

COMMENTS TO AMR SEMINAR #55

CASE NO. 1 – CONTRIBUTED BY PHILIP ALLEN:

Carlos Bacchi: High-grade angiosarcoma. This is an excellent discussion about iron injection being potentially related to the development of this malignant neoplasm.

David Ben-Dor: The lesion is very epithelioid looking and interestingly well circumscribed for a highly malignant tumor. To be honest I wasn't overly impressed with the number of mitoses and with their atypicality with the relatively cursory look-over I gave. I occasionally receive excision specimens of soft tissue masses in previous injection sites from the buttock which showed reactive/degenerative changes. However, this case should be a wake-up call to examine them carefully.

Gerald Berry: Agree with diagnosis. I had not been aware of this association - angiosarcoma arising in injection sites. Nice case.

Michele Bisceglia: Injection site high grade angiosarcoma. Interesting case. This case also stimulates some speculations on the link between trauma and sarcoma.

Ira Bleiweiss: High grade angiosarcoma, epithelioid on my slide.

Tom Colby: Agree with diagnosis.

Kum Cooper: Thanks Phil. This looks like an epithelioid angiosarcoma to me. We recently saw a case in a 33- year-old male with a "hematoma" in the liver that was followed for three years with radiological evidence of decrease in size following FNA at the time of initial diagnosis (which incidentally did see atypical cells). The surgical resection was performed due to a recent biopsy and sudden increase in size.

Otto Dietze: Angiosarcoma, excellent discussion of this association.

Hugo Dominguez-Malagon: It is a very good case of post-injection angiosarcoma, interesting discussion. It is my personal impression, by observation of some cases that epithelioid vascular tumors arise in the context of old hematomas and organized thrombi.

Göran Elmberger: Very interesting case and discussion. Agree on diagnosis of high grade soft tissue angiosarcoma with epithelioid and alveolar-like features. Strange discordance between mitotic rate and low MIB1. Re-test? S-phase? Cyclin A or other markers? However, when it comes to establish a relationship to a previous injection, I guess I am a bit sceptic. Age and sex of patient and definitive history regarding to what type of injection previously administered could help? Trace element analysis to look for remnants of iatrogenic components of iron deposition? What are the proofs that iron was actually injected? Hemosiderin deposits in setting of angiosarcoma would not be unexpected... Furthermore the location and the gross anatomy would be fairly characteristic of published soft tissue angiosarcomas including multinodularity and spontaneous tendency for hemorrhagic necrosis. Presence of sarcoma cells intracapsularly in lesion interpreted as rest of fatty necrosis could also just be remnants of necrotic angiosarcoma nodule. Post FNA? Since probably most people got injections intragluteally, the mere occurrence of sarcoma at injection site could possibly be coincidental. Feline injection site-associated sarcoma seems to be related to previous vaccination site so maybe we should look out for sarcomas at common locations for vaccine administration – upper arm. I guess we all need to keep our eyes open for this possibility and gather more information. Thanks.

Giovanni Falconieri: Predominantly malignant, epithelioid vascular tumor. Not to object to your hypothesis, i.e. angiosarcoma arising at injection site, and your excellent and didactic discussion, Phil. Obviously, this is totally unheard of to me. However, I may add my experience in regard to reference 1 - sarcomas arising in pet vaccination sites. Our house cat developed a 1,5 cm fibrosarcoma within the neck soft tissue, between the scapulae near to the spinal processes. That happened right after the third vaccination he received as part of the viral disease prevention program. The tumor measured 2 cm, it was bordered by sclerotic tissue and featured malignant spindle cells consistent with fibrosarcoma, high grade. The diagnosis has been confirmed by Dr. George Hensley, who is an accountable expert of veterinary pathology. During the exchange of correspondence, George told me that that the adjuvant material used to suspend the partially inactivated virus may be responsible for development of sarcomas. Injection sites such as the posterior neck and the proximal paw are the anatomic areas most commonly involved by such tumors. In the case of our cat, radical surgery (mass resection plus removal of spinous processes and small portions of medial scapular tissue) was successful (>2,5 years free of tumor recurrence).

Cyril Fisher: Epithelioid angiosarcoma at longstanding injection site, great case.

Andrew Folpe: Entirely agree with angiosarcoma. The association with the injection site is intriguing. The association of angiosarcomas with foreign materials is very interesting- as I'm sure Phil is aware, one of the last combat-attributable

fatalities of the First World War was an Australian veteran who died of an angiosarcoma that arose adjacent to retained shrapnel, 50 or 60 years after the war.

Christopher Fletcher: Convincing example of high-grade angiosarcoma. The apparent association with a prior injection site for an iron compound twenty years earlier is indeed quite remarkable.

Jerónimo Forteza Vila: Thank you for this interesting case. It's great to know the oncogenic role of iron. I haven't known it.

Masaharu Fukunaga: What a beautiful epithelioid angiosarcoma! I have never seen any cases with iron injection. Thank you very much for the detail comments and references.

Allen Gown: Thank you, Phillip, for a masterful write-up of this injection site angiosarcoma.

Thomas Krausz: I agree, most areas represent epithelioid angiosarcoma. The association with previous injection site is interesting. Thank you for the helpful discussion on this topic.

Janez Lamovec: Injection site angiosarcoma, predominantly epithelioid. We have never encountered such a case. The only treatment related angiosarcomas we saw were those following radiation.

Thomas Mentzel: An interesting case of a relatively well-differentiated angiosarcoma of soft tissues with abundant hemosiderin deposits arising on the site of a previous injection.

Markku Miettinen: Agree on high-grade angiosarcoma, with epithelioid features. I don't recall seeing an example at an iron injection site before. Another possible kind of iatrogenic angiosarcoma.

Liz Montgomery: This epithelioid vascular neoplasm is very strange. Dismissing this as benign would be out of the question but, in contrast to case 10, the "brother case" arising in association with a Dacron graft, this is very well-circumscribed at low power with a vaguely lobular pattern like epithelioid hemangioma. Interesting that the Ki-67 index was low.

Giuseppe Pelosi: This is a very interesting case of high-grade sarcoma with vascular formation coupled with histological features of old fat necrosis. For me, this is the first time I have observed a similar case, because fat necrosis is usually thought of as a regressive phenomenon unable to progress to malignancy. In this setting, it is remarkable that medical history showed iron injections 20 years previously. I agree with Philip Allen that this example of angiosarcoma is very interesting and appealing for the particular condition in which it has grown up. As far as the general issue of malignant tumors arising in prosthetic implants is concerned, I remember at least two cases of CD30-positive anaplastic lymphomas that developed close to mammary prosthesis several years after removal of breast cancer. Congratulations on this interesting case, the appropriate discussion and updated references!

Santiago Ramon y Cajal: Difficult case. I was in favor of epithelioid hemangioendothelioma. The differential diagnosis with a florid reactive process can be challenging.

Juan Rosai: Spectacular case of epithelioid angiosarcoma, in all likelihood related to material that was injected at this site 20 years ago. In my experience, angiosarcoma is one of the most common types of foreign body-related sarcomas. Many years ago, while at Minnesota, I saw the most spectacular case ever of this phenomenon. The patient was a lady who had had a cholecystectomy for stones many years before and in whom the surgeon had forgotten a gauze in the operative area. She was told about it, but decided to keep it. Something like 20 years later, a mass developed around the gauze. It was taken out, and it showed a large epithelioid angiosarcoma with the gauze in its center. The patient died shortly thereafter of generalized metastases. We reported that case together with a few others, including one or two of Australian soldiers with shrapnel from WW1 (Cancer 62:2436-2444;1998). By the way, some of these cases have been referred to in the older literature as "granulation tissue sarcoma", the idea being that there is a phase of reactive granulation tissue formation before the development of the sarcoma.

Joshua Sickel: High grade angiosarcoma with epithelioid features. I've never seen one arising from a previous site of injection. Amazing case!

Dominic Spagnolo: Agree Phil. Spectacular epithelioid angiosarcoma at an injection site. Thanks.

James Strauchen: Imferon angiosarcoma! Most hematologists use Imferon only by IV infusion now.

Saul Suster: Spectacular case! Thanks for sharing it.

Larry Weiss: This is a real pain in the butt. Beautiful slide showing both the sarcoma and the necrotic space.

CASE NO. 2 – CONTRIBUTED BY CARLOS BACCHI:

Phil Allen: Sclerosing extramedullary hematopoietic tumour. I have missed this condition several times in the past but I spotted it this time.

David Ben-Dor: The megakaryocytes are very bizarre looking and pleomorphic with at least one atypical mitosis, but the numerous immature eosinophilic cells should be a tip off as to the myeloid nature of the proliferation. It seems that the clinical history wasn't immediately available so all the more credit to Carlos for figuring this out. What happens if the patient undergoes emergency laparotomy (especially at an inconvenient hour) and the frantic surgeon sends this as a frozen section for apparent tumor?- would present a difficult problem.

Gerald Berry: Another new entity for me!

Michele Bisceglia: Sclerosing extramedullary hematopoietic tumor associated with chronic idiopathic myelofibrosis. Beautiful case. Previously there was a similar case in AMR Seminar by JK Chan in Seminar 33 (orbit in a chronic myeloid leukaemia patient). There was also a case of myeloid metaplasia of the breast by J. Lamovec in Seminar 23.

Ira Bleiweiss: Neat case. In all honesty, I thought this was a sarcoma and did not recognize the cells as megakaryocytes.

Tom Colby: Agree with diagnosis. I did not find any red cell precursors, but I didn't really have a differential once megakaryocytes and immature myeloid elements were identified.

Kum Cooper: Thanks Carlos. Beautiful example of SEHT. Yes we did see one previously in the AMR seminar but well worth the review/revisit! I recall that the Mayo published a series.

Otto Dietze: Typical example of this rare entity, I remember a case from a needle biopsy in the last year.

Hugo Dominguez-Malagon: Sclerosing extramedullary hematopoietic tumor, difficult diagnosis, I missed it.

Göran Elmberger: Great case.

Giovanni Falconieri: Great case of extramedullary myelopoiesis. Reminds me of a breast lesion I shared many years ago with Janez Lamovec. Your case shows, in addition, an access of fibrocytes along with a sclerosing ground substance. A useful clue is the good number of myelopoietic cells featuring granules and immature looking nuclei. Thanks for this valuable contribution.

Cyril Fisher: Extramedullary hemopoietic tumor, rare case.

Christopher Fletcher: Beautiful example of sclerosing extramedullary hematopoietic tumour – we see two or three such cases each year and they are most often mistaken for well-differentiated liposarcoma.

Andrew Folpe: Agree with SEHMT- very nice example.

Jerónimo Forteza Vila: It's a nice case. I haven't seen it before.

Masaharu Fukunaga: Thank you very much for the excellent SEMHT, Carlos. Is it a neoplasm of multipotential hematopoietic cell or reactive process (myeloid metaplasia)?

Allen Gown: Thanks for the case, Carlos.

Thomas Krausz: Great case. I have seen a couple of cases before, but the "dysmorphic" megakaryocytes confused me again.

Janez Lamovec: We contributed a case of SEMHT presenting as a tumor in the breast for AMR Seminar 23, case 10. In our case, we were not given any information that the patient had primary myelofibrosis diagnosed 6 years previously. The breast lump was sent for frozen section and we were not sure what kind of tumor it was; in the fibrotic background pleomorphic cells predominated, and we even considered pleomorphic ILC. We fortunately deferred the definitive diagnosis. On permanent sections, pleomorphic cells were recognized as dysplastic megakaryocytes; there were relatively few other types of cells seen. The surgeon later informed us on patient's history. Following excision of the breast lump, the latter recurred some years later (diagnosis was confirmed by aspiration cytology). The patient died of acute leukemia 17 years following diagnosis of myelofibrosis, 11 years after the breast operation.

Thomas Mentzel: Thanks for sharing this rare neoplasm.

Markku Miettinen: Agree on sclerosing extramedullary myeloid tumor. Dysplastic megakaryocytes also support a chronic myeloproliferative disorder.

Liz Montgomery: What a fantastic tumefactive example of extramedullary hematopoiesis. I had one a few weeks ago on "confirming consults" [patient came here for treatment and brought his slides for review], a needle biopsy in a patient with essential thrombocythemia that had been diagnosed as a well-differentiated liposarcoma at a nearby hospital. I fear that I would have "rubber stamped" the outside diagnosis in my usual haste except the orthopedic surgeon was smart enough to tell me that the patient had a "bone marrow disorder" so I picked up on the erythroid islands and then realized the "atypical adipocytic cells" were actually megakaryocytes.

Giuseppe Pelosi: I agree with the diagnosis of sclerosing extramedullary hematopoietic tumor (SEMHT) associated with chronic idiopathic myelofibrosis mastocytosis, but I am not experienced in this kind of lesions in my daily practice. Thank you again for learning something about this unusual tumor.

Santiago Ramon y Cajal: Great and interesting case of SEMHT. The fact that it is so myxoid and that the megakaryocytes are so dysmorphic make the case particularly challenging.

Juan Rosai: Fantastic case. It almost fooled me in thinking that this was a sarcoma with the so-called inflammatory MFH pattern and, therefore, most likely a liposarcoma. I believe that the clinical information and immunohistochemical profile that Carlos provided leave no doubt that his interpretation is the correct one.

Joshua Sickel: High grade angiosarcoma with epithelioid features. I've never seen one arising from a previous site of injection. Amazing case!

Dominic Spagnolo: Beautiful case of extramedullary hemopoietic tumor. I agree one can never see too many of these!

James Strauchen: Sclerosing extramedullary myeloid cell tumor. The megas are the key!

Saul Suster: Great case Carlos! I missed it on initial review, and I don't think I could have made the correct diagnosis in the absence of a history.

Larry Weiss: Pretty case.

CASE NO. 3 – CONTRIBUTED BY IRA BLEIWEISS:

Phil Allen: Compensatory hypertrophy of ectopic breast tissue with pseudoangiomatous stromal hyperplasia, subcutis, mons pubis, in a patient with previous bilateral mastectomy for breast hyperplasia associated with pseudoangiomatous stromal hyperplasia. I have never heard of this before.

Carlos Bacchi: Breast tissue with mild pseudoangiomatous stromal hyperplasia. I checked the clinical history provided in the short summary of cases several times in order to confirm the exact anatomic location of the lesion.

David Ben-Dor: Certainly bizarre finding and clinical situation. The breast tissue looks like what one would expect from gynecomastia in a male- is she a genetic female?

Gerald Berry: The clinical history is very dramatic. Agree with diagnosis.

Michele Bisceglia: Ectopic breast tissue with PASH. Interestingly PASH has also been described in mammary-like anogenital glands (Kazakov DV, et al. Pseudoangiomatous stromal hyperplasia in lesions involving anogenital mammary-like glands. *Am J Surg Pathol.* 2005 Sep;29(9):1243-6).

Tom Colby: Agree with diagnosis.

Kum Cooper: This looks like PASH in extra-mammary ectopic breast tissue. Ira, I have no clue as to why she is growing ectopic breast tissue.

Otto Dietze: I have never seen this or heard about it before.

Hugo Dominguez-Malagon: Recurrent massive growing of breast tissue with PASH?, I have never heard of a case like this. I suppose it may be related to hormonal induction interacting with normal or abnormal receptor signaling.

Göran Elmberger: Hmm, poor woman. I don't know what could cause anything like this but at least evidence for the milk-line hypothesis. Seems odd that no acinar portion of breast grew which could be expected if hormonal hyperactivity – secretion was the cause. Large ducts of areolar type and stromal overgrowth with PASH-like features. Reminds me of what can be seen in virginal hyperplasia of young women or gynecomastia in young men. In case of virginal breast hypertrophy, increased end-organ sensitivity is believed to be responsible for abnormal response to pubertal hormonal rise. ER, PgR, AR expression? Any response to endocrine therapy? Any medications? Dietary habits?? Familial? PHF6

mutations? (Börjesson-Forsmann-Lehman syndrome) Paraneoplastic? Something is wrong in regulatory pathways but what...

Giovanni Falconeri: Agree with ectopic breast. I agree with the PASH, actually this was a useful hint to recognize the mammary type of stroma. Great case, Ira, thank you!

Cyril Fisher: Ectopic breast tissue in a patient with exuberant mammogenesis.

Christopher Fletcher: A truly remarkable case – I have never seen multifocally prominent ectopic breast tissue of this type. It is disappointing that there appears to be no logical explanation.

Andrew Folpe: Ectopic breast tissue, microcalcifications not identified.

Jerónimo Forteza Vila: Thank you for this case.

Masaharu Fukunaga: The case is very nice with PASH and the patients had interesting history. The histology is very similar to gynecomastia.

Allen Gown: This case takes the prize as the most bizarre lesion in the set. Thanks, Ira. I have never seen nor heard of such a case!

Thomas Krausz: No, I haven't come across with similar clinicopathologic situation before. Whatever is the cause of macromastia (gigantomastia) is probably driving the ectopic breast tissue. There are no diagnostic features of diabetic mastopathy in this ectopic breast tissue but on the basis of scattered lymphocytes, fibrosis, apoptosis in the epithelial structures together with involvement of all the "breast sites" I would speculate also about some kind of autoimmune etiology.

Janez Lamovec: Most bizarre case! I don't understand the reason why patient's breast tissue keeps growing on and on.

Thomas Mentzel: Very impressive history, and I've never heard about a case like this!

Michal Michal: I would not call it ectopic breast tissue. The lesions arise on anogenital glands (mammary-like glands), which are present in most of the women in the perineal region. These glands often produce tumors identical to breast. We have now in breast 13 tumors having morphology of cystosarcoma phyllodes or mammary type fibroadenoma including lactation changes in one case (*Kazakov D.V., Spagnolo D.V., Stewart C.J., Agaimy A., Magro G., Bisceglia M., Vazmitel M., Kacerovska D., Kutzner H., Mukensnabl P., Michal M.: Fibroadenoma and phyllodes tumors of anogenital mammary-like glands: a series of 13 neoplasms in 12 patients, including mammary-type juvenile fibroadenoma, fibroadenoma with lactation changes, and neurofibromatosis-associated pseudoangiomatous stromal hyperplasia with multinucleated giant cells. American Journal of Surgical Pathology, in press.*). In analogy to the breast I would call it "fibrosing vulvopathy"

Markku Miettinen: Agree on ectopic breast tissue, site is consistent with occurrence of ectopic breast.

Liz Montgomery: And other women have breast augmentation operations. Looks like this pubic lesion even has PASH. No lobules on my slide. Have never heard of such a thing before.

Giuseppe Pelosi: This is a spectacular case of ectopic breast tissue presenting as pubic mass, with diagnostic features for this entity. Very nice and instructive description! Although we seen many types of breast lesions, either benign or malignant, this is for me the first time to personally observe a similar presentation of breast growths along milk line.

Santiago Ramon y Cajal: Striking case. Quite abnormal breast tissue in the sense that it is formed by scant tubules and lots of fibrotic stroma and impressive PASH. This lady has the unfortunate coincidence of having heterotopic breast tissue and massive breast hyperplasia.

Juan Rosai: Very nice case of ectopic breast tissue. Not exactly a microscopic challenge but a remarkable biologic phenomenon, which has given rise to quite a few mythologic figures..

Joshua Sickel: This is the nicest example of this condition I've seen. Thanks for the great teaching slide!

Dominic Spagnolo: Nice PASH changes in anogenital mammary-like glandular tissue (looks gynaecomastoid with nodular PASH). Michal Michal and colleagues have described this before (*Am J Surg Pathol 2005; 29:1243-46*), and there is a series in press - am sure Michal will have more to say!

James Strauchen: Wow, Ira!

Larry Weiss: I have never heard of this clinical situation.

CASE NO. 4 – CONTRIBUTED BY JOHN CHAN:

N. Volkan Adsay: Thanks for this great example. There is another interesting paper in press titled "*Comparison of Gene Expression Profiles in Tubulocystic Carcinoma and Collecting Duct Carcinoma of the Kidney*" by *Osunkoya et al* Am J Surg Pathol (in press) suggesting that these tumors are distinct from conventional collecting duct carcinomas.

Phil Allen: Tubulocystic carcinoma of the kidney. Thanks for this case, John. I would not have a hope of keeping up were it not for the assistance of these seminar cases.

Carlos Bacchi: Thanks for this nice example of tubulocystic carcinoma of the kidney.

David Ben-Dor: The "hobnail" cells characteristic of collecting duct carcinoma are seen (or at least well-developed) only focally. On the whole the tumor looks relatively low grade. Focally there is cytoplasmic pigmented granularity- any significance? This lesion is alluded to briefly in the latest kidney tumor AFIP fascicle in the rubric devoted to collecting duct carcinoma which also offers the option of this being a distinct tumor.

Gerald Berry: Tubulocystic carcinoma. Nice example.

Michele Bisceglia: Kidney – Tubulocystic carcinoma. This is the first case I see. Thank you.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis. I seem to be getting further and further behind on these new renal cell carcinoma entities.

Kum Cooper: Thanks John. I think we just had one recently. The March AJSP has a nice series from Mahul Amin.

Otto Dietze: I have seen a few cases in seminars and one case several years ago in our department.

Hugo Dominguez-Malagon: Tubulocystic carcinoma of kidney, a new entity, never seen one before, thank you for the case.

Göran ElMBERGER: New to me. Appealing name. Nice fit with referenced articles. It looks very low-grade including low-grade cytological atypia and absence of overtly aggressive infiltration. Good with experience and clinical follow-up to establish new entities 2/31 with metastasis according to Amin et al.

Giovanni Falconieri: I did not know the entity. Yet, I could notice that tumor cells have enough qualities to be designated as malignant. Nice case, thanks for contributing this new entry of renal tumors.

Cyril Fisher: Tubulocystic carcinoma, fine example of a rare entity.

Christopher Fletcher: Very convincing example of this new and somewhat enigmatic entity – did we really lump together all these different type of renal carcinoma in the past? Or are some of these newer variants truly 'new'?

Andrew Folpe: I don't think that I have seen an example of this previously, but it seems to fit well. I thought it was carcinoma, based on the growth pattern, and was wondering about some type of collecting duct carcinoma. I need to go read that paper.

Jerónimo Forteza Vila: Thank you for this interesting case.

Masaharu Fukunaga: Thank you very much for the rare tumor, John. This is the second time I see this type of tumor. It resembles renal cell carcinoma associated with dialysis.

Allen Gown: Thanks for this case, John.

Thomas Krausz: Genetic studies also suggest that this is an entity. I am wondering, how did we classify this tumor type before?

Janez Lamovec: Thank you for showing us this rare kidney tumor that I've never seen before.

Thomas Mentzel: Thanks for this low-grade renal neoplasm.

Markku Miettinen: Thank you – I can accept carcinoma, although the differential from a dysplastic cystic process may be difficult on limited material (and limited experience).

Liz Montgomery: Thanks for sending this terrific timely case.

Giuseppe Pelosi: This is an interesting and difficult example of tubulocystic carcinoma of the kidney. I never saw similar cases thus far and congratulate John for providing this unusual tumor.

Santiago Ramon y Cajal: Thank you for this beautiful case of tubulocystic carcinoma.

Juan Rosai: Very instructive case of tubulocystic carcinoma of the kidney, a tumor, which in the past, I may have misdiagnosed at multilocular cystic nephroma with epithelial overgrowth.

Joshua Sickel: Great example of this rare tumor...looks fairly low-grade.

Dominic Spagnolo: Beautiful example of this "new" rare tubulocystic carcinoma of the kidney. The Amin paper has since appeared in AJSP 2009; 33(3):384-92.

James Strauchen: Never heard of this one! Thanks!

Saul Suster: Thank you, John, for contributing this great example of a new entity.

Larry Weiss: Yet another renal neoplasm. I had never seen one before.

CASE NO. 5 – CONTRIBUTED BY KUM COOPER:

Phil Allen: I never even thought of a GIST on looking at the slide "blind." This is yet another example to support the argument that soft tissue rhabdoid tumors are not a single entity.

Carlos Bacchi: This is indeed unusual morphology (rhabdoid) for GIST cases. It is also highly malignant. It is rare to see this morphology in primary GIST, indeed.

David Ben-Dor: Honestly, some of the cells reminded me strongly of plasma cells! (this of course without the benefit of the clinical history). I guess one could add GIST to the list of impostors of other tumors. One memorable case of mine from years ago was an inguinal mass from an elderly man with epithelioid/spindle cell features that was subsequently seen by several very well known and authoritative pathologists. It was only when a surgeon reminded himself and me that the patient had had a gastric tumor resected that the case was deciphered. This was from the pre-GIST and pre-c-kit era when these tumors were called "leiomyoblastoma".

Gerald Berry: Without the prior history of GIST, I might not have thought about the possibility of this malignant variant.

Michele Bisceglia: Recurrent malignant GIST with diffuse rhabdoid morphology. Thank you, Kum. Nice case. Rhabdoid morphology in this case approaches plasmacytoid features.

Ira Bleiweiss: Rhabdoid, for sure, but I definitely would never have thought of a GIST variant. Another AMRoma.

Tom Colby: Agree with diagnosis. I was hoping for something more bizarre like a plasmacytoid/rhabdoid carcinoma.

Otto Dietze: Excellent case, increasing the spectrum of tumours with rhabdoid morphology.

Hugo Dominguez-Malagon: GIST with rhabdoid phenotype, conceptually I would consider this change as a de-differentiation phenomenon.

Göran ElMBERGER: Got as far as malignant, mesenchymal and rhabdoid on blind review. GIST is not what first pops up in mind and that should be worth remembering. What should we accomplish without clinical information? Thanks.

Giovanni Falconieri: Superb case, Kum. Without clinical back up it would be difficult to get to the right track. The rhabdoid changes are impressive, never seen before.

Cyril Fisher: GIST with rhabdoid morphology post Rx, very nice example.

Christopher Fletcher: Without the history, this tumour would certainly pose a broad differential diagnosis but, in context, the appearances indeed fit very well with a gastrointestinal stromal sarcoma showing eosinophilic hyaline cytoplasmic inclusions. As these patients can now be kept alive for five years or more, even with metastatic disease, using tyrosine kinase inhibitors, then all manner of less usual morphologic patterns are becoming evident in patients with persistent disease.

Andrew Folpe: Wonderful case, Kum. Without the history, I was thinking MERT. It would be interesting to do an INI1-I suspect it would be retained (normal).

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Very interesting to see a case of treated GIST. It will be very difficult to make a diagnosis of metastatic lesions without history or immunostains. I looked at Thomas's case. There is a wide spectrum of cytology and histology.

Allen Gown: Would be curious to know if this case shows INI-1 loss.

Thomas Krausz: Agree with diagnosis. Highly educational case. Thanks, Kum. Interestingly, epithelioid GISTs in stomach with rhabdoid morphology behave more in a benign fashion.

Janez Lamovec: We are repeatedly surprised by a variety of morphological appearances of GIST. Your case of rhabdoid (or even plasmacytoid!) subtype is just one example. Thank you for this case.

Thomas Mentzel: A nice example of a high-grade, pleomorphic GIST with rhabdoid cells after therapy. Did neoplastic cells stain positively for myogenic markers (see AJSP 2009; 33: 218)?

Markku Miettinen: Agree that this can be a malignant GIST, when supported by KIT or DOG1 immunostains

Liz Montgomery: Thanks for sharing this doubly treated very malignant looking GIST with us.

Giuseppe Pelosi: I agree with the diagnosis of malignant GIST with rhabdoid features. The tumor is said to show immunoreactivity for CD117 and CD34, but I am wondering if additional and recent markers of GIST have been tested, such as DOG-1 and PKC-theta, in order to complete the immunoreactivity profile of this type of lesions.

Santiago Ramon y Cajal: Interesting post-treatment morphology for this GIST. With so striking rhabdoid features, I wonder if the tumor cells still harbour LIT expression and other markers like CD34, desmin or EMA.

Juan Rosai: This case fooled me because it looked so plasmacytoid that my first (and second) impression was that the lesion was either a plasmacytoma or a malignant lymphoma with plasmacytic differentiation. In retrospect, it looks more rhabdoid than plasmacytoid. With the history and the immunohistochemical profile that were provided, there is little doubt that this tumor has to be interpreted as a GIST with rhabdoid features. I guess this proves once again that the rhabdoid appearance is a phenotype rather than a specific entity (perhaps even in the kidney).

Joshua Sichel: Spectacular case. Without the history, my first impression was anaplastic plasmacytoma. Never seen a GIST with this appearance.

Dominic Spagnolo: Pretty spectacular case Kum. I have not personally encountered such extreme rhabdoid morphology in a GIST, and without the history I suspect I may not have even considered it. Is anything known of the mutational status of the KIT and PDGFRA genes in this case?

James Strauchen: Rhabdoid (?rhabdomyosarcomatous) GIST! In the recent series of malignant GIST's with rhabdomyosarcomatous differentiation reported by Chris Fletcher in the February AJSP, the rhabdomyosarcomatous areas were negative for KIT although the KIT mutations were present.

Saul Suster: Beautiful case of GISS with rhabdoid morphology. We reported a case with identical morphology to this many years ago before we had even developed the concept of GIST (Am J Surg Pathol 11:575-580, 1987).

Larry Weiss: Looks almost plasmacytic.

CASE NO. 6 – CONTRIBUTED BY IVAN DAMJANOV:

Phil Allen: Subcutaneous Rosai-Dorfman disease, thigh. I looked at this case quickly and missed it, for which I will have to undertake appropriate penance, particularly as I saw John Chan in Adelaide only last weekend.

Carlos Bacchi: I agree with the diagnosis of Rosai-Dorfman disease. I also agree that the presence of regressive changes may have contributed to the difficulty in the diagnosis of RDD.

David Ben-Dor: I really don't know how John Chan figures all these things out! This lesion on the surface looks like fibro- fatty tissue with fat necrosis and abundant chronic inflammation, with some hemosiderin deposits. Thus one could

think of this as possibly being traumatic, along the lines of the injection site lesions discussed earlier. There are histiocyte-like cells with delicate pale or retracted cytoplasm (which blend into the background making them difficult to notice) which I would also assume to be reactive. However on very careful examination some of them do show phagocytosed cell nuclei but this is very focal and limited to one nucleus per cell where I did see it. I don't recall having seen a true-blue case of this condition in routine practice making this presentation all the more difficult. I can't wait to read Dr Rosai's opinion!!

Gerald Berry: Agree with diagnosis. Unfortunately Dr. Dorfman was not available to review the case!.

Michele Bisceglia: Rosai-Dorfman disease of soft tissue. Despite its rarity we also have now another case in this seminar (case 22) and we had at least another one in the past (Seminar 35 case 18: extranodal - skin by LM Weiss). Since (to my knowledge) likely no case in its classic location (lymph node) has not been circulated yet, I will be personally contributing in one of these next seminars a case of lymph nodal involvement by Rosai-Dorfman disease, which recently occurred to my observation (sinus histiocytoses with massive cervical and mediastinal lymphadenopathies).

Ira Bleiweiss: I had no clue.

Tom Colby: Agree with diagnosis.

Kum Cooper: Yes, Ivan - agreed. Subtle but the nuclear morphology and emperipolesis is notable. I wonder what other people think about the evolving spectrum of inflammatory pseudotumor (IPT) and RDD (see reference 3)? I have noticed IPT like-areas in RDD (especially extra-nodal). I have also tried the converse; doing S-100 in IPT to determine if there are residual RDD cells.

Otto Dietze: Convincing but difficult diagnosis in an extranodal site.

Hugo Dominguez-Malagon: Rosai-Dorfman, I missed that, thank you for the case.

Göran Elmberger: Very difficult. I started out thinking about inflammatory pseudotumor – IgG4 related disease (just signed out one in lung – mediastinum) but noted light cells with emperipolesis that made me wonder. Not sure I would have raised the differential dx of RD disease. Given S100 +, I could accept the suggested diagnosis. Interesting that some authors discuss a continuum between inflammatory pseudotumor and RD disease... IgG4? I share your admiration for John's pick-up, but wonder how much of a hallmark lesion we need to see before designating the case as a bona fide case of a specific disease – in present case Rosai Dorfman disease. May the occurrence of the RD hallmark cells sometimes merely be a marker for an activated acute phase inflammatory pathogenetic mechanism, such as macrophage colony-stimulating factor (M-CSF) driven inflammatory response? Clearly need to keep the differential up and running - easier said than done. Lesson: very important with hallmark cells and lesions – cells such as RD histiocyte. Would very much appreciate an update from Ivan. Thanks.

Giovanni Falconieri: A very instructive case, Ivan. I share all your comments. Needless to say, I could not recognize RDD at my first look at the slide

Cyril Fisher: Consistent with RDD, very difficult case.

Christopher Fletcher: Convincing example of Rosai-Dorfman disease – because of the very distorted/biased life that I lead, virtually all the examples of RDD which I see each year are (not surprisingly!) located in soft tissue.

Andrew Folpe: Absolutely- Rosai-Dorfman disease of soft tissues. I've seen quite a few of these over the years- it seems to be more common than is usually appreciated.

Jerónimo Forteza-Vila: I agree with your diagnosis. It could be a lupic panniculitis but there is a highly histiocyte proliferation for this entity.

Masaharu Fukunaga: I considered that this represents septal panniculitis or RDD, but not convincing. Thank you very much for the diagnostic clue, Ivan and John.

Allen Gown: Thanks Ivan for this great example of Rosai-Dorfman disease.

Thomas Krausz: Ivan, I sympathize with the diagnostic struggle. I have seen several cases of Rosai-Dorfman disease in soft tissue, most were classic, without regressive changes.

Janez Lamovec: The diagnosis of extranodal Rosai-Dorfman disease is often a diagnostic challenge, as was in this case.

Thomas Mentzel: Many thanks for the fascinating case and for teaching us the diagnostic clues on this disease arising at unusual sites. We probably have to think on RDD more often!

Markku Miettinen: Agree on Rosai-Dorfman disease.

Liz Montgomery: A nice classic look for soft tissue/extranodal Rosai-Dorfman disease. I think Dr. Rosai will buy this one!

Giuseppe Pelosi: I feel that a diagnosis of Rosai-Dorfman disease may be reasonable. I do not have specific comments to do.

Santiago Ramon y Cajal: Difficult case. The regressive changes make the diagnosis extremely challenging.

Juan Rosai: I agree that this lesion of the soft tissues of the thigh is of inflammatory rather than neoplastic nature, and I would buy as an example of Rosai-Dorfman disease, although it is not the most typical case of that entity I have seen. There is emperipolesis, and I gather the histiocytes are positive for S100 protein. I worry about this entity because it is getting too large for its own good in terms of sites of occurrence, morphologic appearances and evolution.

Joshua SICKEL: Beautiful case of Rosai-Dorfman disease.

Dominic Spagnolo: Very nice case of Rosai-Dorfman disease in soft tissue. Have seen this before in skin and soft tissue, among other sites.

James Strauchen: Soft tissue Rosai-Dorfman. Nice case!

Saul Suster: Agree with diagnosis. Nice case!

Larry Weiss: I have a mini-series of cases of RDD being missed as non-specific inflammation in soft tissue just within the past year.

CASE NO. 7 – CONTRIBUTED BY OTTO DIETZE:

N. Volkan Adsay: Thanks for this great example of diversion colitis. Incidentally, in my slide there was an accessory duct with interesting morphology which made me wonder about a prostatic-appearing duct (presumably related to the patient's known history of atresia?).

Phil Allen: Diversion procto-colitis post colostomy for anal atresia. Yet another most instructive case. Many thanks.

Carlos Bacchi: Thanks for sending this case. It is the first time I saw this lesion (diversion colitis).

David Ben-Dor: To a non-dedicated GI pathologist, this would look like severe IBD but with a remarkable degree of follicular hyperplasia which isn't usually seen in that situation. The crypts in the slide I have don't look "normal". Hopefully one would get accurate clinical information along with the biopsy in this situation but this can't be counted on. I appreciate being informed of this possible pitfall.

Gerald Berry: Diversion colitis. Agree. Nice example.

Michele Bisceglia: Diversion colitis. Thank you. Very educational.

Thomas Colby: Agree with diagnosis. Thank you for sharing this good-sized specimen.

Kum Cooper: Thank you for reminding us of this phenomenon. The other pitfall with a similar morphological pitfall is diverticular disease-associated colitis; especially with biopsies from the lips of inflamed diverticuli.

Otto Dietze: My case.

Hugo Dominguez-Malagon: Agree with diversion colitis, thank you for the case.

Göran Elmberger: Very nice. Agree that the classical findings of diversion procto-colitis are present and very well illustrated in this resection specimen without evidence of pre-existent inflammatory disease. Thanks for sharing.

Giovanni Falconieri: An important case reminding us that inflammatory changes in bowel mucosa must be put in the right clinical context before committing to more stringent diagnostic opinions. It reminds me of a case of colon biopsy which showed virtually all the microscopic changes associated with Crohn's disease, were it not for the fact that the patient had colonic diverticulosis and the mucosal tissue had been obtained near an inflamed diverticulum – a detail which was disclosed only later by our clinicians.

Andrew Folpe: I don't have anything particularly intelligent to say about diversion colitis. I am curious, however, about what seems to be a prostatic gland within the submucosa. I have never seen prostate within the rectal wall before- has anyone else? Perhaps related to the anal atresia?

Jerónimo Forteza Vila: It's a very interesting case. The differential diagnosis is with Crohn's disease.

Masaharu Fukunaga: It is quite new to me. It looks like IBD. Thank very much for the good example.

Thomas Krausz: Highly educational case, thank you very much.

Thomas Mentzel: A nice case, but what are the diagnostic clues?

Liz Montgomery: This is a beautiful example of diversion colitis in which the degree of crypt distortion is not commensurate with the density of the lymphoid infiltrate, a clue that it is not inflammatory bowel disease. It also has a bit of lymphocytic phlebitis, something that is often seen with diversion colitis and probably means nothing [ref; Chetty R, Hafezi S, Montgomery E. An incidental enterocolic lymphocytic phlebitis pattern is seen commonly in the rectal stump of patients with diversion colitis superimposed on inflammatory bowel disease. J Clin Pathol. 2009 May;62(5):464-7.]

Giuseppe Pelosi: I concur that the diagnosis of diversion colitis is a challenging one and always it has to be differentiated from IBD or ischemic colitis. Therefore, clinical information is mandatory in these cases, in order to avoid perilous diagnostic errors.

Santiago Ramon y Cajal: Very nice example of diversion colitis.

Juan Rosai: Good case of diversion colitis, the first one I have seen or recognize.

Joshua Sickel: Great example of this condition.

Dominic Spagnolo: This is a very instructive case - it beats trying to interpret the changes on a biopsy, especially when one is not told of the clinical background. I shudder to think how many cases I may have misdiagnosed as IBD in biopsies of patients with diversion colitis. Thank you.

James Strauchen: Diversion colitis with striking lymphoid hyperplasia.

Larry Weiss: It appears as if the colon has developed coarse villi.

CASE NO. 8 – CONTRIBUTED BY HUGO DOMINGUEZ-MALAGON:

N. Volkan Adsay: Thanks for this great example illustrating the mimicry of lymphoma. It was a great example for our residents.

Phil Allen: Infectious mononucleosis tonsillitis with geographic necrosis. I have been caught by mononucleosis before, but not this time.

Carlos Bacchi: This is really an impressive case counting by the number of atypical lymphoid cells and RS-like cells all simulating Hodgkin lymphoma and even non-Hodgkin lymphoma in some areas. The clinical history as well as the pattern of necrosis and immunohistochemistry results are helpful features in confirming the diagnosis of severe infectious mononucleosis over lymphoma. Great case!!

David Ben-Dor: Unfortunately, the slide when I got it was faded (maybe due to my receiving the package after a postal related delay) but in places I saw sheets of very atypical cells which led me to believe that this was lymphoma. Personally what I saw in terms of necrosis reminded me more of the fissure ulcerations seen in Crohn's disease. I didn't know that necrosis can be seen in IM which makes the differential with lymphoma all the more confusing. Recently I sent a lymph node biopsy to John Chan with atypicality and geographic necrosis and he told me that this is a feature of Hodgkin's disease (of course in the proper histological setting). I recall a biopsy from the tonsil of a young woman which showed extensive infarction surrounded by sheets of atypical large CD20 positive lymphocytes which I diagnosed as large cell lymphoma without any doubt. Now I wonder- infarction is different than geographic necrosis but can this differentiation always be made in a small biopsy? Pathology can really be scary!! I'm very anxious to read the comments by the other members.

Gerald Berry: Infectious mononucleosis of the tonsil. Thanks for providing another example of a benign lesion that may mimic lymphoma.

Michele Bisceglia: Instructive case. Had the opportunity to see another case of tonsil involvement by infectious mononucleosis (even with necrosis) as a slide seminar presented by JK Chan in Treviso (Italy) a few years ago.

Ira Bleiweiss: Agree. Great case.

Thomas Colby: Agree with diagnosis. This case is virtually identical to the 2-3 other cases of this entity that I have seen.

Kum Cooper: Thank you Hugo. Beautiful example of IM. I find that the "zoning phenomenon" between the central geographic necrosis, the atypical immunoblasts and the peripheral residual areas of retained architecture useful in this regard. Hope that the swine flu' is contained by the time you read this note!

Otto Dietze: I cannot remember a case with similar necrosis in a few personal observations with mononucleosis and tonsillitis.

Göran Elmberger: IM is certainly a lesion that always must be top of differential dx in younger persons – "until proven otherwise" was our saying in cytology clinic where we did encounter these patients on occasion. Luckily they don't make their way to the histology lab so often... I guess EBNA IHC and EBER might be of some help but serology is probably golden standard. I believe this case not only represents the differential diagnosis against high grade lymphoma of Hodgkin and non-Hodgkin type, but also focally well illustrates IM resembling MALT type lymphoma reported by Kojima 2008. At least I was wondering about the striking epitheliotropism of lymphocytes with regard to surface and crypt epithelium. Thanks for reminding me about this always difficult lesion.

Giovanni Falconieri: Impossible case. Because of the necrosis and expansion of interfollicular tissue featuring atypical cells, I would feel uncomfortable to report this just as a reactive condition.

Cyril Fisher: Infectious mononucleosis, rare to see a biopsy of this.

Christopher Fletcher: These changes are indeed extremely florid – many thanks for sharing this educational case.

Andrew Folpe: Yikes. I would have thought it was lymphoma and gone running off to our Hemepath people. I'm so glad they're here!! Thanks for educating me.

Jerónimo Forteza Vila: I agree with your diagnosis. The most dangerous complication of infectious mononucleosis is a wrong histopathological diagnosis.

Masaharu Fukunaga: Another good example of IM. A very good teaching case, thank you Hugo. We hope you, your family and colleagues are all right.

Allen Gown: Shows how scary the morphology of IM can be and why it's such a bad idea to biopsy them as it's so easy to misdiagnose these as lymphoma.

Thomas Krausz: Diagnostically challenging case, not just because of the cytology but also of the extensive necrosis. The clinical follow up data are reassuring.

Janez Lamovec: Fortunately, we never get biopsies of lymph nodes/tonsils affected by infectious mononucleosis! In spite of seeing several slide seminar cases of it. I don't know how I would perform in a real life situation.

Thomas Mentzel: Many thanks for sharing this misleading case.

Markku Miettinen: Agree on mononucleosis. Preserved architecture, although ulceration, necrosis and blastic component are present.

Liz Montgomery: Infectious mononucleosis looks so alarming. Thank you for reminding us to have this in our minds before diagnosing high-grade lymphomas in young people.

Giuseppe Pelosi: Infectious mononucleosis tonsillitis with necrosis: I agree with the diagnosis and thank Dr Dominguez-Malagon for giving me the opportunity of learning about this condition.

Santiago Ramon y Cajal: Interesting and unusual case. Thank you!

Juan Rosai: Beautiful case of infectious mononucleosis, with extensive necrosis and a florid lymphoid proliferation with a "graded" appearance of the lymphoid cells as described by Hartssock. It also has Reed-Sternberg-like cells, like those described in the classic paper by Tindle and Lukes.

Joshua Sickel: I've seen tonsillar IM several times before, and it always scares me. The degree of necrosis in this case makes me even more uncomfortable. Another one of those gray-zone lesions which is histologically malignant and clinically benign? Thanks for this great case!

Dominic Spagnolo: Always a trap for young players (and older ones too). Nice case of acute tonsillar IM, with a HD-like picture.

James Strauchen: Infectious mononucleosis! Can never be too careful with these!

Saul Suster: Thank you, Hugo, for sharing this case. One can never see one too many example of this condition, which can so easily lead to misdiagnosis.

Larry Weiss: Agree.

CASE NO. 9 – CONTRIBUTED BY VINCENZO EUSEBI:

N. Volkan Adsay: I wonder if Dr. Rosai might consider the possibility of a transitional case between Langerhans cell histiocytosis to Rosai-Dorfman disease (SHML) also as a possibility in the differential, similar to a case that he had shown at Memorial in 95 or 96.

Phil Allen: Possible Langerhan's cell sarcoma, ventral base of tongue. Phil Lieberman, who was at Memorial for years, has had a long interest in Langerhan's cell tumors but I don't know if he is still seeing cases. I note that he is no longer on the Editorial Board of the American Journal of Surgical Pathology.

Carlos Bacchi: I agree with the diagnosis of Langerhans cell histiocytosis, probably sarcoma type.

David Ben-Dor: The focal seeming apposition of the cells to the surface epithelium would make one consider carcinoma but the keratin negativity would rule out that obvious possibility. The immuno results would support the proposed diagnosis but somehow I would expect the nuclei not to be so round but more convoluted. But there do seem to be numerous eosinophils. There is another Langerhans cell marker made recently available – Langerin. Could this help?

Michele Bisceglia: Langerhans cell sarcoma of the tongue. Agree.

Ira Bleiweiss: Very odd and difficult case. Despite the IHC, I still think the cells are squamous and I suspect benign, but time will tell.

Thomas Colby: I am not sure what this is. To me, the cytology and cellular arrangement would be unusual for Langerhans' cell histiocytosis. Were all the big eosinophilic cells positive for S-100 and CD1a? I don't have a good alternative.

Kum Cooper: Thank you, Vincenzo, for this malignant LCH. Nice that the IHC wrapped it all together. Any experience with langerin?

Otto Dietze: Langerhans cell histiocytosis, I have never heard of a primary presentation in the oral mucosa.

Hugo Dominguez-Malagon: Langerhans cell histiocytosis, I am not sure to call this a sarcoma because there are few mitosis.

Göran Elmberger: Magnificent case with exuberant PEH. Epithelial reaction reminds me of what can be seen in granular cell tumor on occasion. With CD68+, S100+, CD1a+, cell cytology and eosinophilic granulocytes, I guess a Langerhans cell proliferation is the most probable explanation. However, with regards to malignancy grading, I would prefer to be somewhat guarded. Even LCH is recognized to have a multifocal multisystem variant (Letterer-Siwe) so multiorgan proliferation does not by itself guarantee malignancy. Cytology of the Langerhans cells is certainly in favor of sarcoma, but rich cytoplasm, few mitotic figures (< 50/10 HPF), many eosinophils and absence of necrosis does challenge an unequivocal malignant diagnosis. P53, ploidy, MIB1? Any follow-up yet? Atypical Langerhans cell proliferation of uncertain malignant potential?

Giovanni Falconieri: Difficult case. If an eosinophil-rich squamous carcinoma is ruled out (and that possibility seems not supported based on HE and immuno results), I agree that Langerhans cell disorder is a reasonably grounded option because of the heavy eosinophilic infiltrate and some cells exhibiting wrinkled nuclear membrane. Did you try EM? May be that follow-up may dispel the matter.

Cyril Fisher: LCH in rare location, nice slide.

Christopher Fletcher: We saw a very similar case recently, in which I thought that the diagnosis would be histiocytic sarcoma but the immunophenotype clearly supported Langerhans cell differentiation. These two tumour types are likely closely related and an immunophenotypic continuum is not difficult to imagine.

Andrew Folpe: Langerhans cell histiocytosis. I'm not so sure about the "sarcoma" part.

Jerónimo Forteza Vila: I think so but I want to see the electronic microscopy.

Masaharu Fukunaga: Thank you very much for the rare tumor. It is very tricky with florid pseudoepitheliomatous hyperplasia.

Thomas Krausz: Vincenzo, I agree that the Langerhans cells are large and atypical. I also found rare mitotic figures. I am not sure that I would be brave enough to use the "sarcoma". Hopefully the follow up will reveal the malignant potential of this tumor.

Janez Lamovec: Histiocytic cells are quite pleomorphic and nuclei don't show typical grooves. The background is more suggestive of Langerhans' cell lineage of histiocytes, and, of course, immuno results.

Thomas Mentzel: Did large cell stain positively for langerin? In a case or very rare Langerhans cell sarcoma I would expect a more pleomorphic sarcoma-like neoplasm ("MFH"-like) and not so many eosinophils.

Michal Michal: I saw emperipolesis in some of the large cells. The cells do not have morphology of Langerhans cells with cleavage of the nuclei. In spite of CD1a, the process reminds me more of Rosai-Dorfman disease than Langerhans cell granulomatosis. Maybe it is neither of these processes, and it is an unclassified process.

Markku Miettinen: Agree on Langerhans histiocytosis with atypical features. I would also agree that the diagnosis of malignancy needs staging and clinical correlation.

Giuseppe Pelosi: This is a spectacular case of Langerhans cell sarcoma with unusual oral cavity location. Differential diagnoses also include sarcomatoid carcinoma, but positivity for CD1a along with CD68 and S-100 protein points clearly to that diagnosis. This case has been for me very difficult and stimulating!

Santiago Ramon y Cajal: I agree with your diagnosis, although the site is quite unusual. Please give us some follow-up if possible on the behavior of the neoplasm.

Juan Rosai: I agree with the fact that this lesion is made up of Langerhans cells, but I can't call it a sarcoma. Actually, I think the atypia is relatively modest. I would rather regard it as a case of Langerhans cell histiocytosis with florid pseudoepitheliomatous hyperplasia of the overlying epithelium. In the differential diagnosis, I considered an epithelioid type of Spitz nevus with pseudoepitheliomatous hyperplasia of the kind that we described some years ago in this very location (*Am J Surg Pathol* 56: 774-777; 2002).

Joshua Sichel: The glassy cytoplasm reminded me of reticulohistiocytoma, but the atypical nuclei excluded that possibility. I've seen CD30(+) anaplastic large cell lymphoma of skin with associated pseudoepitheliomatous change. This is a weird case! I will defer final judgement on this lesion to the lymphoma experts.

Dominic Spagnolo: No doubt about a pleomorphic histiocytic/dendritic cell neoplasm with zillions of eosinophils, and the immunophenotype is in keeping with Langerhans cells - would be nice to see if langerin is positive to clinch it, or show Birbeck granules. Despite the impressive pleomorphism, mitotic activity is very low, and the massive eosinophilia is unusual for Langerhans cell sarcoma, but I guess that is the most likely diagnosis. An indeterminate cell tumor (if langerin is negative) would be unusual too given the numerous eosinophils. It will be interesting to see if the node shows the same process, or harbours a non-Hodgkin lymphoma. I look forward to the follow-up!

James Strauchen: LCH can show a spectrum of cytologic atypia, and I am very reluctant to make the diagnosis of Langerhans Cell Sarcoma since the natural history is unpredictable. In the oral location, so called "eosinophilic traumatic ulcer" (actually an oral CD30-positive lymphoproliferative disorder) would be in the differential but seems to be excluded in this case by the immunophenotype.

Saul Suster: This must be one of the prettiest examples of Langerhans cell histiocytosis I have seen! Scattered clusters of Langerhans cells in a sea of eosinophils! Doesn't get any better! Please let us know the clinical follow-up on this patient!

Larry Weiss: This is not my idea of a Langerhans cell sarcoma—the nuclei are not atypical enough and the cytoplasm is too abundant. One needs to perform a Langerin stain. I place my money on either an indeterminate or interdigitating cell neoplasm (how focal is the CD1 positivity), but additional stains are necessary. Many of these patients have coexisting low-grade B-cell lymphomas, particularly follicular lymphoma, which may explain the enlarged lymph node.

CASE NO. 10 – CONTRIBUTED BY CYRIL FISHER:

Phil Allen: Angiosarcoma arising in a surgically constructed arteriovenous fistula in an immune-suppressed renal transplant patient, flexor surface, forearm. Many thanks, Cyril. This makes a nice companion for the injection site angiosarcoma (case 1 of this seminar). Incidentally, I don't believe this high grade angiosarcoma has anything to do with angiolymphoid hyperplasia with eosinophilia or epithelioid hemangioendothelioma.

Carlos Bacchi: Nice example of angiosarcoma arising in AV fistula.

David Ben-Dor: I can't help but being reminded of the case submitted by Phil Allen of injection site angiosarcoma. Funny how both cases are submitted to the same seminar!! Admittedly there was no obvious reason to assume that the other patient was immunosuppressed but both show angiosarcoma arising at the site of previous iatrogenic injury.

Gerald Berry: A terrific case that complements Case 1.

Michele Bisceglia: Angiosarcoma arising in AV fistula previously used for dialysis in renal transplant recipient. I was aware of this occurrence, but (of course) never seen one. Thank you, Cyril.

Ira Bleiweiss: Agree. Angiosarcoma. The theme of this seminar?

Thomas Colby: Agree with diagnosis.

Kum Cooper: Thank you, Cyril, for this instructive case. A semantic question: why not a malignant EHE? You describe an adjacent vessel wall with tumor arising/involving the wall. Not that this makes a difference to the morphological aggression it displays!

Otto Dietze: I have known about this association only from the literature before.

Hugo Dominguez-Malagon: Interesting case of angiosarcoma arising in A-V fistula, there are reparative phenomena with thrombus and hematoma organization. As I discussed in Case 1, there is some association between epithelioid endothelial neoplasm and old hematoma/thrombus. Perhaps related to growth factors (platelet or fibroblast derived)?

Göran Elmberger: Thanks for sharing this unique case. Just learned about this relationship when reading up on Phil Allen's case for this seminar.

Giovanni Falconieri: Pretty unusual presentation of epithelioid angiosarcoma of which I was unaware. Thank you for this excellent contribution.

Christopher Fletcher: Another very convincing example of angiosarcoma arising in an exceptional context, albeit cases such as this (associated with an A/V shunt) have been more convincingly documented than those at injection sites – many thanks Cyril.

Andrew Folpe: A very nice pair with Phil's case.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Thank you for the special case of angiosarcoma, Cyril. This type of angiosarcoma is quite new to me.

Allen Gown: Lovely example of yet another angiosarcoma. Thank you, Cyril.

Thomas Krausz: I haven't seen this association before.

Janez Lamovec: Another angiosarcoma in this seminar!

Thomas Mentzel: A rare and interesting case of an angiosarcoma arising at the site of a AV-fistula, many thanks.

Markku Miettinen: Agree on angiosarcoma arising in AV fistula site, with epithelioid features.

Elizabeth Montgomery: This is a fantastic case, Cyril. A real classic! Thanks.

Giuseppe Pelosi: I never had seen before a case of angiosarcoma arising in AV fistula previously used for dialysis in a renal transplant recipient, but I concur completely with the final diagnosis.

Santiago Ramon y Cajal: Angiosarcoma arising in a surgically constructed AV fistula. That is unusual and unfortunate.

Juan Rosai: Fantastic case of **epithelioid angiosarcoma** arising in a surgically constructive arteriovenous fistula. Interestingly, the tumor is associated with a well differentiated component that looks like a cavernous hemangioma. It is an incredible experiment of nature (with a heavy contribution by the surgeon), very similar to the case reported in the Am J Surg Pathol 22:1154-1159;1998. You will have to admit that in the more malignant component the tumor cells look histiocyte-like (just compare them with those of Case 9) and hopefully you forgive me for having originally suggested the qualifier "histiocytoid" for this family of tumors.

Joshua Sickel: Lightning strikes twice...2 angiosarc's in the same seminar...incredible!

Dominic Spagnolo: Two angiosarcomas in unusual settings in the one seminar! Have never seen this association with AV fistula before - very instructive case. Thanks Cyril.

James Strauchen: Wow! I didn't know an AV fistula was a risk factor. Thank you!

Saul Suster: Three examples of angiosarcoma in a single seminar – coincidence or conspiracy?

Larry Weiss: Nice juxtaposition with case 1.

CASE NO. 11 – CONTRIBUTED BY CHRISTOPHER FLETCHER:

Phil Allen: Scrotal lymphoedema with smooth muscle hyperplasia. Funnily enough, I had a similar case in consultation only 3 days ago. There was more mucoid lymphoedema in my case and the patient was said to be "not unduly large." However, the surgeon himself was described as "large" by the skinny pathologist who referred the case to me.

Carlos Bacchi: The smooth muscle hyperplasia is really striking in this edematous tissue.

David Ben-Dor: This slide is almost meaningless if not examined with the clinical background in mind. The smooth muscle hyperplasia in that context is striking. The dilated lymphatic spaces some surrounded by lymphocytes and especially one focus showing a congeries of irregular small dilated lymphatics would be a tip off as to the diagnosis though most of the slide shows unremarkable fibrotic tissue.

Gerald Berry: Agree with diagnosis. Before I read the clinical history, I keep looking to find the subtle neoplasm!

Michele Bisceglia: Scrotal lymphoedema (with smooth muscle hyperplasia). Interesting. Had not seen one before.

Ira Bleiweiss: Agree. Ouch! 2 years??? 18 cm???? What was the guy thinking?

Thomas Colby: Agree with diagnosis. Some of the dilated lymphatics are somewhat lymphangiomatous in appearance but that appears to be a focal finding and probably secondary.

Kum Cooper: Thank you for this education. Trust you to present a case of "massive external genitalia"!!!

Otto Dietze: Smooth muscle hypertrophy is quite impressive.

Hugo Dominguez-Malagon: Scrotal lymphedema with smooth muscle hyperplasia, there are also prominent (hyperplastic?) nerves. Interesting lesion, thank you.

Göran Elmberger: Great case. On blind review, I was considering a hamartomatous lesion with smooth muscle bundles and nerves running criss-cross but with history of chronic lymphoedema, I fully subscribe to your interpretation and terminology. Previous nomenclature acquired smooth-muscle hamartoma (ASMH) is, however, catching...Muscle looks mature – smoothelin?

Giovanni Falconieri: Thanks, Chris, a very interesting case which I think is underreported merely because most pathologists, including me, are not aware of the condition. Probably, I would have signed it out descriptively suggesting a vascular dysplasia or something else.

Cyril Fisher: Scrotal edema with remarkable smooth muscle hyperplasia, I have not seen this before.

Christopher Fletcher: My case.

Andrew Folpe: Looks like lymphedema. Would be interesting to see what the causes are of these non-obesity associated cases. I have also seen this in obese patients.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Very interesting case of a huge mass. I only paid attention to lymphoedema. Yes, smooth muscle hyperplasia is prominent.

Thomas Krausz: I haven't seen/paid attention to this lesion before. I will look out for it in the future. I do not know whether the prominent perivascular lymphocytic infiltrate, not only around the lymphatics, has any significance.

Janez Lamovec: Never heard of this condition. Thank you for teaching us.

Thomas Mentzel: Given the amazing size of the scrotal lymphedema it seems not surprising to have such a reactive smooth muscle hyperplasia.

Markku Miettinen: Agree on scrotal lymphedema.

Liz Montgomery: Fascinating process and, of course, not quite like any of the many genital region angiomoid things. I seem fixated lately on collections of lymphocytes that like to live in the veins in various conditions, a feature that is prominent in this lesion – makes one think of a contact dermatitis/immune type thing. Maybe the poor man was using the wrong type of laundry soap or some strange pomade bought through an establishment sending lots of spam e-mail and promising more avoirdupois.

Giuseppe Pelosi: Scrotal lymphoedema with smooth muscle hyperplasia: excellent presentation of an unusual and intriguing case!

Santiago Ramon y Cajal: Thank you. Very impressive. The smooth muscle hyperplasia is quite remarkable.

Juan Rosai: As Dr. Lauren Ackerman would have said, "Not very romantic ..."

Joshua Sickel: I thought this was from an obese patient.

Dominic Spagnolo: More exotica - heard of, but never seen. Very impressive case of massive scrotal lymphoedema - thanks.

James Strauchen: Wow, elephantiasis! Is the filarial form histologically identical to the idiopathic?

Saul Suster: Thank you, Chris, for sharing this unusual lesion. It's the kind of pathology one does not quite know what to do with when you first review the slides (everything looks normal!). The edema and the smooth muscle hyperplasia are the clue, and of course, also the correlation with the gross specimen.

CASE NO. 12 – CONTRIBUTED BY ANDREW FOLPE:

N. Volkan Adsay: Great case.

Phil Allen: Cytokeratin, EMA positive bone sarcoma with homozygous deletion of INI 1 gene, left iliac bone. I don't think this tumour is related to Enzinger's epithelioid sarcoma and I also believe the so-called proximal epithelioid sarcoma is a completely different entity from Enzinger's tumour. I don't know how to interpret the immunohistochemistry and insitu hybridization results in this case.

Carlos Bacchi: Good pick up, Andrew, and great discussion.

David Ben-Dor: This is not the sort of material I'm personally familiar with. Not having seen a case of this in the flesh, I wouldn't think of the cells here as being particularly "epithelioid" though I wouldn't know how exactly to describe them. The standard descriptions of epithelioid sarcoma (at least the peripheral type) stress the presence of necrosis giving a resemblance to granulomas. I don't see this in this sample. The point about carcinomas very rarely showing CD34 positivity is interesting in light of a case I saw some years ago of widespread metastatic tumor with no primary mass which I sent to two consultants who both found keratin and CD34 positivity- on this basis they diagnosed metastatic epithelioid sarcoma despite the lack of a known mass. The possibility of carcinoma in this situation cannot be absolutely ruled out – I guess that in pathology unicorns can exist if searched for.

Gerald Berry: I find that this lesion is difficult enough to diagnosis in the soft tissues. I suspect I might have suggested an epithelioid metastasis and would be searching for the primary.

Michele Bisceglia: Primary epithelioid sarcoma of bone. Thank you for this novelty and for the pictures.

Ira Bleiweiss: I am surprised at this diagnosis. This reminded me of chondroblastoma purely on the H+E.

Thomas Colby: Agree with diagnosis. Wonderful discussion, Andrew.

Kum Cooper: Fascinating case, Andrew. Great write-up, work-up and morphology. Thank you! You should publish this case.

Otto Dietze: Fascinating case and excellent presentation, I have never seen a well proven case of proximal type of epithelioid sarcoma or a peripheral type ES in the bone.

Hugo Dominguez-Malagon: Nice case of epithelioid sarcoma arising in bone, excellent discussion.

Göran Elmberger: Thought we were up for third angio this seminar given pseudoangiomatous pattern and tendency to vasoformative cytoplasmic vacuolization. Value of immunohistochemistry and marker chromosomal change appreciated. Thanks

Giovanni Falconieri: Out of my reach, Andrew. I would await the opinions of the accountable soft tissue experts of the club.

Cyril Fisher: Epithelioid sarcoma in bone, with typical IHC and genetic support, without apparent primary elsewhere, great case and discussion.

Christopher Fletcher: Indeed the morphology of this lesion is very convincing for conventional-type epithelioid sarcoma. I cannot recollect such a case arising primarily in bone in the past – although I have to admit to becoming increasingly forgetful as middle age advances! Certainly, however, it is my experience that virtually any type of soft tissue sarcoma may very occasionally arise in bone.

Andrew Folpe: My case. Does anyone recall having seen a similar case in the past? There must be more epithelioid sarcomas in bone- of course the bone people have probably just called them all "osteosarcoma".

Jerónimo Forteza Vila: It's a very interesting case. It's important to determinate the cytogenetic alterations in familiar cases.

Masaharu Fukunaga: I thought it was chondroblastoma with atypia. Thank you very much for detailed information, Andrew. I will read your paper in Am J Surg Patho.

Allen Gown: Lovely and well documented case of epithelioid sarcoma; thanks, Andrew.

Thomas Krausz: Primary epithelioid sarcoma of bone – great diagnosis, superb discussion. Thank you.

Janez Lamovec: Without immuno, I would diagnose this tumor as osteosarcoma.

Thomas Mentzel: What a case! Before looking to the case history, I was thinking on a malignant giant cell tumour with a peculiar epithelioid cytomorphology. Thanks for sharing this extraordinary case.

Markku Miettinen: High-grade sarcoma with epithelioid features. Have to agree that the immunophenotypic features are epithelioid sarcoma-like, and that before accepting it as a primary bone epithelioid sarcoma, a thorough clinical study is in order. Also, I wonder whether INI-loss can be a feature in the evolution of various tumor types undergoing rhabdoid differentiation; there might be some evidence for that. Very interesting case.

Elizabeth Montgomery: With the ancillary studies, skeletal epithelioid sarcoma seems a reasonable diagnosis. I am sure I would have misdiagnosed it as a vascular neoplasm. As Andrew and I have discussed, there must be similar cases in all of our filesbut hiding under which misdiagnoses?

Giuseppe Pelosi: I usually see epithelioid sarcoma in soft tissue location with a few examples of proximal type variant too, because my institution is not devoted to orthopedic disease care. The morphology and immunohistochemical profile are truly consistent with epithelioid sarcoma primary to bone, and I thank Dr Andrew Folpe for giving me the opportunity of learning about this condition and reading the excellent and detailed discussion presented on the case.

Santiago Ramon y Cajal: Thank you for this extremely challenging case. Good discussion. I do not feel sure with a final diagnosis with the H.E. slide.

Juan Rosai: I suppose we will have to accept the diagnosis of epithelioid sarcoma on the basis of the sophisticated molecular genetic evaluation, the veracity and significance of which I am in no position to judge. I would add, however, that from a purely morphologic standpoint, I would have favored the diagnosis of a bone tumor showing a cartilaginous differentiation, and more specifically a malignant form of chondroblastoma. As a matter of fact, the only two cases of malignant chondroblastoma that I have ever seen were located in the pelvic bone. One was subsequently reported (J Bone Joint Surg 57-A: 549, 1975). By the way, chondroblastomas are often keratin-positive.

Joshua Sickel: Reminded me of chondroblastoma (but too atypical). Great discussion...there is so much to learn out there. Andrew, thanks for sending this extraordinary case!

Dominic Spagnolo: I'm convinced - apparently primary osseous epithelioid sarcoma. Stunning case.

James Strauchen: I wasn't aware these occurred in bone. The histology with "chicken wire" calcification in this case resembles a chondroblastoma.

Saul Suster: I was not even aware that such a thing could happen (primary ES of bone)! Hopefully an occult primary somewhere else will not surface in this patient. The molecular studies certainly seem to support your interpretation. There's much still to be learned...

Larry Weiss: Very nice discussion.

CASE NO. 13 – CONTRIBUTED BY JERÓNIMO FORTEZ VILA:

N. Volkan Adsay: Fascinating case. I believe this tumor exhibits several features in keeping with a fibrolamellar variant of hepatocellular carcinoma, including the oncocytic nature of the cells, irregular nests, with intervening laminated fibroblastic stroma. FVHCC often lacks cirrhotic background and occur in younger patients as in this case. Mucoïd matrix is something we see occasionally in HCC, but this case is intriguing because it also shows rare goblet-like cells. I would not consider the possibility of a conventional pancreatic ductal adenocarcinoma. In my experience, when ductal adenocarcinoma forms this nested pattern, the cells tend to be very pleomorphic, there is necrosis and invariably there is more conventional glandular differentiation. As for the prognosis, FVHCC can present with widespread metastasis in some cases. (*Hepatology. 1997 Oct;26(4):877-83.*)"

Phil Allen: Hepatocellular carcinoma with metastases to lymph nodes, pancreas, spleen, heart, intestinal mucosa and scalp. I agree with the diagnosis. Thanks for the case.

Carlos Bacchi: I agree with the diagnosis of hepatocellular carcinoma. CD34 immunostaining could be helpful in the differential diagnosis as it can highlight the sinusoidal cells lining the tumor trabeculae, which is characteristic of hepatocellular carcinomas.

David Ben-Dor: Interesting analysis and workup. The neoplastic cells looked oncocytic to me and while at least in places can be interpreted as forming trabeculae the stroma is fibrotic and on the slide present I can't be sure whether the tumor is forming sinusoids (a vascular marker could help). The mucin looked extracellular and not intracellular. There are cases with mixed hepatocellular-cholangiocellular characteristics though I don't know if the overall morphology here is consistent with that. I thought that the finding of a well defined nodule with non-cirrhotic liver in the background is tantamount to metastasis- I guess this rule doesn't always hold true. I found some dilated spaces in the portal tract containing mucin and a few (or even a single) tumor cells- are these lymphatics and if so is the tumor outward or inward bound?

Michele Bisceglia: Hepatocarcinoma with metastases to lymph nodes, pancreas, spleen, heart, intestinal mucosa, scalp. Agree with HCC diagnosis, even if I am surprised for CK7 +ivity in this tumor. HCC is able to metastasize in strange locations: in a personal case solitary vulval metastasis occurred, which was previously diagnosed (by another pathologist) as primary vulval apocrine carcinoma.

Ira Bleiweiss: Hepatocellular carcinoma.

Thomas Colby: Agree with diagnosis of hepatocellular carcinoma. Was all the bluish material on the H & E mucin? I don't see a comment regarding a mucin stain. Some lamellar fibrosis is present. Combined hepatocellular/cholangiocarcinoma could also be a consideration depending on how extensive the mucin production is.

Kum Cooper: HCC, fibrolamellar variant. These are not as indolent as we previously thought. (see Kakar and Burgart et al. Mod Pathol).

Otto Dietze: Convincing diagnosis based on the reported findings.

Hugo Dominguez-Malagon: Agree with hepatocarcinoma, the trabecular pattern and cytological features are consistent with the diagnosis.

Göran Elmberger: Nice case and important point. Early spread and overlapping phenotype made problems for me more than once. In present case, I do recognize fairly typical hepatocytoid features, including bile production within tumor, so I am convinced it represents a hepatocellular carcinoma. Bad action can be foreseen with extensive LVI spread. Thanks.

Giovanni Falconieri: I agree with your interpretation, I would also favor hepatocarcinoma because of the tumor architecture and some cytologic features including granular material which might reflect abortive bile production. I do not feel so much distressed by either the focal pseudoglandular changes and the mucin production as well since both may be occasionally seen in hepatocarcinoma. Likewise, clinical features such as fast clinical course, HCV negativity status and absence of cirrhosis are also possible in variable combinations. Finally, I also agree with you that immunostains may not be not fully conclusive. In my experience, immuno panels commonly used with HCC are good once you have already done it (or ruled out) on routine stains. They have a confirmatory role, at best.

Cyril Fisher: Hepatocellular carcinoma, rarely mucin-secreting.

Christopher Fletcher: Very convincing example of hepatocellular carcinoma.

Andrew Folpe: Hepatocellular carcinoma. Interesting case.

Masaharu Fukunaga: I considered it was fibrolamellar carcinoma. Thank you very much for the case and the description.

Allen Gown: Did the CEA immunohistochemistry delineate bile canalicular structures? Was there a sinusoidal pattern of cell positivity noted with antibodies to CD34?

Thomas Krausz: Agree with diagnosis. The focal mucinous differentiation perhaps suggests "incipient" cholangiocarcinomatous differentiation.

Thomas Mentzel: An interesting case, especially in regard to the differential diagnosis.

Markku Miettinen: Agree on hepatocellular carcinoma, with ? fibrolamellar features.

Liz Montgomery: Not a diagnostic problem for hepatocellular carcinoma faced only with the naked glass slide and no history but a bizarre case in light of knowing the history.

Giuseppe Pelosi: The diagnosis of hepatocarcinoma often is hard to render, even on surgical or autopsy samples. The morphology and immunohistochemical reactions are consistent with hepatocarcinoma, and I agree that the mutation study strategy for K-ras gene is an excellent strategy for excluding metastatic pancreatic adenocarcinoma. Interesting and difficult case!

Santiago Ramon y Cajal: Difficult case. We are facing a neoplasm with hepatoid morphology, however it is quite infrequent for a hepatocellular carcinoma to present with an iliac mass, the age is not typical, and the mucus also makes the diagnosis quite unlikely. I think that a wider differential should be considered in this case beyond pancreas and liver, and I would consider among others a gonadal/germinal origin (? Undescended testis).

Juan Rosai: I agree with the diagnosis of hepatocellular carcinoma, but I would have placed it into the fibrolamellar (oncocytic) variant category.

Joshua Sickel: I saw occasional cells with intracytoplasmic mucin and favored hepatoid adenocarcinoma of pancreatic origin. Unfortunate case.

Dominic Spagnolo: This looks like fibrolamellar HCC to me. The young age, absence of cirrhosis, large granular eosinophilic cells, occasional pale (?fibrinogen) inclusions, fibrous stroma, mucin, normal AFP would all seem to be OK for this.

James Strauchen: HCC. By the way, I like the term "exitus"!

Larry Weiss: What about a pancreatic carcinoma with hepatoid differentiation. What about CK17?

CASE NO. 14 – CONTRIBUTED BY ALLEN GOWN:

Phil Allen: Poorly differentiated, primary, CD117 and synaptophysin positive thymic carcinoma with some suggestion of squamous differentiation. Thanks for this instructive case.

Carlos Bacchi: Nice case.

David Ben-Dor: Histologically looks like undifferentiated carcinoma of the nasopharynx. I thought that defining a mediastinal mass as thymic carcinoma was done by exclusion- i.e. no other logical location for a primary tumor was identified. In this situation the immuno can be a great help as a positive identifier. I remember that previously Allen

submitted a tumor in the pleural space as being metastatic from the thymus based on immunohistochemical findings which presented a similar problem at least histologically

Gerald Berry: Thymic carcinoma with epidermoid features.

Michele Bisceglia: Thymic carcinoma. Completely agree on your discussion concerning with the importance of the immunophenotype and its specificity for the diagnosis of thymic carcinoma. Quite recently I had a case (fine needle biopsy) in the lung, in a patient who underwent previous surgery for "thymoma" (they said so): based on CD117 +vity along with CD5 +vity as well, the correct diagnosis of thymic carcinoma with squamous features (p63+ve) could be rendered (subsequently we were notified that the primary tumor which had been resected a few years before was thymic carcinoma "not thymoma"). CD70 is also said to be helpful in the differential diagnosis of thymic carcinoma vs carcinoma of other sites.

Ira Bleiweiss: Thymic carcinoma with squamous and spindle cell features.

Tom Colby: Agree with diagnosis. H & E definitely looks "thymic" and my issue with cases like this is where type B3 ends and carcinoma begins. This case has compelling cytology for carcinoma.

Kum Cooper: Thanks, Allen, for the CD 117. I was not aware of that distinction between thymic carcinoma and thymoma. The other useful way to distinguish between lung SCC and thymic SCC is to demonstrate the presence of CD 99 positive lymphocytes (thymocytes) in the stroma (as shown by John Chan many years ago).

Otto Dietze: I did not realize the importance of c-kit expression in this tumours, thank you for the reminder.

Hugo Dominguez-Malagon: Thymic carcinoma, still keeps some organotypic (angulated nests surrounded by dense stroma).

Göran ElMBERGER: Thanks for pointing out occurrence of CD117 and neuroendocrine cells in thymic carcinomas. I wonder if it could occur in thymomas too. I have somewhat of a problem to make up my mind if this lesion with obvious desmoplastic stromal response but without much cellular atypia, intercellular bridges or overt squamous differentiation should be classified as carcinoma or thymoma B3 spindle cell variant. Nature of TIL's?

Giovanni Falconieri: I agree. I also believe that this is thymic carcinoma. Nice case, thank you.

Christopher Fletcher: Nice case, Allen. I agree that CD117 staining can be very useful in this context.

Cyril Fisher: Thymic carcinoma, useful to be reminded of role of CD117 here.

Andrew Folpe: I'll get out of the way of the thymic gurus, but what I have on my slide looks more like an invasive thymoma. I don't really see thymic carcinoma here.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Thymic carcinoma. I did not know the immunohistochemical phenotypes of this type of carcinoma. Thank you very much for the information and a beautiful case.

Thomas Krausz: Agree with Diagnosis.

Janez Lamovec: Thymic carcinoma with squamoid features.

Thomas Mentzel: Thanks for this case of a thymic carcinoma with neuroendocrine features.

Markku Miettinen: Agree on poorly differentiated thymic carcinoma with squamous features.

Giuseppe Pelosi: Good example of thymic carcinoma, squamous cell variant. The discussion is exhaustive, with several diagnostic clues to exclude metastatic squamous cell carcinoma from the lung. All considerations are absolutely true, reasonable and appropriate: however, one should bear in mind that every single immunohistochemical marker found in thymic carcinomas of this histological variant may be also shared by squamous cell carcinoma primary to the lungs. In particular, I would like to make a reference to CD117 and neuroendocrine markers (chromogranin A and synaptophysin) immunolabeling that may be sometimes observed in squamous cell carcinomas of the lung too (pan-neuroendocrine markers along with true hormone production detected by immunohistochemistry, even though in a limited number of tumor cells). I remember a few cases of squamous cell carcinomas of the lung with a spectacular, strong and diffuse immunoreactivity for CD117. Another related and challenging phenomenon is the simultaneous appearance of carcinomas primary to thymus and lung, sometimes with different histologies, sometimes with similar histological features: in the latter case may be hard to decide whether they are primary or secondary tumors. Thanks again for this exciting case!

Santiago Ramon y Cajal: Thank you for this nice case and for pointing out the interesting phenomenon described by Kuo.

Juan Rosai: I think this case is quite compatible with thymic carcinoma, a tumor which I still like to call type C thymoma. There is focal infiltration by eosinophils, a feature usually associated with a squamous morphology, but this is not the case with this tumor. The lobulation induced by the wide fibrous bands is pretty characteristic.

Joshua Sichel: Agree with diagnosis of thymic carcinoma.

Dominic Spagnolo: Undifferentiated thymic carcinoma seems fine to me - the squamous differentiation is focal and subtle. How much synaptophysin positivity was there? Cytologically, neuroendocrine carcinoma is in the mix for me, or mixed squamous/neuroendocrine.

James Strauchen: Thymic carcinoma. Do they respond to imatinib?

Saul Suster: I agree that this case is consistent with the diagnosis of thymic carcinoma, but disagree with regards to the "specificity" of either CD5 or CD117 for making this diagnosis. I have seen cases of primary squamous cell carcinoma of the lung and other sites that have stained with CD117. CD5 is also a loose cannon when it comes to making this diagnosis. As far as I am concerned, thymic carcinoma (with very few exceptions) remains a diagnosis of exclusion and I would never make that diagnosis (CD117/CD5 positivity notwithstanding) a-priori unless thorough clinical and radiographic studies fail to identify a tumor elsewhere. I have not yet found a reliable, much less a "specific" marker that would allow me to make that diagnosis based on immunohistochemical staining alone.

Larry Weiss: We still like CD117 as marker of thymic carcinoma. It sure beats CD5 (worthless).

CASE NO. 15 – CONTRIBUTED BY JANEZ LAMOVEC:

Phil Allen: Apocrine carcinoma with sebaceous and mucinous differentiation, skin of right breast. I accept the diagnosis. The tumour was probably a low grade carcinoma that has taken 11 years to metastasize. The tumour growth spurt 6 months before surgery probably indicates tumour progression to a more malignant state.

Carlos Bacchi: Thanks for the nice case and discussion.

David Ben-Dor: There many cells with microvesiculated cytoplasm typical of lipid content though it's commendable that you had the presence of mind to have frozen section slides put aside for fat stains. I've heard it said that the breasts are in truth oversized sweat glands and it is known that their tumors can be homologous. Sometimes I guess one has to rely on anatomical-clinical correlation to resolve these issues. Can myoepithelial cells (whose presence was demonstrated in this case) be seen in sweat gland tumors? - if not maybe this can be used as an argument for breast origin. Lipid rich carcinomas of the breast have been described.

Michele Bisceglia: Apocrine carcinoma of the skin with sebaceous (sebaceous-like) and mucinous differentiation. Agree on your diagnosis, Janez. Interesting cases. Any time I see sebaceous differentiation in a tumor, I always think of Muir-Torre syndrome. No other sebaceous tumor in the skin? No other tumor in visceral organs?

Ira Bleiweiss: I agree that this is a skin primary, secondarily involving the breast- most unusual. I would call it a sebaceous carcinoma.

Thomas Colby: Agree with diagnosis and agree that this is most likely of skin origin.

Kum Cooper: Thank you Janez. I like apocrine with sebaceous differentiation.

Otto Dietze: I agree with the diagnosis but was surprised about the strong ER positivity.

Hugo Dominguez-Malagon: Apocrine carcinoma of the skin with sebaceous and mucinous features (you may choose a fancy name for this combination). Never seen a case like this.

Göran Elmberger: Tricky lesion to classify. I guess adnexal carcinoma is most probable dx given location, look and possible presence of precursor lesions within tumor (cited basal-myoepithelial peripheral cells!?). The histology is not typical of an apocrine or sebaceous neoplasm, but I share your judgement that the tumor shows what is probably partly apocrine and sebaceous differentiation. EMA and AR could be helpful. Metastases or breast origin is otherwise difficult to rule out given the large size of the tumor and absence of Pagetoid growth. Negative mammography does not necessarily rule out breast tumor.

Giovanni Falconieri: What a case, Janez! This looks extraordinarily exotic because of the differential entailed by that particular site, i.e. the mammary skin. I shall look forward to reading the comments of the cutaneous pathology experts. Thanks for this beautiful contribution.

Cyril Fisher: Adnexal carcinoma with sebaceous and mucinous differentiation.

Christopher Fletcher: This is indeed an unusual case – but, as far as I can tell, no two skin adnexal carcinomas ever look quite the same! Classification of these lesions is a chronically frustrating problem.

Andrew Folpe: Agree with apocrine carcinoma. I guess it is a skin primary, if there was no breast lesion. Nice case.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Thank you very much for the interesting skin adnexal tumor, Janez. It is very difficult to make a definite diagnosis.

Thomas Krausz: Difficult case. Favor variant of sebaceous carcinoma. I am not sure about the apocrine, although the tumor cells are distinctly eosinophilic. I also considered high grade mucoepidermoid with sebaceous differentiation, but I do not think so.

Thomas Mentzel: A fascinating case of a large cell, pleomorphic adenocarcinoma, however, I did not see convincing sebaceous differentiation. Can we exclude a high-grade breast cancer arising from accessory breast tissue?

Markku Miettinen: Agree on skin adnexal carcinoma with sebaceous differentiation. I don't strongly disagree on "apocrine" because my experience of this type of apocrine differentiation is limited.

Liz Montgomery: Amazing skin appendage carcinoma case.

Giuseppe Pelosi: Apocrine carcinoma of the skin with sebaceous and mucinous differentiation: great and very unusual case!

Santiago Ramon y Cajal: It is a very challenging case, and the diagnosis of a primary adnexal skin tumor is not the first thing that came to me when I looked at the slide, however you are probably right if you ruled out a breast primary (rich in lipids carcinoma) and a metastasis.

Juan Rosai: I think the evidence of dual apocrine and sebaceous differentiation in this breast tumor is pretty convincing.

Joshua Sichel: I favored a tumor of mammary origin. I've seen breast tumors with this degree of apocrine and sebaceous-like differentiation. Could this have arisen from ectopic breast tissue?

Dominic Spagnolo: I would call it a mixed apocrine-sebaceous carcinoma. I think there is convincing evidence of both lines of differentiation here.

James Strauchen: Apocrine carcinoma.

Larry Weiss: I agree with your diagnosis. I think that the GCDFP-15 is good for apocrine and the morphology is good for sebaceous.

CASE NO. 16 – CONTRIBUTED BY MICHAL MICHAL:

Phil Allen: Cortico-medullary tumour of adrenal glands (mixed pheochromocytoma/cortical adenoma) with an additional spindle cell component. Looks like a very convincing case. I was not aware of the entity. Thanks for the contribution.

Carlos Bacchi: Amazing case. First time I saw one. Thanks for sending it.

David Ben-Dor: There are foci in which the pheochromocytoma cells appear to be gradually spindling out while elsewhere there are sharply delineated groups of spindle cells which look totally different than the surrounding pheochromocytoma cells without any transition. These cells are rather bland and show variable whorling or a herringbone pattern. Could this component be reactive?

Gerald Berry: Corticomedullary tumor of the adrenal gland.

Michele Bisceglia: Corticomedullary tumor of the adrenal glands. Extraordinary composite tumor. Thank you, Michal. Concerning with the link between the pheochromocytoma component and the 3rd component of your tumor in this case, I also recall all those multilineage differentiations you described in the (carotid body) neck tumors (*Int J Surg Pathol.* 2007 Oct;15(4):429-36) and of which you shared a slide with us (Seminar 53 - case 17).

Ira Bleiweiss: A new one on me.

Thomas Colby: Agree with diagnosis (once I was educated by Michael). I sailed right past the small clusters of eosinophilic cells.

Kum Cooper: Michal, I have seen mixed cortical adenoma-pheochromocytoma in this seminar before; but have not encountered the spindle cell sarcoma that may arise in the latter. Thank you for this education.

Otto Dietze: Without your description I found it difficult to see the cortical and medullary differentiation, but now it is well appreciable.

Hugo Dominguez-Malagon: Corticomedullary tumor with sarcomatous component. What a casei, thank you.

Göran Elmberger: Thanks for sharing this rare and, to me, new tumor. Your clear description of new tumor entities is like the most beautiful poetry to me. However, I am intrigued by the composite morphology of the three tumor components described. I would have loved to look at the immunos or even more to perform CGH analyses of the three components individually. I am not sure I share your interpretation of the emergence of a spindle cell sarcoma secondarily to the corticomedullary adrenal tumor. Any follow-up indicating malignant behavior? Any indication of aggressive growth pattern on original slides? (Couldn't open your article. Our library at Karolinska did not have access rights!!) The multifocal growth and the intimate continuous transitions between spindle cell component and the pheochromocytoma component, to me, rather indicates a phenotypic plasticity, already well documented by the tumor with respect to transition between pheochromocytoma part and adenoma part, rather than the emergence of a secondary malignant sarcoma clone. Looks a bit like morular differentiation described sometimes in pheochromocytomas. ER-beta? Beta Catenin? BROCN-family tumors?? Just curious. Beautiful case.

Giovanni Falconieri: Pretty difficult case, Michal. I have no experience with this. Thanks for this unusual contribution.

Cyril Fisher: Corticomedullary tumor, another rare entity.

Christopher Fletcher: Remarkable case. Since the cortical and medullary components seem to merge imperceptibly with one another, did immunostains clearly distinguish the two populations? The spindle cell component is another exceptional and very interesting twist in this case.

Andrew Folpe: Everything I have on my slide looks like pheochromocytoma. I'm having a bit of a hard time believing in a true "corticomedullary" tumor, given the embryology of this (composite) organ. Why can't the cortical elements be simply an unusual form of reactive hyperplasia secondary to the internal mass lesion?

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Thank you very much for the rare interesting case. It was very difficult to identify the cortical adenoma; however, three components were easily recognized on low power view.

Allen Gown: Fascinating case!

Thomas Krausz: Great case. I have difficulty to determine the lineage of differentiation of the spindle cells (I assume they do not express melanocytic immuno-markers).

Janez Lamovec: Many years ago we described a case of pheochromocytoma producing immunoreactive ACTH with subsequent adrenocortical hyperplasia and clinical Cushing' syndrome (*Ultrastruct. Pathol* 1984; 7: 41-48); not quite the same but somewhat similar lesion.

Thomas Mentzel: Many thanks for sharing this heterogeneous adrenal neoplasm.

Markku Miettinen: Agree on adrenal corticomedullary tumor. My slide was mainly composed on pheochromocytoma component with a few foci of pale cortical type cells. The spindle cell component seems to be qualified as a sarcomatous component, based on significant mitotic activity. I have seen previously an S100 positive spindle cell sarcoma arising from pheochromocytoma (? A sustentacular cell sarcoma) *Ultrastruct Pathol* 1988;12:513-527).

Elizabeth Montgomery: Thanks for once again educating me on an entity that is new for me.

Giuseppe Pelosi: Nice case of corticomedullary tumor of the adrenal glands with spindle cell sarcoma component. I have seen several examples of pheochromocytomas and adrenal cortical tumors, either benign or malignant, as well as

few cases of composite pheochromocytoma with spindle cell sarcoma resembling MPNST, but this is for me the first time that I have the opportunity of seeing this spectacular case of adrenal tumor with tripartite components.

Santiago Ramon y Cajal: Thank you very much for this very nice case.

Juan Rosai: I see the pheochromocytoma and I see within it the hypercellular spindle cell nodules which have been interpreted as a sarcomatoid component of the tumor, but in my section I did not see an adrenocortical component. I guess it is just a matter of sampling.

Joshua Sickel: Fascinating composite tumor. I've never encountered one in my practice.

Dominic Spagnolo: Great case of adrenal mixed corticomedullary tumor with sarcomatous stroma. I am not convinced of transition between the phaeo and the spindle stromal element on this section. Was any immuno workup done on the case?

James Strauchen: Corticomedullary tumor (pheo/cortical adenoma). I had difficulty identifying the cortical component on my slide which was almost all pheo. The spindle cells may represent Schwannian differentiation.

Saul Suster: I do not recall having seen a case like this before. Thank you for the education!

Larry Weiss: This is an amazing case. I have never seen spindle cell areas such as this in a pheochromocytoma.

CASE NO. 17 – CONTRIBUTED BY MICHAL MICHAL:

Phil Allen: Salivary gland type adenoma of the hypophysis. Never heard of it before. Many thanks again for the contribution, Michal.

Carlos Bacchi: Common tumor in unusual location is always difficult!

David Ben-Dor: How could this have arisen - ectopic salivary gland tissue? Any clinical endocrinological changes?

Michele Bisceglia: Salivary gland type adenoma of the hypophysis. Nice case. Clearly this is a Rathke's pouch-related derivative.

Thomas Colby: Agree with diagnosis. A new entity for me.

Kum Cooper: Another first for me, Michal. Salivary gland adenoma of the hypophysis. And yes I did consider adenomyoepithelioma as well. Thank you.

Otto Dietze: Unique case, despite the literature I cannot remember to have heard about it before.

Hugo Dominguez-Malagon: A unique case salivary gland-type adenoma, the sellar location is new for me.

Göran ElMBERGER: Very interesting. Something like craniopharyngioma but definitively more rare. Illustrative embryology. Rathke's pouch derivative. How would you classify given-accepting salivary gland histogenesis? EMEC? Thanks.

Giovanni Falconieri: Weird case. Yet, why not if all things fit? Thanks for reminding us that all is possible in pathology.

Cyril Fisher: PSA of pituitary gland, another incredible rarity!

Andrew Folpe: Wow- never heard of that before. Salivary tumors in the hypophysis- sure, why not?

Jerónimo Forteza Vila: Interesting case. I haven't seen it before.

Masaharu Fukunaga: I have never seen such a case. I am very pleased to share this case with you, Michal.

Allen Gown: Very interesting case; I recently saw a pleomorphic adenoma in a specimen labeled "contents of sella" and found the same paper you did about the existence of salivary gland like tumors in this region.

Thomas Krausz: This is new to me. Thank you.

Janez Lamovec: What a case! I found the cited article and it seems that this type of adenoma must be exceedingly rare.

Thomas Mentzel: Another exceedingly rare neoplasm, many thanks for this as well.

Michael Michael: My case.

Markku Miettinen: Without having any experience on this particular tumor, have to agree with on the diagnosis and conclusions. The findings do match with the given reference.

Liz Montgomery: Thanks again for supplying us with yet another weird lesion.

Giuseppe Pelosi: Salivary gland-type adenoma of the hypophysis: very nice example of an almost unique case!

Santiago Ramon y Cajal: Very unusual morphology for an hypophyseal adenoma.

Juan Rosai: I was not aware of this entity. I suppose it is OK to call it a salivary gland type tumor, although I am not sure exactly what type of salivary gland tumor this particular lesion would be the equivalent of. I was intrigued by the thyroid-like appearance in some of the follicles. I even thought of so-called Heffner tumor, but neither the location nor the morphology fit.

Joshua Sickel: Thanks for submitting this rare case. This is an example where the anatomic location makes histologic interpretation more confusing!

Dominic Spagnolo: Hard to say anything except "you can't be serious" . I thought it had to be a salivary mixed tumor in an exotic location, but hypophyseal.....? Thanks for the case!

James Strauchen: I was unaware of this tumor but it makes sense if the pituitary is derived from pharyngeal epithelium that there could be salivary differentiation.

Saul Suster: Wow! My first thought was that I was looking at the wrong slide! Never seen this before – many thanks again!

Larry Weiss: Another amazing case. I am speechless.

CASE NO. 18– CONTRIBUTED BY MARKKU MIETTINEN:

Phil Allen: Dendritic reticulum cell tumour arising in Castleman's disease. I missed both the Castleman's and the dendritic reticulum cell tumour. I think I need to go back to the AFIP for a few years retraining.

Carlos Bacchi: I agree with the diagnosis. Castleman's disease in the adjacent lymph node can be really appreciated. Great case.

David Ben-Dor: I hope that if I ever see a case like this I'll be able to recognize it. Very interesting combination of pathologies.

Gerald Berry: Agree with the diagnosis of dendritic reticulum cell tumor.

Michele Bisceglia: Dendritic reticulum cell tumor (sarcoma) arising in Castleman disease. Very interesting. We need to underline once more how (relatively) often we see such rare cases: we have some of these in AMR Seminars (see Archive at the official website).

Thomas Colby: Agree with diagnosis. The DRC sarcoma is readily apparent and the lymphoid tissue at the edge fits nicely with Castleman's.

Kum Cooper: Thank you Markku. This case brings back great memories from Africa for me. I spent more time looking for "dysplastic" FDC than the tumor itself. The intra-abdominal tumors carry a potentially worse prognosis too.

Otto Dietze: Although I know about this association from the literature, I have never seen this before; thank you.

Göran Elmberger: Beautiful case. Without nodal sampling and evidence of Castleman, it would not be at the top of my differential spontaneously. Need to remember Hallmark lesions: TIL's, 360°-whorls?

Giovanni Falconieri: I agree, it belongs to the DRC tumor family, and it is adjacent to hyaline-vascular CD. I also believe it is malignant despite the lack of a pronounced mitotic activity, hence the rubrication under the sarcoma heading is appropriate.

Cyril Fisher: FDCS in Castleman's, very nice example.

Christopher Fletcher: The morphology would certainly fit with a follicular dendritic cell sarcoma arising in Castleman's disease, although the immunophenotype, as Markku comments, is somewhat unusual.

Andrew Folpe: Looks good for follicular dendritic cell tumor.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Very beautiful case of follicular dendritic cell tumor with Castleman disease, thank you, Markku.

Allen Gown: Lovely example of this!

Thomas Krausz: Agree. Highly educational case. Thank you very much.

Thomas Mentzel: A wonderful case.

Elizabeth Montgomery: It is nice to see the Castleman's disease background.

Giuseppe Pelosi: Dendritic reticulum cell tumor arising in Castleman disease. I agree with this difficult diagnosis.

Santiago Ramon y Cajal: Beautiful case.

Juan Rosai: Nice case of dendritic follicular cell tumor. The syncytial appearance is very well demonstrated, as well as the sprinkling of lymphocytes throughout. The abdominal cavity has turned out to be a common site for this tumor type, the claim being that in this location they tend to be particularly aggressive.

Joshua Sickel: Agree with DRC tumor. I overlooked the Castleman's component. Beautiful case.

Dominic Spagnolo: Despite the unexplained focal desmin expression, I agree this is a beautiful FDC sarcoma arising *ex* hyaline vascular Castleman disease. Thanks!

James Strauchen: FDCT. I didn't appreciate the Castleman disease component on my slide. One of our residents reported a similar case with a small focus of FDCT in a Castleman lymph node.

Saul Suster: This is as convincing a slide as I've seen to support the close relationship between these two conditions.

Larry Weiss: Thank you so much for proving a section with both components next to each other. Were there increased numbers of CD21+ cells in the interfollicular regions of the Castleman lesion?

CASE NO. 19– CONTRIBUTED BY JAMES STRAUCHEN:

Phil Allen: I can't see any immature fat cells. Has a sclerosing extramedullary hematopoietic tumour been excluded? Could the giant cells be megakaryocytes?

Carlos Bacchi: Nice example of inflammatory well-differentiated liposarcoma.

David Ben-Dor: Given the relative sparsity of adipose cells (and the lack of lipoblasts) I would not have thought of a liposarcoma on initial examination. Would idiopathic retroperitoneal fibrosis enter into the differential, especially given the variety of inflammatory cells? There are some histiocytic cells whose cytoplasm is stuffed with eosinophilic granules.

Michele Bisceglia: Atypical lipomatous tumor/inflammatory well differentiated liposarcoma. Agree.

Thomas Colby: Agree with diagnosis of inflammatory well-differentiated liposarcoma.

Kum Cooper: Lovely example of WDLS, inflammatory type. Did you do the MDM-2 and CDK4 markers?

Otto Dietze: The differential diagnosis of this lesion is an important contribution for our routine work, esp. with regard to small biopsies.

Hugo Dominguez-Malagon: I agree that the best diagnosis is an inflammatory well differentiated liposarcoma. However the tumor is well circumscribed and the giant cells show a basophilic cytoplasm, other possibility would be: inflammatory myofibroblastic tumor.

Göran ElMBERGER: Great case. Am I right in assuming that bizarre stromal cells are not part of clonal proliferation but mere hallmark cells of lesion? They certainly look "bad". Given atypical features including Cyclin D1 overexpression and absence of positive IHC markers, I wonder about outcome of FISH, RT-PCR or other molecular techniques with regard to amplification of 12q14-15 and MDM2 – CDK4. Bizarre stromal cells?

Giovanni Falconieri: Nice case. I also believe that this is inflammatory liposarcoma of the retroperitoneum. In my experience, it is quite rare. I saw an example a few years ago in which the inflammatory reaction was characterized by well formed, epithelioid granulomas, compounding the microscopic interpretation further. That particular case was reviewed by Chris Fletcher who wrote to me that this is pretty unusual in inflammatory LPS, may be I can contribute it in the near future.

Cyril Fisher: Consistent with inflammatory WD liposarcoma/ALT.

Christopher Fletcher: Beautiful example of well-differentiated inflammatory liposarcoma (*Am J Surg Pathol* 1997; 21:518-527) – I have no personal experience of cyclin D1 expression in liposarcomas and will be interested in the comments of others.

Andrew Folpe: Inflammatory WDL.

Jerónimo Forteza Vila: Thank you for this interesting case.

Masaharu Fukunaga: Inflammatory well differentiated liposarcoma. Very tricky case! Initially, I consider that it was a kind of hematopoietic lesion.

Allen Gown: Were mdm-2 FISH studies performed on this case to corroborate this diagnosis by demonstrating amplification?

Thomas Krausz: Agree with diagnosis. I haven't studied cyclin D1 in this context.

Janez Lamovec: Inflammatory liposarcoma; most difficult diagnosis on frozen section.

Thomas Mentzel: Did you find MDM2 and/or CDK4 overexpression by immunohistochemistry or by FISH-analysis?

Elizabeth Montgomery: Nice bread and butter case of well-diff liposarcoma with a lot of lymphoid tissue. Years ago when my colleague Pete Argani and Juan reported a batch of such cases, they noted that the lesions were T rather than B cell rich [Argani P, Facchetti F, Inghirami G, Rosai J. Lymphocyte-rich well-differentiated liposarcoma: report of nine cases. *Am J Surg Pathol.* 1997 Aug;21(8):884-95.] so interesting that this one has mostly B cells.

Markku Miettinen: Agree on inflammatory/lymphocyte-rich variant of well-differentiated liposarcoma. Comparison with case 2 shows here multinucleated wreath-like cells and large cells with eosinophilic globules, and reveals that the hematopoietic component is lymphatic or mature eosinophils, but one can appreciate that liposarcoma and sclerosing extramedullary myeloid tumor have some histologic similarities.

Giuseppe Pelosi: Inflammatory well differentiated liposarcoma. Great case! I have seen several cases of WDL of the retroperitoneum, especially with more conventional histological features, either lipoma-like or sclerosing type.

Santiago Ramon y Cajal: No wonder that the frozen section pathologist initially thought that this could be a hematopoietic neoplasm. It could be very confusing.

Juan Rosai: Very nice example of the tumor variously called inflammatory well differentiated liposarcoma or inflammatory atypical lipomatous tumor (*Am J Surg Pathol* 21:884-895;1997). I think there is a relationship between this appearance and that of dedifferentiated liposarcoma, but I don't think they are quite the same thing.

Joshua Sickel: Well differentiated inflammatory-type liposarcoma. I would never have gotten the diagnosis on frozen section. Nice teaching slide.

Dominic Spagnolo: Agree with inflammatory well differentiated liposarcoma. A small biopsy could lead one on a merry dance. As for cyclin D1, it is positive in a wide array of tumors (yes, even in some CLL cases though not diffusely so).

Saul Suster: Agree with diagnosis. This can be a significant diagnostic trap due to the prominence of the lymphoid component.

Larry Weiss: Agree with diagnosis. Another great mimic for a hematomolymphoid disorder. I love the hyaline globules.

CASE NO. 20– CONTRIBUTED BY SAUL SUSTER:

N. Volkan Adsay: Thank you Saul, for bringing up this challenging issue for the discussion of the group. I must confess that my threshold for FVPTC has gone down significantly over the past few years due to the shared cases with our expert colleagues from Philadelphia and Toronto. As Chris Fletcher pointed out recently in the ADASP meeting, in the US unfortunately the trend (at least among some pathologists) is to call everything papillary carcinoma, and I must admit, rightfully or wrongfully, I have had to gradually give in to this flow too. Having said these, I thought the majority of this lesion in this case did not even remotely qualify for FVPTC; however, there is one minute focus, at least in my slide, that was very different from the rest of the lesion, and I believe did qualify for FVPTC even with more stringent criteria. Perhaps we can share the pictures of that particular focus to discuss that issue further.

Phil Allen: 10 cm follicular adenoma, right lobe of thyroid. I know nothing about well differentiated thyroid follicular neoplasms so I can afford to say unequivocally that this is benign. I feel safe in the knowledge that I have only about a 1% chance of being proved wrong by the development of metastases, and even if they appear, it could well be long after I have retired or died. I am adverse to being responsible for 99% of patients with well differentiated follicular thyroid tumors living for the rest of their lives in the unnecessary fear of thyroid cancer. I would rather get 1% of the cases wrong. Actually, I don't think any of the alleged histological criteria for well differentiated follicular carcinoma of the thyroid are any good. The few metastases from those tumors that I have seen have been histologically normal thyroid, and most of the thyroid tumors with extra capsular vascular invasion that is not apparent to the surgeon at operation do not develop metastases. As for the nuclear features of well differentiated papillary thyroid carcinoma, I never have any trouble finding them in most nodular goiters. In other words, I believe even the Chernobyl Pathology Group has been too kind to the thyroid over-diagnosers.

Carlos Bacchi: Favor follicular variant of papillary thyroid carcinoma but I would rather hear the opinions of more experience members of the club.

David Ben-Dor: To the extent that the features of any of the nuclei of these tumor cells approach those of classical papillary carcinoma of the thyroid, this is not uniformly seen and most don't seem to make the grade. John Chan has argued that given the fact that encapsulated follicular variant of papillary carcinoma never metastasizes (as long as there is no vascular invasion) nothing practical is gained by making the diagnosis.

Gerald Berry: I agree that this case does not quite have all the features to call follicular variant of papillary carcinoma. Specifically I do not see enough nuclear clearing or molding. We try to use the diagnosis of follicular neoplasm of UMP sparingly to avoid the pitfall of it becoming a wastebasket diagnosis that does not particularly help patients of clinicians.

Michele Bisceglia: Follicular neoplasm of undetermined malignant potential. Agree. Look forward to see what the "thyroidologists" think of this case.

Ira Bleiweiss: Call me old school but I favor follicular variant of papillary carcinoma.

Thomas Colby: Favor follicular adenoma.

Kum Cooper: Saul, I agree entirely with your sentiment. However, in this case I would have been very happy to call it a papillary carcinoma, follicular variant based on the nuclear features which are very evident to me. The term follicular neoplasm with UMP, I reserve for those encapsulated lesions that are suspicious but not obviously carry all the nuclear features

Otto Dietze: Sorry, I belong to the group favouring FVPTC.

Hugo Dominguez-Malagon: I think you are right Saul by calling it: Follicular neoplasm of undetermined malignant potential. However it would be a "perfect crime" if it is called FVPTC, encapsulated.

Göran ElMBERGER: Saul. First, I will admit that I am a complete amateur in endocrine pathology. Only saw cases during my residency time. Since moving to Karolinska, our endocrine pathologist guards these eggs well. Secondly, I just have to state you have a "saul" mate in matters of patho philosophy. I think today's daily work and our present classifications often oversimplify real life problems. Too few organ systems embrace the category of undetermined/uncertain malignant potential. We all strive so hard at reaching an unequivocal decision on malignancy so I believe we create statistically defined tumor entities that does not necessarily hold true for the individual patient. The history of acinic cell tumor→carcinoma or mucoepidermoid tumor→carcinoma is illustrative. If a few cases looking like X behave in a malignant way, we automatically come to the conclusion that all X are malignant. Overprotective? Logical? Practical! And what about "benign metastasizing..." I miss the old WHO fascicles when the categories of others and unclassified were

still spelled out. If nothing else as a reminder. Maybe sometimes I would also be tempted to add unclassifiable as diagnostic category. On the other hand, given a case like this, my other (better or worse) half tells me – go molecular. Morphology is after all a formalin fixed static surrogate for tumor biology. What about clonality, CK19, RET, HBME-1, Galectin 3 immunohistochemistry? If this does not solve the question, move onto RET/PTC/TRK rearrangements with molecular dx. or mutation screening for multiple pathways, such as RAS or BRAF? Even if I am proud to be a member in this group of “hard core pathologists”, I truly believe that one day soon the ability to read all genetical, epigenetical, metabolic and proteomic information from a tumor will help me and the patient more than our sharp eyes looking out for capsular invasion on a multitude of blocks or the single perineural growth in a low-grade salivary gland tumor that makes me swing from a benign cellular pleomorphic adenoma diagnosis to a PLGA dx. My molecular lab increased case numbers by 600 % last year, and I am using it every day. Sorry for getting philosophical and talking about molecular diagnostics but today is actually Easter holiday in Stockholm. Hope you forgive me.

Giovanni Falconieri: It stinks like cancer but I can't prove it. I would say the same you said, Saul, since this tumor has cytologic features suggesting a close parentage to a papillary tumor although it grows in a follicular fashion.

Christopher Fletcher: I agree entirely with Saul that the follicular variant of papillary carcinoma seems to have become massively overdiagnosed during the past ten years or so, perhaps reflecting the increasing prevalence of 'defensive' medicine. Although I claim no expertise whatever in thyroid lesions, I also agree that this particular lesion does not seem to show convincing cytologic features (at least as I was taught!) of papillary carcinoma.

Andrew Folpe: I'm going to defer to the thyroid experts in the group. I am not all that impressed with the PTC nuclear changes and favor a follicular neoplasm. It might be helpful to do some of the ancillary markers, just to see if those point strongly in one direction or the other.

Masaharu Fukunaga: It is really problematic, Saul. How about FNA? As a classic pathologist, I would call this lesion as an adenomatoid nodule. Cytologic features compatible with papillary carcinoma are often observed in adenomatoid nodule or adenomatoid goiter.

Allen Gown: I defer to our thyroidologists on this one; I am one of those borderline pathologists when it comes to these lesions.

Thomas Krausz: Saul, you summarized the diagnostic dilemmas beautifully. I also frequently struggle with such tumors. This particular case is also difficult. It is encapsulated, mostly follicular but focally there is compressed papillary architecture with enlarged/crowded nuclei. The more typical nuclear features of papillary carcinoma are not impressive. However, on balance I would probably favor encapsulated/mostly follicular variant of papillary carcinoma.

Janez Lamovec: I agree with you that this may be a borderline lesion although I wouldn't be sure whether the “borderlines” were of follicular or papillary follicular nature. There are really rare nuclei resembling ground glass nuclei, no nuclear inclusions and very very rare nuclear groove. We also have experience that some, but only some, experts would diagnose this tumor offhand as follicular variant of papillary carcinoma.

Thomas Mentzel: Despite the presence of some tumour cell nuclei showing similarities to features of papillary carcinoma, I had the impression that the overall features fit best with an unusual follicular neoplasm. So let's see what the opinion is of the experts in this field.

Markku Miettinen: Would have called it follicular variant of papillary carcinoma, based on what I learned of thyroid long time ago. Definitely would appreciate the controversy with this case. However, I suppose treatment would be the same – lobectomy, is that right?

Giuseppe Pelosi: This is an interesting case of follicular neoplasm of undetermined malignant potential.

Santiago Ramon y Cajal: I think that I agree with you, I don't see enough to go up to FVPTC. My first impression was benign. In my slide (tissue?) there is some artefact which makes the diagnosis more difficult.

Juan Rosai: I'm very pleased to hear that Saul likes the Chernobyl proposal and that he is using that terminology. Actually, I find that this is being used more and more on both sides of the Atlantic (although not in Japan). Having said that, I think that the Seminar case makes it for the follicular variant of papillary carcinoma on both architectural and cytologic grounds.

Joshua Sichel: I suspect I am still one of those pathologists who would have called this FVPTC. Considering that so few people actually die from papillary carcinoma of thyroid, is that lesion ready for a name change?

Dominic Spagnolo: I agree with you say about thyroid tumors which are difficult to classify as follicular or papillary CA (follicular variant). In this particular case, despite the absence of the classical nuclear features, for my money it is a papillary lesion admittedly with follicular areas, though many of these are the elongated tortuous tubules that I associate with papillary CA. The papillary areas show genuine fibrovascular cores and are lined by cells having elongated nuclei; very few are cleared and have heavy membranes, and as you say some are grooved, but hardly overwhelming. There

are small psammoma bodies. With this lesion I have a very high index of suspicion that one is dealing with an encapsulated papillary carcinoma (and I probably would not call it follicular variant). In this setting I do find HBME1 and CK19 staining helpful, and I would expect that to help with the dilemma. So for me this is a papillary carcinoma until proven otherwise. But I do agree that with some lesions I cannot make the call, I show those around to all and sundry, and typically find that everyone has the same problem! For those cases, I would do exactly as you suggest. This is definitely one case I would seek others' opinions and do IHC.

James Strauchen: I would have considered this the follicular variant albeit at the low end of what one could call. The excellent prognosis of the "encapsulated follicular variant" of papillary thyroid carcinoma suggests that many of them are benign.

Larry Weiss: I think that there is vascular/capsular invasion on my slide, so I favor carcinoma. As for papillary vs. follicular, I think that it is difficult, but I favor papillary.

CASE NO. 21– CONTRIBUTED BY PAUL WAKELY, JR.:

Phil Allen: Adamantinoma with squamous pattern, left tibia.

Carlos Bacchi: Nice example of adamantinoma.

David Ben-Dor: The squamous element is very nicely exhibited here. The epithelial islands look syringoid to me (at least as far as they're shaped; there's no ductal differentiation).

Gerald Berry: Agree. The squamous pattern is very evident.

Michele Bisceglia: Adamantinoma, squamous pattern, left tibia. Thanks, Paul. Beautiful example of a very rare entity.

Ira Bleiweiss: Agree.

Thomas Colby: Looks like adamantinoma.

Kum Cooper: Thank you Paul. Yes, I do enjoy it!

Otto Dietze: I have never seen this dominating squamous pattern in adamantinoma and the few slides of adamantinoma in my experience were primarily from seminars.

Hugo Dominguez-Malagon: Completely agree with the diagnosis of adamantinoma, squamous type. Thank you, Paul.

Göran Elmberger: Being severely damaged by seeing too many H&N cases, my diagnosis on blind review was squamous odontogenic tumor (SOT). Very good fit including central microcystic degenerations. I guess tibia is far from teeth so I would gladly accept your dx. Beautiful case. Maybe SOT is not so odontogenic... (GE).

Giovanni Falconieri: I cannot comment since I have little experience with bone tumors. Thanks anyway for submission of this instructive case.

Cyril Fisher: Adamantinoma with squamous morphology very pretty.

Christopher Fletcher: Fantastic case – I have never seen such prominent squamous differentiation in this context. Many thanks!

Andrew Folpe: Lovely adamantinoma.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: I have never seen such an adamantinoma with prominent squamous elements. Thank you very much, Paul.

Thomas Krausz: Very nice example.

Janez Lamovec: A teaching example of bone adamantinoma. In some cases epithelial nature of the lesion is not so evident.

Thomas Mentzel: This case represents adamantinoma with squamous differentiation, very nice !

Elizabeth Montgomery: This is amazing. Looks too bland for SCC but of course that's with knowing that the patient does not have one!

Markku Miettinen: Agree on adamantinoma.

Giuseppe Pelosi: Adamantinoma of the left tibia. I recently have had the opportunity of observing at least two cases of multiple metastases to the lung of mandible adamantinomas with classical features whose primary had been operated on many years before. This raises the question on the malignancy criteria to adopt for those lesions at least arising in the mandible.

Santiago Ramon y Cajal: Nice case of adamantinoma, Thank you!

Juan Rosai: Beautiful example of so called adamantinoma of long bones, the most mysterious tumor in the pathology catalogue. This particular case is more squamous and keratinizing than most, but it also has the typical ramifying cords that make one think of a skin adnexal tumor.

Joshua Sickel: Beautiful, classic case. Paul, thanks for the collector's item!

Dominic Spagnolo: Very nice adamantinoma with squamous features.

James Strauchen: Classic! Thank you.

Saul Suster: Beautiful example of squamous variant of adamantinoma of the tibia.

Larry Weiss: It may look squamous in areas, but the cords are still distinctive.

CASE NO. 22– CONTRIBUTED BY PAUL WAKELY, JR.:

Phil Allen: Gelfoam embolization of something or other with bone chips and a pronounced inflammatory reaction.

Carlos Bacchi: I agree with the diagnosis of RDD.

David Ben-Dor: Two lesions from the left tibia from adults in their fifties one after the other! And two cases of extranodal Rosai-Dorfman disease in the same seminar. Is this pure coincidence? If this seminar were to be recovered by an archaeologist a thousand years from now he might think that R-D disease was the most common affliction of mankind in this era. Seriously, a great pick-up by Paul. It's scary because I think I would have signed it out as suppurative granuloma. What is the nature of the lace like blue deposits? Are they osteoid?- I remember Unni mentioning in a lecture that osteoid in osteogenic sarcomas is often delicate and lace like? I don't think this is sarcoma.

Michele Bisceglia: Extranodal Rosai-Dorfman disease, left tibia. I agree on the diagnosis of extranodal Rosai-Dorfman disease. As said in my comment to case 6, am going to contribute a case of Rosai-Dorfman disease in the classical location.

Ira Bleiweiss: Agree.

Thomas Colby: Looks like Rosai-Dorfman disease.

Kum Cooper: Wow, another treat, Paul, (RDD of bone)! Now you have me truly nostalgic for Africa!

Otto Dietze: Another unusual presentation of RD disease in this seminar.

Hugo Dominguez-Malagon: I believe osteomyelitis with xanthomatous reaction should be also considered. There is a mixed population with many neutrophiles forming microabscesses, and I see sequestered bone spicules.

Göran Elmberger: I missed RDD once again. Blind spot. I guess on second look those histiocytes look pretty particular. Almost as a lipid storage disease with cholesterol clefts. A positive S100 certainly is helpful. Emperipolesis is not striking to me but difficult to evaluate given intense background inflammation. Need to include S100 to every case besides Htx-eos in future. However, when we expand the original concept of professor Rosai - that of a "Sinus histiocytosis with massive lymphadenopathy" – a clinicopathological entity with typical site presentation and age distribution, I believe we need to be cautious. The mere finding of a non-dominant tissue component of the RDD hallmark histiocyte (CD68+, S100+, CD163+, CD1a-; emperipoletic) may certainly be evidence of the activation of the main pathogenetic mechanism in RDD, but does that always equate with a unequivocal diagnosis of RDD? I think we should treat RDD dx outside its original context maybe more like we treat a diagnosis of sarcoidosis - another disease without yet proven

etiology. A diagnosis of exclusion. All non-necrotizing granulomatous inflammations are not sarcoidosis and even after a battery of negative microbe histochemistry stains, I still sign out the cases as non-necrotizing granulomatous inflammation possibly suggesting the consideration of sarcoidosis as a clinicopathological entity. Is the expanded concept of RDD a spectrum of inflammatory and possibly occasionally neoplastic histiocyte proliferations with the activation of a common pathogenetic mechanism – M-CSF mediated stimulation of immune suppressive macrophages? The situation reminds me a little about the ongoing saga of IgG4 related sclerosing diseases – a rapidly growing group of diseases sharing a common pathophysiological mechanism.

Giovanni Falconieri: Difficult case, until I saw the clue histiocytes with lymphocytes inside - I have just thought of some sort of tumoral osteomyelitis. Thanks for this contribution.

Cyril Fisher: Extranodal RDD, I don't see this for ages then two come along!

Christopher Fletcher: Another very nice case of extranodal Rosai-Dorfman disease!

Andrew Folpe: I'm not really sure. I guess it could be extranodal RD, but the cells look a bit small and the intensity of the neutrophilic infiltrate is unusual. The S100 immunostain would be interesting to see.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: Extranodal Rosai-Dorfman disease, again. There seems to be a wide histologic spectrum of this disease. I have never made a diagnosis RDD myself and I guess I have missed many RDD.

Thomas Krausz: Very nice example.

Janez Lamovec: Nice complementary case to the previous one of the present seminar!

Thomas Mentzel: This case represents a neutrophilic-rich inflammation of bone with enlarged histiocytic cells and focal emperipolesis.

Elizabeth Montgomery: Looks like a great example of Rosa-Dorfman disease. Again, we'll see what the master [JR] makes of it.

Markku Miettinen: Agree on Rosai-Dorfman. My experience of bone cases include multifocal disease with nasal mucosal and lymph node involvement (Am J Clin Pathol 1987;88:270-277, also submitted to Rosai-Dorfman Registry), and another one which grew Mycobacterium tuberculosis from the lesion.

Giuseppe Pelosi: I agree with the diagnosis of extranodal Rosai-Dorfman disease. This location is another challenging demonstration that the mentioned lesion may arise everywhere in the body and pathologists should be always aware of these diagnostic possibilities in their daily practice in order to avoid missing cases or rendering incorrect diagnoses.

Santiago Ramon y Cajal: Interesting case! Although I guess that you are right. I wonder the relationship with the previous traumatism and the large number of plasma cells.

Juan Rosai: Very flattering! Two cases of Rosai-Dorfman disease in the same Seminar!. An interesting side aspect of this case is the presence of abundant packing material (Gelfoam). The first time I saw this material as a pathology resident in Argentina, I called it a cavernous hemangioma. The brand name of the compound, for those interested in trivia, was Spongostan. It sounds like a Superman-type character.

Joshua Sickel: I think I'm getting light-headed....2 cases of extranodal Rosai-Dorfman in one sitting!?

Dominic Spagnolo: Agree with extranodal Rosai-Dorfman disease. The typical cells are there, but the picture is dominated by a less specific xanthomatous appearance, and given the tibial location, and a pulmonary lesion, Erdheim-Chester enters the differential. But I agree the diagnosis is as you say, Paul. Nice case.

James Strauchen: Rosai Dorfman disease of bone. I have seen one or two similar cases involving bone but don't know the long term clinical follow up.

Saul Suster: Very difficult case to diagnose. Kudos to Paul for this excellent diagnosis!

Larry Weiss: There are a lot more secondary changes than the first case presented above, but the atypical Rosai-Dorfman cells are still there, albeit infrequent to my eye (without the S100 stain to help).

CASE NO. 23– CONTRIBUTED BY LAWRENCE WEISS:

Phil Allen: Gamma delta lymphoma. This one is too hard for me, Larry!

Carlos Bacchi: T-cell lymphoma, possible hepatosplenic T-cell lymphoma but the absence of sinusoidal infiltration does call our attention.

David Ben-Dor: Rosai-Dorfman disease? Just kidding- or am I?

Michele Bisceglia: Difficult case. Peripheral T-cell lymphoma – unspecified would have been my diagnosis.

Ira Bleiweiss: Lymphoma is as far I go, not being a lymphomaniac.

Thomas Colby: Agree with diagnosis; particularly aggressive course.

Kum Cooper: I have only seen these rare unusual lymphomas in Africa (not in the US)!

Otto Dietze: I have never seen this type of lymphoma in the spleen, thank you.

Hugo Dominguez-Malagon: No experience with this type of lesions.

Göran Elmberger: Interesting case. Thanks.

Giovanni Falconieri: Sorry, I cannot provide any opinion. Very difficult for me.

Andrew Folpe: Way out of my league.

Jerónimo Forteza Vila: I agree with your diagnosis.

Masaharu Fukunaga: This is the first case of Gamma-delta lymphoma for me. Thank you very much for sharing the rare tumor.

Allen Gown: It really does seem to be a 'hybrid' T cell lymphoma with a 'partial' gamma/delta lineage.

Thomas Krausz: I found this case diagnostically very difficult, however, I agree with your conclusion. Are some of the large multinucleated cells megakaryocytes?

Thomas Mentzel: Thanks for this rare splenic lymphoma.

Markku Miettinen: Agree on large cell lymphoma with white plus red pulp distribution (with some architectural preservation of the former), and have no disagreement about gamma delta T-cell lymphoma.

Giuseppe Pelosi: I agree with the diagnosis of lymphoproliferative disease, but I cannot give valuable comments to this case, since it is beyond my diagnostic expertise.

Santiago Ramon y Cajal: I agree that it may correspond to an aggressive variant of hepatosplenic T-cell lymphoma.

Juan Rosai: After some struggling, I concluded that this was a malignant lymphoma involving the spleen, but I would not have gone further without the "battery". For better or worse, that's the way it is for most lymphomas these days. Time to retire.

Joshua Sickel: I've only seen a few similar cases. Both patients died of their disease very rapidly.

Dominic Spagnolo: For all the reasons you give, I would not call this hepatosplenic T-cell lymphoma of the usual type. Looking at it blind, it reminded me of cases of aggressive NK-cell leukemia/lymphoma (I prefer the earlier WHO terminology) both morphologically and on the clinical history. The pleomorphism, the cordal rather sinusoidal distribution, the activated cytotoxic phenotype and hemophagocytic features focally, are appropriate. CD56 expression in the few cases I have seen can be focal (I don't know about cases occurring in Asia) and I usually do this on a couple of blocks at least, and EBER is typically positive in these cases; was EBER staining done? The T-associated markers that are positive in your case do not allow absolute distinction between a gammadelta T-NHL or NK lineage, and I would look at TCR gene rearrangements in such a case. Having said all that, your case does have similarities to a handful of others in the literature (e.g. *Histopathology* 2000; 36:127-35; Ohshima K et al), which I also would not call hepatosplenic T-cell lymphoma (with the implied clinicopathological entity as presently iterated in WHO). So rather than force the issue of classification, if this is proven to be of T-cell lineage, I would report it as aggressive "unclassified hepatosplenic T-cell lymphoma, activated cytotoxic phenotype".

James Strauchen: "Double negative" T-cell lymphoma. Lacks many of the usual features of hepatosplenic TCL.

QUIZ CASE 1– CONTRIBUTED BY MARKU MIETTINEN:

Phil Allen: Inflammatory fibroid polyp must be too easy for a quiz case in this seminar.

Michele Bisceglia: May be several things. Would need some immuno as well. Stromal tumor – NOS (favour myofibroblastic sarcoma).

Thomas Colby: Myofibromatosis lesion.

Kum Cooper: IMT/inflammatory fibrosarcoma (ALK-1); Rule out GIST.

Otto Dietze: Inflammatory pseudotumor?

Hugo Dominguez-Malagon: Myofibroma vs. inflammatory myofibroblastic tumor vs. GIST.

Göran Elmberger: Gastric schwannoma? Palisading? Sprinkled I_c and I_c cuff! If not GIST in unusual age or any of the other spindle cell tumors that can occur in stomach – IHC!

Giovanni Falconieri: No history sheath. Admitted, we are dealing with a boy (I remember a “12 year-old male” case submitted by Saul many years ago as a quiz: that was a dog!) It looks malignant though not so terrific, tumor cells have a myoid/myofibroblastic appearance. Because of the age, I would put on top of my list, differential myofibroblastic tumor/inflammatory fibrosarcoma.

Christopher Fletcher: Inflammatory myofibroblastic tumour seems most likely. We have seen quite a number of these lesions in the stomach.

Andrew Folpe: Would favor inflammatory myofibroblastic tumor.

Jerónimo Forteza Vila: GIST.

Masaharu Fukunaga: Inflammatory fibrosarcoma.

Janez Lamovec: Inflammatory myofibroblastic tumor

Thomas Mentzel: Inflammatory myofibroblastic tumour

Santiago Ramon y Cajal: I would wait for the stainings including antibodies for Schwannoma, leiomyoma, GIST and even dendritic cell tumors.

Joshua Sickel: ALK (+) inflammatory myofibroblastic tumor.

James Strauchen: Considered GIST, eosinophilic fibroid polyp, and inflammatory myofibroblastic tumor. Favor the latter.

Paul Wakely, Jr.: It looks like an inflammatory myofibroblastic tumor, but I would still do the stains.

Markku Miettinen: Inflammatory myofibroblastic tumor. Admixture of spindled “rhabdomyoblast-like” cells and lymphoplasmacytic infiltration with some sclerosis are typical histological features. In this case, cytoplasmic ALK positivity and ALK-gene rearrangement by FISH were present. KIT-positivity if present is typically limited to neovascular endothelia and mast cells. This case was submitted to consultation as a GIST in a child, and it seems that some cases reported as GISTs in children (especially young), are IMFTs.

QUIZ CASE 2– CONTRIBUTED BY JOSHUA SICKEL:

David Ben-Dor: Obviously a parasite- Schistosoma? I think there's a point at the end of an animalcule in one image. It would be interesting to have some history. I went to college in Rochester and never heard of Schistosoma in Lake Ontario (though at that time I never heard of Schistosoma anywhere).

Michele Bisceglia: Pulmonary Dirofilaria (Dirofilaria immitis). In Europe we have (occasionally) the subcutaneous and or subconjunctival form (Dirofilaria repens).

Kum Cooper: Dirofilaria.

Otto Dietze: Dirofilaria or similar helminths?

Göran Elmberger: That is a worm! Fine details difficult to see. Nematode? Dirofilaria? Ascariasis-ascaridioma? Gnathostomiasis?

Giovanni Falconieri: Looks like a small worm, don't have a name.

Andrew Folpe: Nasty worm.

Jerónimo Forteza Vila: Strongyloides stercoralis.

Masaharu Fukunaga: Parasite, I do not know what it is.

Janez Lamovec: ?Hookworm infestation.

Markku Miettinen: Worm, parasite.

Santiago Ramon y Cajal: Ascaris lumbricoides.

Dominic Spagnolo: Looks like Dirofilaria - thick multilayered cuticle, suggestion of longitudinal ridges. Am I imagining 2 reproductive tubes and single intestine suggesting it is a female?

James Strauchen: Dirofilaria is my first (and last) guess.

Paul Wakely, Jr.: *D. immitis* – dog heartworm.

Joshua Sickel: My case....Dirofilaria immitis. Haven't seen any cases in California yet!

QUIZ CASE 3– CONTRIBUTED BY JOSHUA SICKEL:

David Ben-Dor: Are those actinomycetes? If so then does the patient have myeloma and was he receiving bisphosphonates? Actually one of the earlier (or earliest) reports concerning this phenomenon originated in our center: Severe osteomyelitis of the jaw in long-term survivors of multiple myeloma: a new clinical entity. Lugassy et al, *Am J Med.* 2004 Sep 15;117(6):440-1. If I'm right I don't know what the corpuscles in the center of the image are.

Michele Bisceglia: ? Intraepithelial hyaline bodies (?Rushton bodies) occurring in periapical radicular cysts.

Kum Cooper: Amebiasis (Naegleria, acanthamoeba or Balamuthia).

Otto Dietze: Bugs....?

Göran Elmberger: Guess we are dealing with a protozoa. Amebiasis? Giardiasis?

Giovanni Falconieri: Another bug?

Andrew Folpe: Amoebae? (Josh- where do you get this stuff?)

Jerónimo Forteza Vila: Osseous necrosis.

Masaharu Fukunaga: I do not know what they are.

Janez Lamovec: ?Mycetoma

Markku Miettinen: Actinomycosis?

Santiago Ramon y Cajal: Amoebas in a tooth abscess!

Dominic Spagnolo: Actinomycotic osteomyelitis?? Are there amoebae there too????

James Strauchen: Amebic abscess.

Paul Wakely, Jr.: Looks like Amebiasis and Actinomycetes.

Joshua Sickel: My case....Entamoeba gingivalis resting comfortably on a lawn of Actinomycetes. I think this is how they grow in culture.

QUIZ CASE 4– CONTRIBUTED BY SAUL SUSTER:

Phil Allen: Radiation induced sarcoma, possibly angiosarcoma, pericardial fat, pleura and skin of the chest wall.

David Ben-Dor: Synovial sarcoma?

Michele Bisceglia: Spindle cell high grade sarcoma (?spindle cell angiosarcoma). Would perform also immunohistochemistry for Kaposi's sarcoma due to some hyaline globules seen in the tumor cell cytoplasm. We had another case (in a different location and in a different clinical setting) by Thomas Krausz of KS vs angiosarcoma diagnosis (Seminar 44 – case 12).

Thomas Colby: ? angiosarcoma.

Kum Cooper: Metastatic fibromatosis-like breast carcinoma.

Otto Dietze: Fibrosarcoma dd spindle cell carcinoma?

Hugo Dominguez-Malagon: Spindle cell angiosarcoma, (?) post-radiation.

Göran Elmberger: Post-radiotherapy angiosarcoma probably arising in skin and chest wall and secondarily involving thyroid gland (presuming thyroid gland was leaded during radiation...). The pattern of infiltration very much reminds me of what I see in a lung with primary or metastatic sarcomas. I would do immunos to verify my morphological impression of vasoformative tumor in this rather poorly differentiated neoplasm. If I don't catch the fish, I will tighten net.

Giovanni Falconieri: Spindle cell malignant tumor. If primary in thyroid, I guess it is sarcomatoid carcinoma.

Christopher Fletcher: Looks like high-grade angiosarcoma, presumably radiation-associated and arising in adjacent soft tissue. The primary angiosarcomas of thyroid seem more often to have epithelioid morphology.

Andrew Folpe: Angiosarcoma.

Jerónimo Forteza Vila: SETTLE tumor.

Masaharu Fukunaga: Spindle epithelioid tumor with thymus-like differentiation.

Janez Lamovec: ?Angiosarcoma, ?Anaplastic carcinoma

Thomas Mentzel: Diffusely infiltrating malignant spindle cell neoplasm. Spindle cell sarcomatoid carcinoma ?

Markku Miettinen: Favor angiosarcoma, extending/metastasizing from post-radiation angiosarcoma of chest wall. Histological differential diagnoses include Kaposi sarcoma and CASTLE/SETTLE (scenario unlikely, histology not really perfect for either of those). Kaposi would though be the closest histological mimicker.

Santiago Ramon y Cajal: We are facing a poorly differentiated neoplasm with a high mitotic index. The cellular component is pleomorphic with a predominance of spindle cells with high N/C ratio and prominent vascularity. My differential would include Anaplastic Carcinoma vs. High Grade Angiosarcoma. (By patient's medical history, a metastatic origin should be considered).

Joshua Sickel: Post-irradiation angiosarcoma? Whatever it is, it looks really bad!!

Dominic Spagnolo: If this arising from thyroid, anaplastic (sarcomatoid) carcinoma until proven otherwise. I don't see an underlying differentiated thyroid carcinoma. If not of thyroid origin, could be any of a number of malignant tumors, mesothelioma included. Immunohistochemistry needed to sort it out.

James Strauchen: Anaplastic thyroid cancer seems too obvious! The previous history of mastectomy and RT and suggestion of vascular differentiation at the periphery favor Stewart-Treves angiosarcoma.

Paul Wakely, Jr.: Angiosarcoma – however, Saul showed me the slide previously.

Saul Suster: Post-radiation angiosarcoma arising in the chest wall and secondarily invading the thyroid. Stains showed strong positivity for CD31/CD34, and were negative for other markers.