrophilic or histiocytic dermatosis as my differential. After reading your discussion I notice the epidermotropism. A dual reminder for me to stay away from lymphoma and skin!

Otto Dietze: My first idea was granulomatous slack skin disease, but I agree with the experts diagnosis.

Goran Elmberger: Interesting case with potential pitfalls as pointed out. Thanks.

Giovanni Falconieri: Great case, Thomas. Never seen before. Another collectible skin!

Franco Fedeli: Granulomatous mycosis fungoides of the skin. Nice case of this entity, with typical epidermal involvement by haloed lymphocytes, small Pautrier abscess, mycosis fungoides cells and the granulomatous features in the dermis.

Cyril Fisher: Granulomatous mycosis fungoides, striking epidermotropism helping the diagnosis.

Christopher Fletcher: Beautiful case Thomas – the extensive epidermotropism would represent a valuable clue in what might otherwise be readily mistaken for an inflammatory process.

Andrew Folpe: Granulomatous MF. Nice example. Thank you!

Allen Gown: Great case, thank you.

Thomas Krausz: This is the first example of granulomatous mycosis fungoides I have seen. I am sure I would have investigated the possibility of infection also, just to be sure.

Masaharu Fukunaga: I often have a problem of a making diagnosis of early phase of mycosis fungoides. A very nice case and discussion. Thank you, Tom.

Janez Lamovec: Mycosis fungoides, granulomatous variant. Very typical example.

Elizabeth Montgomery: This is very subtle for a skin lymphoma novice. Thanks for the education.

Cesar Moran: Interesting case, one can easily dismiss this case as infectious.

Juan Rosai: Another case to be framed. The epitheliotropism of the neoplastic lymphocytes is very evident, including the formation of nice Pautrier's microabscesses.

Brian Rubin: Interesting case. I agree with granulomatous mycosis fungoides.

Dominic Spagnolo: Very nice case of granulomatous mycosis fungoides. As you say the distinction from, and relationship to granulomatous slack skin is a vexed issue. In this case, the large giant cells with numerous nuclei, the elastophagocytois and the leucocyte emperipolesis are typically seen in granulomatous slack skin, emphasizing your point that distinction on histological grounds alone cannot be made with any certainty.

James Strauchen: Granulomatous mycosis fungoides. Very nice case!

Bruce Wenig: Not much to say other than I agree.

Ady Yosepovich: Agree; never saw this type, thank you for sharing.

CASE NO. 15 – CONTRIBUTED BY ELIZABETH MONTGOMERY:

Phil Allen: Littoral cell haemangioma, spleen. Thanks for reminding me of this entity.

David Ben-Dor: When I first looked at the slide, the word "peliosis" jumped to mind - but that condition is supposed to be widespread whereas here the findings are focal. Obviously the features of the lining cells so nicely demonstrated in this slide would rule it out. Can these cells be compared to those lining the vessels in angiolymphoid hyperplasia with eosinophilia?

Michele Bisceglia: Littoral cell angioma of the spleen. Nice to see it again. We previously had two such cases in our seminars (Sem. #7 & Sem. #19). In Sem. #11, Marku Miettinen circulated a case of littoral cell angiosarcoma. Noteworthy littoral cell angiomas of the spleen are associated with visceral malignancies, mainly carcinomas of the colon, lung, kidney, stomach, and pancreas (Ref. Tumori. 1998;84:595-9). From a gross review of the literature this rate is around 25-30% of the total published cases.

Ira Bleiweiss: OK. Is this different from peliosis? I haven't looked at spleens in a while.

Thomas Colby: Agree with diagnosis. Lovely case.

Kum Cooper: Thank you for sharing this lovely example Liz. And thank you for visiting South Africa.

Otto Dietze: I know it only from the literature, I can't remember having seen a convincing case in several benign and malignant vascular lesions of the spleen.

Goran Elmberger: Thanks for submitting a case of this unusual lesion. Wonder if the entity is specific for spleen. Mixed endothelial and histiocytic differentiation could serve a purpose in this organ filter.

Vincenzo Eusebi: Vascular spaces lined by tall cells positive for CD31 and histiocytic markers consistent with littoral cell angioma as reported by Glauco Frizzera.

Giovanni Falconieri: Extraordinary teaching case. Thank you Liz! A "book entity", had never seen so far.

Franco Fedeli: Littoral cell angioma of the spleen. Beautiful case. When I saw for the first time a case like this, I had no idea what it was and sent it to Dr. Frizzera; it was September 1991, just two months before its publication ("Littoral cell angioma. A novel splenic vascular lesion demonstrating histiocytic differentiation" Falk S, Stutte HJ, G. Frizzera Am J Surg Pathol. 1991 Nov; 15 (11) :1023-33).

Cyril Fisher: Littoral cell angioma, very nice slide.

Christopher Fletcher: Perfect example of littoral cell angioma. Vascular tumors of the spleen are one of the few 'haematolymphoid' lesions that get sent to soft tissue pathologists!

Andrew Folpe: Terrific example of littoral cell angioma of the spleen.

Masaharu Fukunaga: Littoral cell angioma. I have no experience with this type of splenic vascular tumor. Thank you very much for the educational case.

Allen Gown: Lovely example, thank you.

Thomas Krausz: Very nice example.

Janez Lamovec: We've seen some cases of this entity, very similar to this one. **Thomas Mentzel:** A nice example of littoral cell angioma.

Cesar Moran: Nice case.

Juan Rosai: Spectacular cases. Alternative terms one could have considered for this splenic lesion are: littoral cell hemangioendothelioma (it is very cellular and architecturally complex), epithelioid hemangioendothelioma (self-

explanatory) and (hem)angioendoteliomatosis) (because of the multiplicity of the lesions). I would not be unduly surprised if this lesion were to metastasize.

Brian Rubin: Agree with littoral cell angioma.

Dominic Spagnolo: Nice splenic littoral hemangioma.

James Strauchen: Littoral cell hemangioma versus splenic lymphangioma**.**

Bruce Wenig: Littoral cell angioma**.**

Ady Yosepovich: Very nice case, thank you.

CASE NO. 16 – CONTRIBUTED BY CESAR A. MORAN

Phil Allen: I can't offer a better diagnosis but I would expect a lot of people to be skeptical. I saw a few meningothelial whorls but I won't even try to persuade you that the vacuoles indicate lipoblastic differentiation.

David Ben-Dor: Definitely an outlier. Hats off for thinking of it though having seen intrathoracic meningiomas at the AFIP would make you a prepared observer. If this was situated in the normative location would it be considered angioblastic type?

Ira Bleiweiss: Wow. I never would have thought of meningioma.

Michele Bisceglia: Malignant meningioma, primary in the pleura (C Moran). Incredible case, Caesar. The immunoprofile of the tumor is right for meningioma. Cytology is consistent too. The whorled pattern is absent, with diffuse sheeting, but this is consistent with malignant meningioma as well. Maybe psammomatous bodies were present elsewhere in this tumor, but this finding is not necessary. Interesting are also those scattered vacuolated cells not clearly discernible (lipomatous metaplasia or secretory differentiation? or what else?).

Thomas Colby: Agree with diagnosis. I must say I am impressed that you thought of meningioma on a small biopsy from this location. I have not seen meningioma involve the pleura and have not seen a malignant meningioma (at least that I recognized as such) in the lung. How big was the mass?

Kum Cooper: Cesar, my DD was pretty wide but did not include meningioma. This tumor is above my pay-grade!

Otto Dietze: Unique case, I did not see this before.

Goran Elmberger: Cesar, the answer to your question is no. At least I never made the diagnosis. As a matter of fact, blindly reviewing the case I considered meninges as possible location. From a morphological and IHC perspective I could possibly support your diagnosis. I don't have anything better to offer myself. Ectopic primary meningiomas have been described in many organs, i.e., sinonasal, skin, mediastinal, soft tissue, pulmonary and along peripheral nerves so why not in the pleura. Probably menigothelial differentiation is not unique to the meninges and the cell type might serve some more generalized supportive function. The major problem is the lack of specific markers for menigioma. PgR? CD99? D2-40? It thus becomes a diagnosis difficult to establish in new and undescribed localizations.

Vincenzo Eusebi: Lipid rich malignant meningioma. Primary in the pleura I have never seen.

Giovanni Falconieri: Impossible and instructive case, Cesar. It eminently deserves reporting in my opinion! The extensive vacuolation of tumor cells were also reminiscent of lipoblasts and raised in my mind the possibility of epithelioid liposarcoma which, as you reported years ago with Saul, may well occur in the pleura.

Franco Fedeli: Malignant meningioma, primary in the pleura. Difficult case. Agree on the diagnosis. Two pulmonary meningiomas have been reported to be malignant. The first case was regarded as a low-grade malignancy because the invasion into the adjacent muscle and connective tissues, but brain imaging studies were not performed. Therefore, a pulmonary metastasis from an intracranial meningioma was not excluded. In the second case, reported by Prayson and Farver, an intracranial meningioma was excluded by TC scan of the head. This primary pulmonary

meningioma was classified as being a high-grade malignancy regarding its loss of architectural pattern, mild nuclear pleomorphism, increased mitotic count, prominent nucleoli and focally rhabdoid features. It is unclear if the same criteria can truly be extrapolated to the pleural variant of meningioma (Ann Thorac Surg 2005;80:1523-5). Indeed pleura can be occasionally the site of origin of very rare tumors and other lesions (epithelioid sarcoma, synovial sarcoma, Rosai-Dorfman disease, ...).

Cyril Fisher: Malignant meningioma of pleura, amazing diagnosis, Cesar.

Christopher Fletcher: I have to admit that I would probably not even have thought of the possibility of malignant meningioma in this case, although the absence of keratins would certainly have tended to argue against either mesothelioma or carcinoma. This is truly a very educational lesion.

Andrew Folpe: Wow. Incredible case.

Masaharu Fukunaga: Initially, I had no ideal of meningioma of the pleura. It is really a man in Istanbul.

Allen Gown: Wonder if the tumor marks with other more recently described meningioma markers, such as claudin-1 or somatostatin receptors.

Thomas Krausz: Although I know about the entity especially in the differential diagnostic context of mesothelioma, but this is the first real case of primary meningioma of the pleura I have opportunity to see. Cesar, thank you very much for sharing this case with us.

Janez Lamovec: Although I noticed some nesting of cells and intranuclear inclusions, it didn't occur to me to think of malignant meningioma. Fantastic case, thank you, Cesar.

Markku Miettinen: Meningioma seems to be a reasonable conclusion. Cannot see many mitoses in the slide. If this is close to the spine, could be one of those paraspinal ectopic meningiomas.

Elizabeth Montgomery: Have no better diagnosis than bad meningioma but suspect I would not have thought of it!

Juan Rosai: I guess we will have to buy the diagnosis of malignant meningioma of pleura. Lots of nuclear pseudoinclusions. An electron microscopic study could have been very informative (We miss you, Dr.MacKay!).

Brian Rubin: Cool case! Of course I never would have thought of meningioma but the diagnosis is believable once I considered it. I've never seen a similar case. The furthest South I've ever seen meningioma is in the sinuses and face. Makes you think it has to have metastasized even though we know it didn't.

Dominic Spagnolo: Looking at it blind, that's what it smelt like, among other considerations. I have never seen or heard of a genuinely primary ectopic pleural meningioma, benign or malignant. What a case!

James Strauchen: Meningioma of the pleura! Wow!

Saul Suster: Truly spectacular case! I honestly would have not even thought of meningioma. Despite the hint of whorling, there are too many clear vacuoles and even signet-ring cells, which is not something I normally associate with meningioma. Was ER/PR done? Electron microscopy would have been confirmatory – is there any wet tissue left that could be used for EM?

Bruce Wenig: I have never seen such a case as this one. It has a bit of a swirled/meningothelial look but not the "punched out" nuclei of meningiomas (although there are intranuclear inclusions which are not particularly associated with meningiomas). I would never have thought of a meningioma. Great case. Thank you.

Ady Yosepovich: The scattered whorls, intranuclear inclusions are highly suggestive of meningioma. Papillary features are present (ependymoma –like pseudorosettes) so maybe this is the rare papillary meningioma (WHO grade 3). Is the lesion close to the spine?

CASE NO. 17 – CONTRIBUTED BY SANTIAGO RAMON y CAJAL:

Phil Allen: Light chain disease involving the lung. I had great difficulties with this case. I would be interested in our pulmonary pathologists' opinions.

David Ben-Dor: Is this to be conceptualized as a tumor nodule composed of neoplastic plasma cells admixed with non-neoplastic histiocytes and lymphocytes? Is the eosinophilic material considered to be extracellular immunoglobulin secretions which incite an inflammatory response (explaining the presence of the histiocytes)? I hope that this isn't considered quibbling and it certainly makes food for thought - the tendency could be to write it off as a granulomatous infiltrate and leave it at that. Did the patient have systemic light chain disease? Did the bone marrow show anything?

Michele Bisceglia: Light chain disease involving the lung. Am not personally sure this case is light chain disease. Plasma cells should exhibit light chain restriction (maybe you demonstrated it on other basis and in other locations – ?bone marrow). Cannot see the "deposits" of light chain. I see an apparently inflammatory necrotizing process, rich in histiocytes and plasma cells. Difficult case. We had two previous cases of light chain disease in our seminars (a case either in a lymph node or soft tissue, contributed by J. Chan in seminar #28, and another case which was subsequently contributed by myself as a so-called "follow-up case" illustrated with printed pictures relevant to a case of LCD involving the liver). *Note for the new members of the club: "follow-up" cases are defined as those cases which are contributed after another case related to the entity in question has already been circulated, where the second case represented a "true" follow-up relevant to the same patient or was relevant (as a complement) to another case from another contributor, which was prompted by the primary case.*

Thomas Colby: Peculiar case. In my experience, most light chain deposition cases are either single or multiple nodules with lots of pink material looking like (but not staining like) amyloid. This case focally shows some such material but the amount of histiocytes and degenerative reaction are distinctly unusual. Some of the histiocytes look like they might have crystal-like structures in which case crystal storing histiocytosis (well known in association with low-grade lymphomas and immunoglobulin) would be in the differential (although really well-formed crystals are difficult to find). In this case, was there any evidence of systemic disease or abnormal proteins in the serum or urine? It is not clear from the available information that monotypic light chain in the lung was confirmed in this case.

Kum Cooper: Santiago, my working diagnosis was necrotizing granulomatous inflammation with vasculopathy. Stumped again!

Goran Elmberger: Very interesting case. The bluish amyloid material is distinct but not very eye-catching. The dominant histiocytic response including giant cells is reminiscent of crystal storing histiocytosis – a disease maybe not totally unrelated. Is this the same as some people now classify as localized AL amyloidosis? In that case our amyloidosis expert from Uppsala, professor Bengt Westermark, recently published an interesting article claiming that most cases are in reality a low-grade plasma cell neoplasia - " a suicide neoplasm". I do note some monotony to the lymphoid infiltrates reminding me of some subtle lesions ultimately proved to be marginal zone B-lymphomas (MALT-type) after extensive work-up including clonality analyses.

Giovanni Falconieri: Great case, Ramon. Cannot comment anymore! Never seen before.

Franco Fedeli: Light - chain disease involving the lung. Very rare case. Thank you for sharing with us.

Cyril Fisher: Light chain disease, very tough diagnosis to make.

Andrew Folpe: Interesting. It reminded me of crystal-storing histiocytosis, although the macrophages look a bit different and discrete crystals aren't apparent.

Masaharu Fukunaga: Great case! Thank you very much for the beautiful case. I have not seen light-change disease in the lung.

Allen Gown: Wow, interesting case.

Thomas Krausz: The central necrosis/cavitation confused me. I must admit that I did not get the diagnosis until I read your diagnosis and comment. I will try to remember the entity next time. In addition to the references you

provided, there is an excellent review of pulmonary light chain deposition disease by Bhargava P et al, Am J Surg Pathol 2007; 31:267-276.

Thomas Mentzel: Another rare and unusual condition involving the lung. Did you find monoclonality of the plasma cells (because a mixed kappa-lambda expression is mentioned)?

Elizabeth Montgomery: Spectacular case. Thanks for it.

Cesar Moran: Interesting case.

Juan Rosai: No idea.

Brian Rubin: Interesting case. I've never made this diagnosis.

Dominic Spagnolo: I found this difficult. It has a necrobiotic appearance (like rheumatoid lung) but there are the amorphous deposits to account for. Were they PAS-positive? Typically monoclonal light chain deposits do not stain with Congo red in my experience.

James Strauchen: Light chain deposition disease! The globular eosinophilic material in the histiocytes is presumably light chain. The "faint mixed expression" of kappa-lambda is somewhat surprising. Most cases are monotypic kappa.

Bruce Wenig: Necrotizing granulomatous lesion; I would have primarily tried to exclude an infectious etiology.

CASE NO. 18 – CONTRIBUTED BY DOMINIC SPAGNOLO

Phil Allen: Extra-articular diffuse-type giant cell tumour (with scanty giant cells), soft tissues, medial adductor compartment of right thigh. This case corresponds nicely to those reported by Somerhausen and Chris Fletcher.

David Ben-Dor: I've always seen this lesion in the standard clinico-anatomical context. This is a huge lesion not associated with the joint so I'm not sure I would think of this diagnosis. I'm impressed with Dominic's erudition regarding soft tissue tumors.

Ira Bleiweiss: I'm not sure what this is, but I'm having difficulty agreeing with you on this one. Thankfully there are soft tissue moguls.

Michele Bisceglia: Extra-articular diffuse-type tenosynovial giant cell tumour (extra-articular PVNS). Indeed a very difficult diagnosis, especially on the core biopsy. Thanks, Dom, for this contribution and the excellent discussion. In regard to unusual site where PVNS can be seen, would like to mention a rare personal "vertebral" case: the PVNS lesion arose from some small articular facets of 2 lumbar vertebrae, extending into the spinal canal, with medullary cord compression. In addition, this case had few multinucleated giant cells ("giant cell tumor without giant cells" variant) and few foamy histiocytes.

Thomas Colby: I like the diagnosis that Dom has made. Diffuse type giant cell tumor is one of those lesions that takes a while for one to tumble to.

Kum Cooper: Beautiful description Dom. Lovely example. Thank you for sharing this case.

Otto Dietze: I was not aware of this variant of PVNS.

Goran Elmberger: Difficult but obviously important case due to malignant differential diagnoses. How can one explain a cytogenetic karyotype 46 XY and a FISH trisomy 7? Would FISH be the better judge of trisomy?

Vincenzo Eusebi: I agree that the lesion is an extraarticular diffuse type tenosynovial giant cell tumour and I am glad not to have dealt with the core biopsy.

Giovanni Falconieri: Another phenomenal case! Cannot add a single word to the case description and comment. Lovely pictures as well! Thanks Dom for this extraordinary contribution.

Franco Fedeli: Extra-articular diffuse-type tenosynovial giant cell tumour (extra-articular TGCT) The less frequent diffuse TGCT is commonly located in the peri-articular soft tissues, but occasionally these lesions can be purely intramuscular or subcutaneous. The extra-articular form of diffuse TGCT is defined by the presence of an infiltrative soft tissue mass, with or without involvement of the adjacent joint. Purely extra-articular cases of diffuse TGCT are rare and most often arise from the synovium of bursa and tendon sheaths.

Cyril Fisher: Diffuse type giant cell tumour, good photogenic example and images, thanks Dom.

Christopher Fletcher: Extra-articular tenosynovial giant cell tumour, diffuse-type – perfect example. It is a source of frustration that some orthopaedic surgeons still believe this to be a reactive disorder.

Andrew Folpe: Diffuse tenosynovial GCT.

Masaharu Fukunaga: Wonderful case with a very nice discussion, Extra-articular diffuse-type giant cell tumor. It is very difficult to make a decision, benign or malignant histologically.

Thomas Krausz: Great example. The diagnosis of extra-articular diffuse type of tenosynovial giant cells tumor is often problematic, especially in view of the high cellularity of the tumor and the relatively low number of multinucleated giant cells compared to the localized form.

Janez Lamovec: Classic diffuse type of giant cell tumor with all elements needed for diagnosis.

Thomas Mentzel: Many thanks for sharing this wonderful example of rare extra-articular giant cell tumour of tendon sheath with a prominent xanthomatous component.

Markku Miettinen: Agree on tenosynovial giant cell tumor, ? still related with hip joint but now obviously with extra-synovial extension into skeletal muscle.

Elizabeth Montgomery: What a beautiful case with lovely discussion and evaluation. Thanks for this.

Cesar Moran: Very nice case.

Juan Rosai: Spectacular case and erudite discussion of a very rare entity.

Brian Rubin: Nice case. I think the lack of osteoclasts is typical of the TGCTs of soft tissue, which can make them very difficult to diagnose, especially on core biopsy as observed in this case.

Dominic Spagnolo: My case. Last time I checked (? 6 – 8 months ago), no recurrence.

James Strauchen: Extra-articular PVNS! Very nice case! Abundant foamy histiocytes with a paucity of giant cells!

Saul Suster: Great case Dom; thank you for the contribution and for the erudite review.

Bruce Wenig: Yet another case that I get to expand my knowledge. Thank you!

Ady Yosepovich: Tough case.

CASE NO. 19 – CONTRIBUTED BY PAUL E. WAKELY, JR:

Phil Allen: Systemic mastocytosis with sarcomatous mast cells and metastasis to lymph node masquerading as soft tissue malignant fibrous histiocytoma. Yet another cause of malignant fibrous histiocytoma. I would never have got this one right.

David Ben-Dor: Another extremely instructive case. I doubt I would have thought of the diagnosis spontaneously without any clinical prompting. The eosinophils could be a clue.

Michele Bisceglia: Systemic mastocytosis initially masquerading as undifferentiated pleomorphic sarcoma with metastasis to lymph node. Impossible case!. However, assuming I could realize this case was of mast cell origin, then I would call it mast cell sarcoma.

Ira Bleiweiss: Very tough case.

Thomas Colby: Agree with diagnosis. There is some mastocytosis-associated necrotizing vasculitis in the adjacent fat.

Kum Cooper: Thanks you Paul. The wonders of immunohistochemistry!

Otto Dietze: Only on basis of H&E stain with a distinct eosinophilic infiltrate I was between Langerhans cell histiocytosis and malignant mastocytosis.

Goran Elmberger: Great case. Life ain't getting easier. Some giant cells almost have a megakaryocytic appearance. Granulations with some imagination and maximum condenser aperture.

Vincenzo Eusebi: Thank you for this instructive case of systemic mastocytosis

Giovanni Falconieri: Impossible case, Paul. A very educative contribution. Thanks for this submission

Franco Fedeli: Systemic mastocytosis initially masquerading as undifferentiated pleomorphic sarcoma with metastasis to lymph node. Very nice case. The proliferation of epithelioid cells and multinucleated /multilobated neoplastic cells, the atypia and high mitotic activity unequivocally make you think of a pleomorphic undifferentiated sarcoma. About the high component in eosinophils, mast cells produce both primary and secondary chemical mediators that are chemotactic for eosinophils. The main primary mediator is eosinophil chemotactic factor, and secondary mediators include the lipid mediator leukotriene B4, platelet-activating factor, and cytokines such as tumor necrosis factor (TNF)-_ and interleukin (IL)-5.5,6 IL-5 not only promotes differentiation, proliferation, and maturation of eosinophils but also prolongs their survival by inhibiting apoptosis. Mast cells may also enhance eosinophil survival in tissue and peripheral blood by inducing the autocrine production of granulocyte monocyte-colony stimulating factor (GMCSF),which also inhibits apoptosis.

Cyril Fisher: Systemic mastocytosis, great case. Useful reminder to think of it in pleomorphic tumours with eosinophils.

Christopher Fletcher: Very impressive case. One might wonder, given the extreme degree of cytologic atypia, if this might better be regarded as mast cell sarcoma with widespread metastases – it will be interesting to hear the comments of our haematopathology colleagues. Jason Hornick, in my department, currently has a small series of mast cell sarcomas 'in press' in *Mod Pathol* which have quite similar morphologic features to this case.

Andrew Folpe: Fascinating - I would never have thought of mastocytosis. I will have to think of it in the future. Thanks very much for sharing this case.

Masaharu Fukunaga: It is very difficult to make a diagnosis of systemic mastocytosis; it looked malignant. Thank you, Paul, for sharing the educational case.

Thomas Krausz: Highly educational case. I am sure I would have also struggled to arrive to the correct diagnosis.

Janez Lamovec: The name notwithstanding, this mastocytosis appears morphologically malignant with pleomorphic cells, numerous atypical mitoses, and the appearance of metastasis in LN.

Thomas Mentzel: What an impressive case of a pleomorphic sarcoma-like malignant mastocytoma! Did neoplastic cells stain positively for CD25?

Elizabeth Montgomery: Did not realize mastocytosis could be so very pleomorphic.

Cesar Moran: Great case.

Juan Rosai: Another unbelievable case.

Brian Rubin: I didn't have a slide, but it sounds like a cool case. I have seen systemic mastocytosis on bone biopsy when it was not suspected clinically and found it very difficult to recognize.

Dominic Spagnolo: What a case! Mast cell sarcoma it is. I was thinking Langerhans cell sarcoma maybe.

James Strauchen: Spectacular case! I would view this as mast cell sarcoma presenting as an initial manifestation of systemic mastocytosis (akin to granulocytic sarcoma as a manifestation of acute myeloid leukemia).

Saul Suster: Spectacular case – thanks for sharing it! For me it would have been impossible to make this diagnosis in the absence of the proper clinical history.

Bruce Wenig: I may have gone down the tubes on this one thinking it was malignant.

Ady Yosepovich: Amazing.

CASE NO. 20 – CONTRIBUTED BY EDUARDO ZAMBRANO:

Phil Allen: Undiagnosed, 2.5 cm, histologically malignant tumour with foamy macrophages, histiocytes and inflammatory cells, left vulva. I too don't know what this is but I think it is malignant and would advise wide excision.

David Ben-Dor: No clue.

Michele Bisceglia: 29 year-old female with a mobile mass in her left vulvar region. Eduardo, I fear that very few people can help you with this case. My dx would be that of a round cell sarcoma-NOS.

Ira Bleiweiss: Can't help you. Something vascular?

Thomas Colby: Would still wonder about some histiocytic lesion. Real issue is whether to go back and re-excise with negative margins, which I would be in favor of, despite the site.

Kum Cooper: Eduardo, I still like the proximal ES. I notice the INI (FISH) and was wondered if you did INI-1 (IHC)?

Otto Dietze: Some findings to my opinion would fit for angiomatoid FH.

Goran Elmberger: Sorry, no good advice. Always tempting to perform more markers but not sure it will help. Lymphohistiocytic? CD10?? ESS??? (no good histology for that) PgR in favor of local tumor? Will complete resection give more info.

Vincenzo Eusebi: The case is mysterious to me also.

Giovanni Falconieri: Very difficult Eduardo. I look forward to the soft tissue gurus.

Franco Fedeli: 29 year-old female with a mobile mass in her left vulvar region. Malignant neoplasm. Could be an epithelioid sarcoma, central type even if CD34 is negative? Look forward to hearing other views.

Andrew Folpe: I'd still be wondering about malignant extrarenal rhabdoid tumor. Would be interested in seeing the INI-1 studies. MERT tend to have INI-1 mutations, rather than deletions, although protein loss should be present.

Christopher Fletcher: This young woman's vulval mass, taking into account your immunophenotypic findings, appears to be an undifferentiated epithelioid malignant neoplasm. Sadly (and very painfully) we seem to receive such cases in consultation almost every day and it is usually almost impossible to determine whether one is dealing with an undifferentiated sarcoma or else an immunophenotypically aberrant carcinoma or melanoma. As such, it seems that we can rarely be of much help to either the patient or the physician taking care of them.

Masaharu Fukunaga: Difficult case. Proximal type epithelioid sarcoma? Undifferentiated endometrial stromal sarcoma?

Thomas Krausz: Not sure either, but I would consider the possibility of metastasis/spread from low grade endometrial stromal sarcoma.

Janez Lamovec: I don't know but the lesion somewhat reminds me of follicular dendritic cell tumor although I am aware that immuno is not the best for the diagnosis.

Thomas Mentzel: An atypical neoplasm with numerous vessels and foamy cells is seen. Tumour cells that are admixed with inflammatory cells contain enlarged vesicular nuclei – diagnosis?

Markku Miettinen: Unclassified sarcoma, probably low-grade. Some vague similarity with hemangioblastoma (vacuolated cells).

Elizabeth Montgomery: Don't recognize this with certainty.

Cesar Moran: Could this be dendritic reticulum cell tumor?

Juan Rosai: Don't know (?).

Brian Rubin: I'm not certain but I wonder about an epithelioid benign fibrous histiocytoma. Vague areas appear to spindle out a bit to me and the way the histiocytes aggregate suggest this diagnosis to me. I can't explain the EMA if it's real and I have no idea what the nuclear PR means so I'm probably wrong. I'm looking forward to hearing other ideas – I enjoy a mystery, perhaps explaining why I enjoy pathology.

Dominic Spagnolo: Am not sure what this is. Could it be an angiomatoid fibrous histiocytoma with atypia? Recent cases described in the vulva. ??FUS rearrangements also worth looking at.

James Strauchen: Vaguely organoid pattern reminiscent of paraganglioma.
Bruce Wenig: Based on the epithelioid cell morphology, marked nuclear pleomorphism, vesicular nuclei with prominent nucleoli, scattered mitoses including atypical forms and EMA positivity, this may represent a proximal type of epithelioid sarcoma. Against this possible diagnosis would be absence of cytokeratin staining and negative INI-1 rearrangements. I look forward to reading what everyone else thought about this case.

Ady Yosepovich: Don't know – prominent hemangiopericytoma like pattern.