COMMENTS TO AMR SEMINAR #59

CASE NO. 1 – CONTRIBUTED BY PHILIP ALLEN:

Carlos Bacchi: I thought this could correspond to a spindle cell lipoma. Thanks for bringing me up the awareness of this entity (sclerotic fibroma-like lipoma).

David Ben-Dor: For a change something whose name seems to correspond to the histology in a straightforward fashion. This had a vague "neural" appearance to me when I first looked at it. In looking through PubMed I came across a reference to superficial acral fibromyxoma whose abstract states that these lesions had conspicuous mast cells- any relation?

Gerald Berry: I would defer to Michal and Markku but the lesions seems to fit the description of sclerotic (fibroma-like) lipoma. There certainly is a resemblance to spindle cell lipoma.

Ira Bleiweiss: Certainly benign spindle cell lesion. I leave the fancy nomenclature to Phil and the other soft tissue mavens.

Michele Bisceglia: Sclerotic (fibroma-like) lipoma, dorsum of right hand. I did not know this precise entity. Thank you, Phil.

Tom Colby: Agree with diagnosis.

Kum Cooper: Thank you, Phil. I don't recall making the diagnosis of sclerotic lipoma before. Thank you for "reviving" this tumor.

Ivan Damjanov: Right on. I would have never made that diagnosis simply because I did not know about that entity.

Otto Dietze: I do not know about loss of chromosomes in sclerotic lipoma, I believe that I have missed this diagnosis previously and signed out one or the other case due to CD34 positivity as spindle cell lipoma.

Hugo Dominguez-Malagon: Sclerotic (fibroma like) lipoma. My impression is that this lesion belongs to a group of tumors composed of dendritic (as seen by ME) CD34+ cells that includes: giant cell angiofibroma, solitary fibrous tumor, lipomatous hemangiopericytoma and dendritic cell lipoma. Or better, it can be an spectrum of lesions with cellular, myxoid, lipomatous and sclerotic phenotypes.

Göran Elmberger: Indeed a very good fit.

Vincenzo Eusebi: I agree with the diagnosis of spindle cell lipoma with sclerosis.

Giovanni Falconieri: Nice case, Phil. Thank you. I do not know the entity; spindle cell lipoma with plexiform changes would be my non-educated guess.

Franco Fedeli: Sclerotic (fibroma-like) lipoma, dorsum of right hand. I agree. Morphology and CD34 positivity do suggest some link with spindle cell lipoma. Parenthetically another fibromatous tumor which is also CD34 positive is nuchal-type fibroma, which can occur also in extranuchal sites.

Cyril Fisher: Sclerotic lipoma, seems to fit the description although the features overlap with other entities. Genetic analysis would be of interest.

Christopher Fletcher: I think that some of these lesions (perhaps this one too) fit within the spectrum of low-grade spindle cell liposarcoma, which shows a predilection for subcutaneous somatic soft tissue and exhibits more frequent recurrence than spindle cell lipoma. There seems to be mild nuclear atypia and there are small numbers of convincing signet ring as well as bivacuolated lipoblasts with mildly hyperchromatic nuclei.

Andrew Folpe: Lipoma variant sounds ok.

Jerónimo Forteza Vila: Perhaps the tumour might have a common histogenesis with solitary fibrous

tumour. The accentuated sclerosis results in a clear differential diagnosis together with the atypical lipoma. Certainly, the diagnostic key is to identify the entity. I had not seen a similar case before.

Masaharu Fukunaga: It looks like spindle cell lipoma. Sclerotic fibroma is very new to me. Thank you very much the case, Phillip.

Allen Gown: Lovely case, Phil. Curious to know if there is anything known about the molecular pathology in this case, particularly if it sheds any light on its possible relationship to spindle cell lipoma.

Thomas Krausz: Agree with diagnosis. I also would like to know the genetic profile.

Janez Lamovec: I though this was a variant of spindle cell lipoma.

Thomas Mentzel: A nice example of so-called sclerotic lipoma. Although the stroma looks different there are indeed similarities to spindle cell lipoma and it would be very interesting to look for chromosomal changes in these lesions.

Michal Michal: Sclerotic (fibroma-like) lipoma. To answer Phil's question, I am of aware of any information of genetics concerning this tumor.

Markku Miettinen: Agree on sclerotic lipoma. Atypical lipoma is a consideration, but atypia falls short.

Liz Montgomery: Interesting case. The myxoid parts of my slide remind me of superficial acral fibromyxoma but I do not have a better unifying diagnosis than sclerotic lipoma. The collagen is not like the ropy/wiry collagen in spindle cell lipoma. I guess we'll see what Markku thinks.

Santiago Ramon y Cajal: Thanks Phillip for the case. It would make sense to associate this tumor with spindle cell lipoma. I understand that EMA was negative

Juan Rosai: Nice example of the entity described by Laskin et al. I suppose this tumor could also have been called a fibrolipoma, but fibrous tissue gets no respect in the soft tissues (it is the Rodney Dangerfield of this area), in contrast to bone, skin, and many other sites.

Dominic Spagnolo: Agree sclerotic lipoma. Perineurial markers negative??

James Strauchen: Thank you! I was not aware of this entity.

Saul Suster: I think this is a very apt descriptive term and interpretation for this process. It does indeed look like a lipoma that is undergoing secondary fibrotic changes. We reported a series of unusual lipomatous tumors under the term of "dendritic fibromyxolipoma" several years ago (Ann Diagn Pathol 2:111-120, 1998) which we interpreted to be part of the spectrum of spindle cell lipoma/solitary fibrous tumors. I believe all of these lesions are closely related, albeit sufficiently distinct that they merit their own "names". The important thing is to recognize their benign nature and not mistake them for more ominous processes.

Lawrence Weiss: Nice case.

Eduardo Zambrano: My interpretation was that of a fibrolipoma or a spindle cell lipoma. It would be interesting to find out any more recent insights regarding potential nosologic relationships between spindle cell lipomas and sclerotic lipomas.

CASE NO. 2 – CONTRIBUTED BY CARLOS BACCHI:

Phil Allen: Anaplastic embryonal rhabdomyosarcoma, orbit, male aged 2 years. This is the first one of these that I have seen. To my mind, the diagnosis rests as much on the location and the patient's age as on the histology but I accept that it is a variant of embryonal rhabdomyosarcoma. I don't believe in pleomorphic rhabdomyosarcoma of adults. They are merely malignant fibrous histiocytomas with desmin positivity. I find comfort in my consistency, if not my presently unconventional stand, when I also refuse to accept keratin positive malignant fibrous histiocytomas as carcinomas.

David Ben-Dor: These cells are undoubtedly extremely weird. By current understanding these cells which attract the most attention by their ominous features are biologically dead wood, and that a small percentage of the cells (not necessarily the most dangerous looking ones) are biologically active – these are the troublemakers that can cause recurrences or metastasis. Does this variant respond as well to chemotherapy as the other conventional types and is it compatible with long term survival? Is there brain tissue in the background or am I imagining things?

Gerald Berry: When I first looked at the slide, I was drawn to the markedly pleomorphic cells. Many of the surrounding cells resemble more typical rhabdomyoblasts although I could not find terrific cross striations. I agree with anaplastic embryonal RMS.

Michele Bisceglia: Anaplastic embryonal rhabdomyosarcoma. Carlos, have never seen so much anaplasia in an ERMS.

Ira Bleiweiss: Ouch. Wins the prize for the ugliest nuclei ever.

Tom Colby: Agree with diagnosis; this case sort of defines the word "pleomorphic." One can imagine some striations in some of the eosinophilic cytoplasm of the tumor cells.

Kum Cooper: Great case, Carlos. Yes, agree the IHC nicely clinches the diagnosis. Interestingly I saw embryonal rhabdomyosarcomas with anaplasia far more often in Africa.

Ivan Damjanov: I have seen embryonal rhabdomyosarcoma with anaplastic components, but a tumor composed of anaplastic cells must be quite rare. Immunohistochemistry, as you say, makes the diagnosis straightforward. It also shows that it is worth doing it on anaplastic pleomorphic sarcomas

Hugo Dominguez-Malagon: Nice case of anaplastic ERMS, alterations and expression of CDK4, MDM2, GLI and SAR (12q13-15) are particularly prevalent in this variant.

Göran Elmberger: Difficult on blind review. BFUM bizarre. As Carlos says, age and location renders ddx. On retrospective analyses tinctorial quality of cytoplasm is not wrong and I believe I found one cell with striations… Thanks.

Vincenzo Eusebi: Anaplastic embryonal rhabdomyosarcoma, nice case.

Giovanni Falconieri: First example in my collection, Carlos. Thank you. Cannot comment on the diagnosis yet it looks terrifically malignant.

Franco Fedeli: Anaplastic embryonal rhabdomyosarcoma. The degree of anaplasia in this ERMS is impressive.

Cyril Fisher: Anaplastic ERMS, confirmed by IHC. Genetic analysis would be of interest.

Christopher Fletcher: Great case. Personally, I think that tumors such as this would more logically be classified as pleomorphic rhabdomyosarcoma – but such a designation seems to be banned in the pediatric sarcoma community. I think it is very hard to see any real resemblance to either embryonal or alveolar rhabdomyosarcoma in the rare pediatric cases with this type of morphology.

Andrew Folpe: Agree with ERMS with anaplasia. Nice example.

Jerónimo Forteza Vila: Morphology and immunohistochemistry certainly indicate the diagnosis.

Masaharu Fukunaga: Thank you very much for the slide and description. This is my first time I see anaplastic embryonal rhabdomyosarcoma.

Allen Gown: Thanks for the case, Carlos. Looks like we both submitted one of these tumors within a few months of each other!

Thomas Krausz: Anaplastic embryonal rhabdomyosarcoma is still a "mystery" for me.

Janez Lamovec: Pleomorphic sarcoma. In this particular setting (child, head and neck region) the possibility of rhabdomyosarcoma is tenable but on pure morphological ground this is to me just a pleomorphic sarcoma. Thank you for this extraordinary case.

Thomas Mentzel: What are the cytogenetic changes in the presented case? Are there prognostic differences between anaplastic embryonal and anaplastic alveolar rhabdomyosarcoma ?

Markku Miettinen: Agree on anaplastic rhabdomyosarcoma, consistent with origin of embryonal type. Molecular studies for FOX10 rearrangement to rule out derivation from alveolar RMS would still be of interest.

Liz Montgomery: What a horrible looking pleomorphic sarcoma. With the reported IHC seems that anaplastic embryonal rhabdomyosarcoma is the best diagnosis.

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

Juan Rosai: Spectacular example of the anaplastic variant of embryonal rhabdomyosarcoma, a tumor that can be easily misdiagnosed as pleomorphic rhabdomyosarcoma, a mistake with important prognostic and therapeutic implications. This situation reminds me, in a totally different context, of the difference we used to make between the lymphocyte depletion subtype of nodular sclerosis Hodgkin's lymphoma and the real lymphocyte depletion form of the disease.

Dominic Spagnolo: What a horrible looking thing. Agree anaplastic embryonal rhabdomyosarcoma, but have never encountered anything like this before.

James Strauchen: Anaplastic rhabdo. Fabulously bizarre cells!

Saul Suster: First time I see this in a child; I was not familiar with the "entity". I'm not sure I understand what the rationale is for declaring this a "variant" of embryonal rhabdomyosarcoma (other than the age of the patient) and why this cannot be pleomorphic RMS in a child. Is there hard evidence to separate these two types or is this simple dogmatism?

Lawrence Weiss: Wow. What beautiful morphology. I did not know that anaplastic features could exist without a component of typical embryonal features. Thanks.

Eduardo Zambrano: Remarkable cellular pleomorphism in this case, which definitely requires immunohistochemical workup for its diagnosis. The patient's age and the location of the tumor, however, are most in keeping with the diagnosis of rhabdomyosarcoma. I've never seen one with this degree of anaplasia, though.

CASE NO. 3 – CONTRIBUTED BY MICHELE BISCEGLIA:

Phil Allen: Poorly differentiated, high-grade, desmin and pan cytokeratin positive spindle cell malignant tumor, prostate. I don't think this is the same tumor as genuine embryonal rhabdomyosarcoma. Apart from the fact that the patient is old, and the hematoxylin and eosin stain does not look like an embryonal rhabdomyosarcoma to me. The differing response to chemotherapy supports my view. I regard immunohistochemistry in the same light as Macbeth eventually viewed his witches when he said:
"I pull in resolution; and begin to doubt the equivocation of the fiend that lies like truth." (Act 5, scene 5.)

Carlos Bacchi: Nice example and typical of primary embryonal rhabdomyosarcoma of the prostate.

David Ben-Dor: We're getting a real education in mesenchymal/spindle cell tumors of the prostate together with rhabdomyosarcomas!!

Gerald Berry: Agree with diagnosis. We had a similar case 4 years ago in a 28-year old fellow here at Stanford. He developed widespread mets (lung, liver) in short order.

Michele Bisceglia: Primary embryonal rhabdomyosarcoma of prostate in adult. My case (now this is in Int J Surg Pathol, 2011 Mar 21, with literature review).

Ira Bleiweiss: Prostatic sarcoma for sure. We recently had a case of lung metastasis of epithelioid leiomyosarcoma of prostate.

Tom Colby: Agree with diagnosis. This one might have taken me awhile to get to.

Kum Cooper: Two rhabdomyosarcomas in a row! Nice tadpole tails and broken straws. Thank you, Michele.

Ivan Damjanov: Agree. Must be very rare—I kind off do not believe that it accounts for "less than 5%" of prostatic malignancies in adults. Probably less than 1%! Nice juxtaposition with the case #2.

Otto Dietze: Convincing histology and IHC, I have never seen this in an adult patient.

Hugo Dominguez-Malagon: Possibility exists that adult ERMS of prostate could represent sarcomatous overgrowth of a phyllodes-like STUMP, or sarcomatous transformation of a prostatic teratoma.

Göran Elmberger: Thanks for sharing this unusual case. I could appreciate the eosinophilic tint of the strap-like cells but had a hard time looking for striations. I'm sure they are there but it's like looking for the acid fast bacilli today when we have so well-functioning PCR.

Vincenzo Eusebi: Embryonal rhabdomyosarcoma.

Giovanni Falconieri: Great case Michele, as always! The microscopic details are nicely illustrative of the rhabdoid quality of the cytoplasm. Thanks for contributing this extraordinary, collectible case.

Franco Fedeli: Primary embryonal rhabdomyosarcoma of prostate in adult. Four years ago I saw a genital ERMS in 29-year-old male.

Cyril Fisher: Another rhabdomyosarcoma! Great case. In pre-immuno days we published one in an adult (Urology 1982;19:80-82).

Christopher Fletcher: Certainly seems convincing for rhabdomyosarcoma. Whether to classify this as embryonal or spindle cell is probably a moot point, although it is becoming clear that spindle cell rhabdomyosarcoma should probably be separately classified from the embryonal type in the future.

Andrew Folpe: Another ERMS! Must be the theme of this group of cases.

Jerónimo Forteza Vila: It calls our attention the age, but diagnosis is from immunohistochemistry and morphologically consistent. In case 2, age points to diagnosis; in this case, age moves away from diagnosis.

Masaharu Fukunaga: Thank you very much a wonderful case. Michele, I have never seen prostatic embryonal rhabdomyosarcoma.

Allen Gown: Thank you, Michele, for such an excellent case and summary.

Thomas Krausz: Great case. I am hoping that one day the embryonal rhabdomyosarcomas occurring adults will be shown to be genetically different than embryonal rhabdomyosarcomas of infants.

Janez Lamovec: Convincing case of embryonal rhabdomyosarcoma; I was, however, not so sure to spot cross striation.

Thomas Mentzel: Many thanks for sharing this extraordinary case.

Markku Miettinen: Agree on embryonal rhabdomyosarcoma involving the prostate. Rhabdomyoblasts with eosinophilic cytoplasm are easy to come by, but it is difficult to find cross striations, still no doubt on diagnosis.

Liz Montgomery: A stunning example of a rare presentation of rhabdomyosarcoma and a wonderful companion for case 2.

Santiago Ramon y Cajal: This is an extremely interesting case. Thank you for sharing.

Juan Rosai: Good example of embryonal rhabdomyosarcoma, this one showing a much greater resemblance to the traditional form of this tumor.

Dominic Spagnolo: Agree, adult embryonal rhabdomyosarcoma, and nice discussion Michele. Paul Waring , the first author of the paper you cite, did his medical training and pathology training here, and also spent a little time in Adelaide, so Phil will probably remember him too.

James Strauchen: Embryonal rhabdo in an adult. Nice strap cells?

Saul Suster: Nice case. We had a similar case here about a year or two ago.

Lawrence Weiss: Nice discussion. Two rhabdos in two cases. Must be a common neoplasm.

Eduardo Zambrano: Great example of embryonal rhabdomyosarcoma of the prostate.

CASE NO. 4 – CONTRIBUTED BY MICHELE BISCEGLIA:

Phil Allen: Poorly differentiated HHV8 positive sarcoma, probably leiomyosarcoma, adrenal, with massive pelvic recurrence and fatal outcome. Rather than the man from Istanbul, I think we are seeing Macbeth's three women from Scotland. "When shall we three meet again - in thunder, lightning or in rain?" (Act 1, scene 1.) They have met again in this tumor, trying to make us believe that a positive HHV8 stain is always diagnostic of Kaposi's sarcoma.

Carlos Bacchi: What a case!!!

David Ben-Dor: I agree that the spindle cells in the initial resection look more like smooth muscle than they do Kaposi cells, the latter in my experience being more stringy and less plump. The cells in the recurrence look epithelioid to me. I wonder why on reviewing the slides now you readily made the association with KS which eluded you almost 20 years earlier- maybe the result of the stain for CD34 performed at the other hospital (a right stain for what turned out to be the wrong reason) jogged your mind and led you to rethink the issue. This is an example of how the use of panels can contribute but also lead to misdiagnosis. Anyway a great case and thanks for making the effort of submitting it in its entirety.

Gerald Berry: Spectacular case. I also thought the fascicular arrangement of the tumor cells in the original mass was fine for LMS. I did not consider KS! Another lesion to add to the differential diagnosis of retroperitoneal spindle cell neoplasms.

Ira Bleiweiss: I find this case perplexing. I'm OK with KS on for the original tumor, but the recurrence is way more epithelioid than any KS I've ever personally seen.

Thomas Colby: Spectacular case. Thanks for sharing it. I have not seen Kaposi's manifest this way before.

Kum Cooper: Michele, this is truly "the man from Istanbul"! A brilliant diagnosis! Off course on review the signs are all there: slit-like spaces, extravasation of blood and even globules along with tons of plasma cells. The second "recurrent" slide is interesting since I have seen many such cases in Africa in HIV/AIDS patients. In fact I was involved in a study a few years ago where I reviewed the so-called "anaplastic KS". we reviewed over 125 cutaneous cases (unfortunately the study was not published) where both the plump epithelioid cells and the immunoblastic-like cells were evident. The term anaplastic KS was not ours. It was Chris Fletcher who made me aware of a remote publication in a book chapter from an author in Zambia many years ago who first described the anaplasia in KS.

Ivan Damjanov: I must congratulate you on the persistence—I did not even think that the adrenal tumor is a Kaposi sarcoma. I was impressed with the epithelioid appearance of the second sarcoma.

Otto Dietze: Fascinating case history and morphology, I think at the time of the initial diagnosis HHV8 staining was not available for paraffin material.

Hugo Dominguez-Malagon: Kaposi sarcoma, atypical. Difficult diagnosis for me, nice discussion.

Göran Elmberger: An interesting and difficult case. Unusual location and atypical histological presentation… One needs a very high index of suspicion to make that diagnosis. Congratulations!

Vincenzo Eusebi: Incredible case! Many thanks.

Giovanni Falconieri: A quite remarkable case, Michele. I would have a hard time thinking about KS on the initial resection specimen, although some clues may retrospectively be recognized. The recurrent tumor is almost impossible to interpret for me.

Franco Fedeli: Recurrent sarcomatous transformation of retroperitoneal atypical sporadic Kaposi's sarcoma involving the adrenal. I attended the slide seminar during the last National Italian Congress in September 2010 (Bologna, Italy), where Michele presented this case. He and his cases stumped everyone.

Cyril Fisher: KS of adrenal, amazing diagnosis. Good reminder that CD34/CD117 positivity can indicate endothelial differentiation as well as GIST.

Christopher Fletcher: This seems to be a truly unique case and I am not sure that I would have been capable of recognizing this as Kaposi sarcoma. Presentation as a large adrenal mass in the setting of endemic KS would be truly exceptional, as would the apparent 'sarcomatous' transformation.

Andrew Folpe: I'm sorry- I'm having a very difficult time seeing any features of Kaposi sarcoma in either of these slides.

Jerónimo Forteza Vila: Obvious case of Istanbul's syndrome. Once the HHVS is made the case is diagnosed; the problem is to figure it out. If the HHVS weren't done, it would have been necessary to make differential diagnosis with all the spindle sarcomas (sarcomatosis transformation apparently indicates some type of transdifferentiation).

Masaharu Fukunaga: This is a challenging case. Clinically and histologically, it is a very unusual case of Kaposi sarcoma. Some areas look like angiosarcoma. I appreciate to share such a wonderful case very much, Michele.

Allen Gown: What a fascinating case, Michele. Grazie!

Thomas Krausz: This is an extraordinary case. Michele, I fully understand why you called this tumor originally leiomyosarcoma. Although it is inflamed and exhibits spindle phenotype it lacks several of the conventional histologic features of Kaposi sarcoma. This is a large tumor with brisk mitotic activity and tumor necrosis. I have seen an occasional case of "atypical" Kaposi sarcoma on extremity where the tumor looked like a "real" sarcoma and behaved more aggressively. I think the primary tumor is already a "transformed" real sarcomatous Kaposi sarcoma. I am also wondering how many of the previously diagnosed (before HHV8 immuno-era) "inflammatory" leiomyosarcomas would be HHV8 positive.

Janez Lamovec: Most interesting case and very difficult to diagnose correctly. In retrospect, the first tumor somewhat resembles Kaposi sarcoma while in the recurrence it is an epitheloid/spidle cell type of sarcoma and, to me, not so similar to Kaposi sarcoma.

Thomas Mentzel: Congratulation for his outstanding diagnosis ! To be honest I was not even thinking on this diagnosis. The primary lesion looks indeed like a myogenic neoplasm with a prominent inflammatory infiltrate (with many plasma cells !).

Markku Miettinen: Very difficult case, hard to believe Kaposi sarcoma under these circumstances, although some features certainly have resemblance to KS. The overall scenario would be more plausible for primary retroperitoneal sarcoma, and here I suspect dedifferentiated liposarcoma, with more anaplastic transformation of the period of 12 years. Atypical appearing fat is present around the spindle cell sarcomatous component. If this was a huge tumor originally, then is could be also difficult to be certain of adrenal origin. Immunostains for MDM2 would be of interest. Also, it would be interesting to see the HHV8 immunostain. Could this virus be present in other sarcomas?

Liz Montgomery: What a truly astonishing case. The initial sarcoma looks SO myoid but once one considers Kaposi's it makes sense. The more recent material looks like an epithelioid angiosarcoma – there are old reports of HIV-associated KS evolving into something that looks like AS.

Smith KJ, Skelton HG 3rd, James WD, Barrett TL, Anderson DW, Angritt P.
Angiosarcoma arising in Kaposi's sarcoma (pleomorphic Kaposi's sarcoma) in a patient with human immunodeficiency virus disease. Armed Forces Retroviral Research Group. J Am Acad Dermatol. 1991 May;24(5 Pt 1):790-

Santiago Ramon y Cajal: This is really a nice example of "Man of Istanbul" situation. What a remarkable case.

Juan Rosai: If it were not for the stated positivity for HHV-8, I would have wondered about the diagnosis of Kaposi sarcoma in this case. Obviously, at this point it is not longer the conventional form of the disease but rather the type that people have referred to as the *sarcomatous type*. I realize it is somewhat peculiar to talk about sarcomatous transformation of a lesion that is supposed to be a sarcoma to begin with, but we do the same for other tumors, as when we talk about the fibrosarcomatous transformation of dermatofibrosarcoma protuberans.

Dominic Spagnolo: What can one say, Michele – a truly remarkable Kaposi sarcoma, atypical in more ways than one.

James Strauchen: Leiomyosarcoma -> GIST -> Kaposi sarcoma -> Sarcomatous Kaposi sarcoma! Fabulous!

Saul Suster: I'm having a difficult time accepting this as a case of Kaposi's sarcoma of any type (by the way, "sarcomatous transformation of Kapoi's *sarcoma"* is an oxymoron and doesn't make any sense). It takes, indeed, some degree of stretching of the imagination to retrospectively see features of KS in the initial biopsy (which looks more like a leiomyosarcoma or other spindle cell tumor), but the second biopsy requires religious faith to accept as KS. My feeling is that the entire interpretation is hinged here on the HHV8 positivity – another article of faith. I hope we won't find a few years down the road (as invariably happens) that HHV8 can be positive in sarcomas other than KS! Was a CD31 done in this case? Could this not be a spindle cell angiosarcoma showing progression to a more pleomorphic and epithelioid sarcoma?

Lawrence Weiss: Holey moley. I have never seen a case of Kaposi sarcoma in the adrenal. One for the adrenal teaching files. Even though the diagnosis was made in retrospect, I don't think anyone would have considered KS in the initial specimen (I wouldn't have).

Eduardo Zambrano: My interpretation of slide 4A was that of a leiomyosarcoma and 4B that of an epithelioid angiosarcoma. I was having a difficult time finding an association between both tumors, other than the patient presenting with a second unrelated primary or with a post-radiation sarcoma. Thank you for your review of the literature and discussions for this case and the previous one, Michele!

CASE NO. 5 – CONTRIBUTED BY MICHELE BISCEGLIA :

Phil Allen: Massive, recurrent, probable desmoid tumor with extensive keloidal pattern and angiofibromatous foci, subcutis, intergluteal and perianal region in a patient with possible multiple desmoids (?umbilical), epilepsy and short stature. Contrary to a widely held belief, desmoids can occasionally arise in the subcutis. A diagnosis of keloid would not account for the angiofibromatous areas in both slides, and the few nodules in which the keloidal pattern merges with more typical fibrovascular nodules of a desmoid tumor. Keloidal and angiofibromatous patterns are most commonly seen in mesenteric desmoids but can occur in other locations, including musculo-aponeurotic desmoids. The giant size is also against a keloid. The small number of reported cases of giant keloids raises the possibility of misdiagnoses. Desmoids can be multiple and familial and can arise in scars. I would suggest that the patient be investigated for the genetic abnormalities seen in desmoids and desmoid related syndromes. In addition, I have seen two cases of radiation induced sarcoma in desmoids treated by radiotherapy. I do not believe radiotherapy for desmoids can be justified because of this risk.

Carlos Bacchi: Nice case and great discussion.

David Ben-Dor: The histology looks typical but the clinical aspect is obviously remarkable.

Gerald Berry: Giant keloid is understatement! Nice case. I was not aware that radiation was effective.

Ira Bleiweiss: 45 cm? Giant keloid would seem to be an understatement. How about "Monster" keloid. What was the patient thinking for 10 years? I remember a somewhat analogous case years ago when I was a fellow at Memorial Sloan Kettering of a massive colloid carcinoma of the rectum that was exophytic and growing out onto the buttocks serving as a soft pillow.

Tom Colby: Agree with diagnosis. I was assuming I was looking at some new soft tissue tumor that would have the word “keloid” in some colorful multiword diagnosis but “giant keloid” seems reasonable.

Kum Cooper: Thank you for sharing this rather unfortunate story with us.

Ivan Damjanov: Keloid –looks like, but very unusual clinical course. Thanks for the review of the literature, Michele.

Otto Dietze: Thank you for this excellent discussion, very informative also for dermatologists and surgeons.

Hugo Dominguez-Malagon: Typical keloid fibromatosis with hyalinized collagen bundles, in my hospital all fibromatosis (including keloids) are treated with colchicine 1 mg a day for 3 to 6 months (with or without surgery depending on the case) with very good results. Colchicine at this low dose has no adverse effects, and of course is less aggressive than radiotherapy.

Göran Elmberger: Thanks. Great case. Typical histology but remarkable presentation. Wonder about genetical background. Next generation sequencing would undoubtedly find something interesting in germline.

Vincenzo Eusebi: Spectacular case.

Giovanni Falconieri: Giant, tumor-like keloid, agree with the microscopic interpretation, although the clinical aspect of this case is rather impressive!

Franco Fedeli: Giant keloid of the sacral region. Just a few days ago I had the opportunity to look at the shocking clinical images of this case in the current (April) issue of Int J Surg Pathol. Also the title of the article sounds shocking (“crocodile-like” giant keloid of the sacral region).

Cyril Fisher: Another incredible case from Foggia with a bizarre history! Thanks Michele.

Christopher Fletcher: Only in the south of Italy does one see such cases!

Andrew Folpe: Keloid.

Jerónimo Forteza Vila: Given the tumour size, although it is undoubtedly a keloid, it is necessary to think of an intrinsic neoplastic factor that predominates over the permanent reactive.

Masaharu Fukunaga: Giant keloid. It is very good study of keloid.

Allen Gown: Looks like the mother of all keloids, Michele. Thanks for the great discussion.

Thomas Krausz: I have never seen a giant keloid like this before. I am wondering whether the perivascular lymphoplasmacytic infiltrate has a role in the pathogenesis.

Janez Lamovec: Spectacular case! Many years ago we saw large multiple keloids (not so large as in this case) that were self-inflicted by acid substance in a psychotic patient.

Thomas Mentzel: Another beautiful case, and I`ve never seen such a giant keloid.

Michal Michal: Amazing case. I suppose that it is the case you a gross picture you published recently - International Journal of Surgical Pathology 2011:19(2):189.

Markku Miettinen: Agree on a large keloid with recurrence, quite remarkable case.

Liz Montgomery: What a dramatic history for such a dull-looking slide. Looks like very exuberant keloid! Thanks for the education about management of keloids from hell.

Juan Rosai: This case would fit very well in the Madame Tussauds' Museum. For the record, this case will be published by Chiaramonte, Scaramuzzi and Bisceglia in the "Images in Pathology" section of The International Journal of Surgical Pathology, Vol. 19, No. 2, p. 189, April 2011.

Dominic Spagnolo: How giant can a giant keloid be! The poor guy's life must have been truly miserable. A spectacular case , Michele.

Saul Suster: While giant keloid is certainly defensible from the histology, fibromatosis can present with an identical morphology and needs to be first ruled out, particularly given the bizarre clinical presentation.

Lawrence Weiss: One unbelievable case after another.

Eduardo Zambrano: Given the patient's young age at initial presentation, I was considering juvenile hyaline fibromatosis, secondary to mutations in the capillary morphogenesis protein-2 gene (CMG2 or ANTXR2). However, the anatomical site of involvement in this case is unusual for lesions in that disorder.

CASE NO. 6 – CONTRIBUTED BY IRA BLEIWEISS:

Phil Allen: Collision of widely metastatic, ultimately fatal, lobular carcinoma of the right breast, with a primary sarcomatoid tumor of the small bowel and incidental and uninvestigated tumor of the head of the pancreas. I too missed the metastatic lobular breast carcinoma. Are we sure that the primary small bowel tumor is not a sarcoma with epithelioid features such as a GIST?

Carlos Bacchi: You are right. It is so easy to miss the metastatic lobular carcinoma on the slide.

David Ben-Dor: I looked at the slide before reading the handout and I am not to be among those who were congratulated. My attention was monopolized by this obviously very impressive pleomorphic malignancy in the wall and I didn't bother examining carefully the serosa. And even if I did I wonder if I would have picked up those small groups of metastatic lobular carcinoma cells. It's interesting that the concept of "pleomorphic" is relative- these pleomorphic lobular carcinoma cells can't hold a candle to the intramural tumor. Very instructive. I found an interesting presentation on the USCAP website on errors in diagnosis and I have on my wall next to the computer a list of "cognitive diagnostic errors" (originally published in Acad. Med. Aug 03)- this case could fit into anchoring- lock in too early or premature closure- "when the diagnosis is made, the thinking stops". Here obviously the immunos were helpful if not essential but credit should be given to whoever picked this up in the first place.

Gerald Berry: A collision or near-collusion tumor. The breast cancer was very subtle. We have previously seen a collision tumor of metastatic lobular carcinoma of the breast and renal cell carcinoma.

Michele Bisceglia: Collision of metastatic lobular carcinoma of breast with primary sarcomatoid carcinoma of the small bowel. Thank you, Ira. You are right when you say "the main tumor is too distracting" to notice those scattered minute nests of pleomorphic lobular carcinoma of the breast which are present in the subserosal location at the periphery of the main tumor mass. However, if one specifically looks for them, they can be recognized. This form of collision tumor can be regarded as a "tumor to tumor" metastasis. Breast carcinoma is (along with lung and prostate carcinomas) the most common donor tumor in this phenomenon, while meningiomas and carcinomas of the kidney and thyroid are the main recipient tumors. The most exotic examples of tumor to tumor metastasis from breast cancer I was aware of (from the literature) are a case of metastasis to a solitary fibrous tumor in the lung (Gonullu G, Sullu Y, Basoglu A, et al. Indian J Cancer. 2010;47:76-78) and a case of metastasis to a liposarcoma of the thigh (Breast carcinoma metastasis in recurrent myxoid liposarcoma. Kabukcuoglu F, Kabukcuoglu Y, Tanik C, Sakiz D, Karsidag S. Pathol Oncol Res. 2009; 15:467-71). The present case is in line with the latter examples.

Tom Colby: Beautiful example of two malignancies, one of which is incidental but neither of which is insignificant.

Kum Cooper: Ira, I still cannot find the lobular carcinoma even on review! However, I am concerned for metastatic melanoma which dearly loves the small bowel.

Ivan Damjanov: Agree—I would not have noticed the metastasis without your warning.

Otto Dietze: Thank you for this educational case. I probably would have missed the signet ring cells without keratin stain.

Hugo Dominguez-Malagon: Sorry, I missed the neoplastic cells of the serosa.

Göran Elmberger: Certainly two for one. Metastatic lobular carcinoma pick-up deserves a bonus. As for the other BFUM tumor I would need some IHC support since I don't see convincing precursor lesion or overwhelming carcinomatous differentiation on HE. Differential is broad.

Vincenzo Eusebi: Another incredible case of collision tumour from the breast and small intestine. I have to admit that I had not spotted the metastatic breast carcinoma.

Giovanni Falconieri: Amazing, Ira. I am amongst those who would miss the point. Nice case and beautiful illustrations.

Franco Fedeli: Agree. I notice that you were lucky enough in that the so-called sarcomatoid carcinoma of the small intestine was completely negative for CK, otherwise and by contrast you would risk to overlook the main tumor and interpret the components of the tumor mass as a pleomorphic breast carcinoma metastatic to small intestine.

Cyril Fisher: Difficult case without CK immuno, differential diagnosis including metastatic melanoma. As you say the clusters of serosal tumor cells are quite subtle.

Christopher Fletcher: What a crazy case! Can the remote possibility of sarcomatous transformation of the lobular carcinoma (with associated loss of specialised antigens) be an alternative explanation?

Andrew Folpe: The lobular CA is very subtle but definitely there. This is a totally awesome case, Ira.

Jerónimo Forteza-Vila: Up to which point do we think that it is a collision and not a tumour transdifferentiation? However, the truth is that I have no seen a lobular breast cancer transforming into a sarcomatoid cancer, that's why my comment can be only speculative.

Masaharu Fukunaga: It is a tough case. I might miss the lobular carcinoma element. Thank you for sharing the challenging case.

Allen Gown: I guess the only question is whether the 'sarcomatoid carcinoma' is truly primary there or represents a metastasis and further 'dedifferentiation' of the pleomorphic lobular carcinoma noted in the patient's breast. Of course one wouldn't expect such a high grade sarcomatoid tumor to express any breast (or for that matter, GI) markers and thus there may be no simple way of addressing this.

Thomas Krausz: I also missed the metastatic lobular carcinoma. On the intestinal tumor I would consider the possibility of angiosarcoma (epithelioid and spindle) in the differential diagnosis.

Janez Lamovec: The dissemination of ILC into visceral or parietal peritoneum may indeed be very subtle and difficult to spot as in this case if not examined very thoroughly. In regard to collision of ILC and another tumor, we once contributed a case of collision of ILC and malignant phyllodes tumor, AMR#35, case 13).

Thomas Mentzel: Of course we can discuss a collision tumor, however, given the described clinicopathological features I was thinking also on a metaplastic metastasizing breast carcinoma with a poorly differentiated sarcomatoid component.

Markku Miettinen: Agree on sarcomatoid carcinoma in the small intestine. Indeed, small clusters of signet ring cell carcinoma consistent with lobular carcinoma are present (not blindly detected). The sarcomatoid carcinoma can very well be metastasis, perhaps from the pancreatic tumor. Our experience of sarcomatoid carcinoma of the small intestine supports metastatic origin in most cases.

Liz Montgomery: Hmm. The little pockets of obvious breast cancer metastases on the surface are very

cute but the horrendous spindle cell lesion seems also to have a bottom-up pattern although the ulcer could be the site of an old prior precursor. Not 100% sure how a second primary sarcomatoid carcinoma of the small bowel can be diagnosed BUT the small bowel thing certainly looks very different from the obvious breast metastases so it makes “horse sense” to think of two primaries - ??? HNPCC/family history. Thanks for sharing this collision!

Juan Rosai: Pretty bizarre case. I guess the pleomorphic tumor in the wall of the bowel can be accepted as a sarcomatoid carcinoma, although I don’t see how one can completely rule out the alternative possibility of a bonafide sarcoma. As far as the metastatic lobular carcinoma of the breast is concerned, I have missed those cells so many times I have lost count. They are very hard to see even when one knows that they are there.

Dominic Spagnolo: Good pick-up! Was more detailed IHC performed on the biphasic tumour?

James Strauchen: Sarcomatoid carcinoma + "incidental" metastatic lobular. Missed the latter entirely!

Lawrence Weiss: As predicted, I did not see the lobular ca.

Eduardo Zambrano: I confess I did not see the metastatic lobular carcinoma cells until after I read the Discussion.

CASE NO. 7 – CONTRIBUTED BY KUM COOPER:

Phil Allen: Metastatic GIST, dura, right fronto-parietal region. I had a lucky escape from social embarrassment here. I incorrectly recognized him as a metastatic carcinoid from Istanbul when he was actually a heavily disguised GIST from Vermont.

Carlos Bacchi: This metastatic GIST does show morphological findings of aggressive behavior as foci of comedo-type of necrosis, epithelioid morphology and poorly differentiated areas.

David Ben-Dor: …and we're also getting quite an education in GIST turning up in strange unexpected places! At least in this case if you had the history of previous GIST which had already metastasized you would have had a fighting chance to pick it up. But I must admit that even though I was aware that this case would be included in this seminar I was pretty clueless when I saw the slide. Here the cells seem to be forming clusters some of which looked even glomeruloid to me and don't have the classical elongated spindle cell appearance which I associate with GIST. Here obviously the stains come to the rescue. This reminds me of an old (more than 10 years) case of a nodule excised from the inguinal region of an elderly man. I had no idea what it was and the distinguished pathologists who were consulted with couldn't furnish an exact diagnosis. When I got back to the surgeon he suddenly recalled that the patient had a history of a stomach mass removed several years previously. I found the case and the histology was identical- we would nowadays call the gastric tumor GIST. Those were the pre- cKIT days when gastric mural lesions were called "leiomyoblastoma" or were shoe-horned into the category of smooth muscle tumors. Nowadays I guess an immunohistochemical panel would include cd117 which hopefully would provide the diagnosis. I expect that GIST will join the ranks of tumors which behave erratically and can show up as delayed metastases even many years after the original mass was discovered and even the patient may have forgotten about it (shades of those gynecological tumors presented by Paul Wakely and Giovanni Falconieri in past sessions or meetings).

Gerald Berry: Agree. Nice case. I would not have been even close at frozen section without some hint of history.

Michele Bisceglia: Metastatic GIST. What can we say, Kum? Impossible to think of a GIST in that location if you have no clinical suspicion.

Ira Bleiweiss: I agree, Kum. Looks like meningioma. This is why I don't do neuropathology.

Thomas Colby: Agree with diagnosis.

Ivan Damjanov: Easy to be smart in retrospect (after I read your comments!)

Otto Dietze: Is the meningioma-like growth pattern also present in the primary lesion or is it a phenomenon of the intracranial growth?

Hugo Dominguez-Malagon: To my eye it looked neuroendocrine.

Göran Elmberger: History certainly broadens your differential...

Vincenzo Eusebi: Very difficult . Thank you. I admit that I had not considered GIST among the various possibilities.

Giovanni Falconieri: Another impossible case, Kum. I am scared thinking about the hundred, or so, cases of meningioma that we sign out in a year. Perhaps I should go to Turkey more often.

Franco Fedeli: Morphologically this tumor seems consistent with meningioma, even though nuclear pseudoinclusions have not been noticed (but one does not look for them on frozen). Definitely, without clinical history I would miss the correct diagnosis, but immuno and EM would exclude meningioma.

Cyril Fisher: What a fascinating case. Meningioma-like metastatic GIST. This is scarcely diagnosable without the history and GIST metastatic to brain; is very rare anyway with just a few single cases.

Christopher Fletcher: Yet another astonishing case – now that patients with metastatic GIST can be successfully palliated for so many years, it seems that they turn up with metastases at all manner of remarkable locations.

Andrew Folpe: Very easy to mistake this for meningioma if you were going too fast. Thanks for sharing this case.

Jerónimo Forteza Vila: Keys of the case are the C-KIT and clinical history.

Masaharu Fukunaga: It is very tricky, Kum. My impression was paraganglioma or neuroendocrine tumor.

Allen Gown: A great zebra (or should I say DOG?)

Thomas Krausz: What a case! Not just the frozen but the paraffin as well. Thank you Kum.

Janez Lamovec: I didn't recognize your "man in Istanbul"; thought it was meningioma!

Thomas Mentzel: What's for a difficult case on H&E. I was thinking on many things, but not on metastatic GIST – very impressive !

Markku Miettinen: Although histolologically difficult to recognize as a metastatic GIST, it probably is, based on KIT and DOG1-positivity, and overall appearance. However, both lung and meningeal metastases are very rare in GIST (saw 1 lung met and 0 meningeal mets before). It is probably from a gastric GISTs, could be of the succinate dehydrogenase deficient variety seen in young people (sometimes with paragangliomas). As patients are living longer with KIT inhibitor treatment, more unusual metastases may develop.

Liz Montgomery: Wow. A critical appraisal of the slide reveals different cytology than one would expect for a meningioma but in real time speeding through one's pile of cases with the phone ringing this would be treacherous! Thanks for sharing a GIST with rather plasmacytoid features in a place that makes us think of meningioma. Very cool lesion.

Santiago Ramon y Cajal: Great case of GIST with a striking organoid pattern. I wonder if the patient received gleevec after the liver metastasis and would be interesting to compare the histological patterns. Thank you.

Dominic Spagnolo: This is torture. It didn't look like any meningioma I've seen. Metastatic GIST at frozen looking like this....no thanks. The sad part is some years ago I saw a GIST looking very much like this presenting as an umbilical mass.

Saul Suster: Would have never thought of GIST without the history. The histology definitely does not resemble GIST and in this context, an unusual meningioma would have made much more sense. But the history and results of your stains are quite convincing. Never seen GIST metastasize this far!

Lawrence Weiss: Great case. Our neurosurgeons never like to give us the patient's history lest we become biased! This is why we insist.

CASE NO. 8 – CONTRIBUTED BY IVAN DAMJANOV:

Phil Allen: Recurrent malignant melanoma, now osteogenic, skin and subcutaneous, leg.
Thanks for contributing this unusual variant. I knew that they occurred but had not previously seen one. I look forward to reading what Masa has to say.

Carlos Bacchi: It is not a common finding (osteogenic metaplasia) in melanomas indeed.

David Ben-Dor: I thought of this diagnosis simply because I remembered Masaharu 's case (which I think he also showed at the first AMR conference organized by Michele) but was skeptical that it would crop up again. I guess lightening does occasionally strike twice. I don't remember Masaharu 's original argumentation but I assume that the bone is a dystrophic and not malignant phenomenon. On a tragic note one can wonder what unusual pathologies might turn up in Japan years from now resulting from the unfortunate recent events there.

Gerald Berry: Agree. Nice case.

Michele Bisceglia: Malignant melanoma with osteogenic metaplasia. The only case I have previously seen is just the one Masaharu contributed in AMR Seminar # 46 and which he also presented at the 2nd AMR Intl Symposium in Pilsen in 2005. Your case, Ivan, seems to complement Fukunaga's case, in that in your case the mesenchymal metaplastic component is well differentiated, while it was osteosarcomatous (chondroblastic-type) in Fukunaga 's.

Ira Bleiweiss: Agree. Great case.

Thomas Colby: Agree with diagnosis. I think I have seen this at least once before.

Kum Cooper: My colleague in Johannesburg showed me a similar case about 10 years ago. I thought that he had published it but I could not find the reference.

Otto Dietze: With regard to the frequency of desmoplastic melanomas one would expect that ossification is more frequent, however I have not seen it before; thank you for this unusual contribution.

Hugo Dominguez-Malagon: Also desmoplastic melanoma can be S100+, HMB45 -, and show a peculiar myofibroblastic stroma resembling a reparative response, I believe osseous metaplasia may be the result of plasticity of the myofibroblasts that accompany (or come from) the neoplastic melanocytes. Myofibroblasts can derive from fibrocytes, endothelial cells, muscle, bone marrow cells, and epithelial cells (by a mechanism of epithelial-mesenchymal transdifferentiation), and possibly from melanocytes.

Göran Elmberger: Great case. Agree with Masaharu on his thoughts on histogenesis. The osteogenic cells in direct contact with osteoid focally look fully malignant supporting the theory of mesenchymal differentiation (metaplasia) by the melanoma cells themselves. Thanks.

Vincenzo Eusebi: Malignant melanoma with bone metaplasia.

Franco Fedeli: Malignant melanoma with osteogenic metaplasia. I was aware that melanoma can show osteocartilaginous differentiation, when I was shown an Italian case of the finger several years ago which then was published in Surg Pathol 1989;2:73-8. Definitely an exceptional event in melanoma.

Giovanni Falconieri: Beautiful case, Ivan. I remember a case shared with Janez Lamovec many years ago at a slide seminar in Ljubljana when they presented a comparable case of osteogenic melanoma.

Cyril Fisher: Ossifying melanoma, not seen this before. Thanks, Ivan.

Christopher Fletcher: Beautiful example of melanoma with osseous metaplasia – many thanks. I can only recollect seeing perhaps a couple of such cases in the past, as well as at least one case with prominent cartilaginous differentiation.

Andrew Folpe: Agree with osteoblastic melanoma. Very nice.

Jerónimo Forteza Vila: The question is whether the metaplasia is connected with the melanoma, or if it is just a calcification related with the necroses areas and adjacent zones.

Masaharu Fukunaga: Osteogenic melanoma, agree. In my experience of estrogenic melanomas, osseous elements look like osseous metaplasia (reactive bone formation), low or high osteosarcoma or chondrosarcoma.

Allen Gown: Thanks, Ivan. Looks like these melanoma cells have taken a detour away from their usual differentiation pathway!

Thomas Krausz: I have seen rare examples of nevi with focal osseous metaplasia but not melanoma.

Janez Lamovec: We see quite a few melanomas here but I don't remember seeing one with bony metaplasia.

Thomas Mentzel: Many thanks for his rare phenomenon in malignant melanoma. The mentioned paper represents a review of uncommon variants of malignant melanoma, and I can only confirm that osteogenic melanoma is very rare, and we have seen rare examples of malignant melanoma with metaplastic ossification either in a recurrent neoplasm or in the palmoplantar regions. Interestingly, it has been discussed if either the melanoma cells show a metaplastic, osseous differentiation, or if the stromal cells show metaplastic changes induced by the melanoma (Nakagawa H et al. Am J Dermatopathol 1990; 12: 162-168).

Markku Miettinen: Agree on metastatic melanoma with metaplastic bone.

Liz Montgomery: Thanks for sharing this weird looking melanoma. The youthful age of the patient made me worry that it was something else but together with the history melanoma makes good sense.

Santiago Ramon y Cajal: Very impressive case. Thank you very much!

Juan Rosai: Very nice example of "osteogenic" melanoma. In this case the bone is extremely well differentiated and with a metaplastic look, whereas in other cases I have seen it had an obviously malignant appearance.

Dominic Spagnolo: I have never encountered an osteogenic melanoma, and I am pretty sure we don't have any cases on file. Thanks for the case.

James Strauchen: Melanoma with osseous metaplasia. Very nice example! I think there was a previous AMR case some time ago!

Saul Suster: Agree – beautiful example. I believe any malignant tumor can undergo osseous metaplasia. About 4 years ago we submitted an example of DFSP with focal osseous metaplasia; the case was interpreted by many of the members as an extraskeletal osteosarcoma – the patient is still alive without recurrence or metastases.

Lawrence Weiss: Finally, something I have seen before. I have seen melanoma with frank osteosarcomatous areas as well as benign-appearing ossification.

CASE NO. 9 – CONTRIBUTED BY OTTO DIETZE:

Phil Allen: Lymphangioleiomyomatosis, apparently restricted to pelvic lymph nodes, in a 50 year old with endometrial carcinoma. I assume she is at risk of eventually developing pulmonary disease if she survives the carcinoma. Thanks for the contribution.

Carlos Bacchi: Very nice example of LMA in the lymph node. Thanks for the case.

David Ben-Dor: This is probably a very subtle diagnosis but though I see some vascular spaces the cells look mostly like sinus histiocytosis. I'm sure I would have missed this and it's a very clever diagnosis.

Gerald Berry: Agree. We have seen this in hilar lymph nodes at the time of lung transplant for end-stage LAM.

Michele Bisceglia: Lymph node involvement by lymphangioleiomyomatosis not associated with TSC. These small foci can well go overlooked (if just a single or few lymph nodes are involved). At this regard would like to draw attention to the findings of very minute microscopical foci (≤ 2mm sized) of LAM that our friend Kum has recently published: minute nests of myomelanocytic cells in the lymphatics of the deep myometrium in a hysterectomy specimen (uterus removed for other reason – Ref. Clay MR, Gibson P, Lowell J, Cooper K. Microscopic uterine lymphangioleiomyomatosis perivascular epithelioid cell neoplasm: a case report with the earliest manifestation of this enigmatic neoplasm. Int J Gynecol Pathol. 2011;30:71-75).

Thomas Colby: Agree with diagnosis. Occasionally one finds LAM involving the uterus. From the point of view of management, I think the patient should be evaluated for pulmonary LAM. There is a high likelihood that she has it.

Kum Cooper: What was the HMB-45 immunoreaction?

Ivan Damjanov: Agree—easy to miss, however.

Otto Dietze: My case, no clinical evidence of other organ involvement.

Hugo Dominguez-Malagon: Interesting case, I suppose it is positive for HMB45 and myogenic markers. Was the uterine tumor also positive?

Göran Elmberger: Great and morphologically characteristic case. Peculiar distribution. Walls of small capsular/septal lymphatic vessels. Discrete changes in some small extracapsular vessels? Special stains might help to elucidate.

Vincenzo Eusebi: Lymphangioleiomyomatosis involving a lymph node only. Another rare case.

Giovanni Falconieri: Extraordinary case. I believe that the correct microscopic interpretation would be very difficult without evidence of LAM elsewhere. Congratulation to your sharp eye and thanks for this contribution.

Franco Fedeli: Lymph node involvement by lymphangioleiomyomatosis not associated with tuberous sclerosis. A very minute focus of LAM in my section. I could see it since I looked for it after reading your description. I was wondering why it is so frequently observed in lymph node after hysterectomy for cancer.

Cyril Fisher: Another case with subtle changes. I assume the immunophenotype was appropriate.

Christopher Fletcher: Very convincing involvement of lymph node by LAM. One sometimes finds solitary lymphangioleiomyomas involving lymph node in retroperitoneum, which seem not to be associated with the systemic syndrome.

Jerónimo Forteza Vila: Important to reckon it, important to diagnose it and above all avoid the confusion with a metastases, although probably with more frequency is underdiagnosed as reactive node phenomena.

Andrew Folpe: LN PEComa.

Masaharu Fukunaga: LAM. It is very beautiful.

Thomas Krausz: Agree with diagnosis.

Janez Lamovec: Very interesting case. I've seen them only as slide seminar cases.

Thomas Mentzel: This case represents indeed a very unusual presentation of intranodal angiomyolipoma, a term that I would prefer, given the anatomic location and clinical findings.

Markku Miettinen: Agree on lymphangiomyomatosis involving lymph node, usually lung involvement to follow unless already present.

Liz Montgomery: This is a real treat from the PEComa family. Thanks so much for it.

Juan Rosai: Typical example of lymphangiomyoma of lymph node. As usually, it is centered in the nodal capsule. Are we supposed to call this tumor a PEComa, or does the traditional term lymphangiomyoma still holds?

Dominic Spagnolo: Very nice example of sporadic LAM involving abdominal node.

James Strauchen: Very nice example of nodal lymphangioleiomyomatosis!

Saul Suster: Beautiful example of LAM. This case is much more difficult to diagnose and subtle than that great example that Michele Bisceglia presented in Istambul!

Lawrence Weiss: Nice case for the files.

CASE NO. 10 – CONTRIBUTED BY HUGO DOMINGUEZ MALAGON:

Phil Allen: Calcifying odontogenic cyst (tumor) (Gorlin), mandible, crossing the midline. Thanks very much for this case, Hugo. I have never seen one before. In fact, I have hardly seen any tumors and cysts of the jaw. As a result, I am almost totally dependent on the third series AFIP fascicle.

Carlos Bacchi: Thanks for this typical and beautifully illustrated case of calcifying cystic odontogenic tumor.

David Ben-Dor: This case rang a bell due to some overlap in name with something else that I had once seen: calcifying epithelial odontogenic tumor (which has amyloid). The ameloblastic epithelium is nicely demonstrated and I appreciate the photo of the ghost cells which didn't show up in the section I received.

Gerald Berry: Agree. Nice example.

Michele Bisceglia: Calcifying cystic odontogenic tumor (Gorlin cyst). Have seen two cases of this entity (also called calcifying odontogenic cyst, and keratinizing and calcifying odontogenic cyst). Despite its eponymic name this cyst/tumor has no relationship with Gorlin's syndrome (or Gorlin-Goltz syndrome), which also includes odontogenic lesions (i.e. odontogenic keratocysts) among its phenotypic clinical expressions.

Thomas Colby: Agree with diagnosis. Thanks for sharing this case, Hugo. I generally try to avoid jaw tumors.

Kum Cooper: Thank you, Hugo, for sharing this rare entity. Amazingly I saw many more odontogenic and salivary gland tumors in Africa. The old books called this a CEOT; E for epithelial.

Otto Dietze: Thank you, I have seen this tumor nearly 20 years ago in a tutorial with slide seminar and cannot remember a case in our files.

Göran Elmberger: Unfortunately, I rarely get to see these interesting specimens. Appreciate your interesting contribution. In my slide suggestive area is small but definitive. I have a hard time differentiating between dentinoid and immature bone...

Vincenzo Eusebi: Probably there is something that is missing from my slide. The cystic lesion to me looks like cystic ameloblastoma.

Giovanni Falconieri: Thanks, Hugo, for contributing a classic of surgical pathology. I guess that this is the very first I am looking at complemented by such a good clinical and radiological documentation.

Franco Fedeli: Calcifying cystic odontogenic tumor (Gorlin cyst). Thanks for the interesting case. Beautiful section and explicative radiologic images of a rare entity.

Cyril Fisher: Calcifying epithelial odontogenic cyst, something rare to see. Nice gross photograph and imaging. Thanks, Hugo.

Christopher Fletcher: I still find the classification of odontogenic tumors very confusing and there seems to be morphologic overlap between so many of these lesions. This certainly seems to be a nice example of what has been described as calcifying cystic odontogenic tumour – but I am glad that I do not have to classify these lesions very often!

Andrew Folpe: Great example. I gave the recut away to one of our junior H/N people, who was very pleased to have it in his collection.

Jerónimo Forteza Vila: I agree with the fundamental role of the image study for these tumors.

Masaharu Fukunaga: I have never seen this type of tumor, calcifying cystic odontogenic tumor. I thank you very much for sharing the case, Hugo.

Allen Gown: Thank you for this case of a tumor I have never seen - and one of which may be the only one I ever see!

Thomas Krausz: Hugo, thank you very much for submitting this highly educational case.

Janez Lamovec: Never seen it before. I was somewhat worried by basaloid cell nests and thought of cystic ameloblastoma.

Thomas Mentzel: Many thanks for sharing this (at least for me) unusual neoplasm.

Michal Michal: Interesting in the case is cytological similarity with cutaneous pilomatricoma.

Juan Rosai: As usual, I had to go to the books for this odontogenic tumor. It has always been a challenge for me to keep them straight.

Dominic Spagnolo: I never see these lesions and defer to the experts in the area. Thanks for the case.

James Strauchen: Had to look this one up! Thank you for this very nice case.

Lawrence Weiss: Thanks. I no longer see dental neoplasms.

CASE NO. 11 – CONTRIBUTED BY VINCENZO EUSEBI:

Phil Allen: Meningeal hemangiopericytoma with two intracranial recurrences at 5 and 7 years and a subcutaneous metastasis over the left hip 13 years after the original diagnosis. Should we change the name of this tumor to malignant solitary fibrous tumor or should we revert to angioblastic meningioma?

Carlos Bacchi: Thanks for the case.

David Ben-Dor: I once had a case metastatic to the jaw- obviously history is important and is especially helpful if the clinician kindly gives you the full name of the tumor (in my situation I was told simply that the patient had a "meningioma" and not hemangiopericytic meningioma- the first diagnosis may not lead to any particular suspicion though with hindsight any vascular tumor appearing in a patient with a history of meningioma should prompt verification of the exact diagnosis).

Gerald Berry: An unusual sequence of metastasis!

Michele Bisceglia: Subcutaneous nodular metastasis from intracranial recurrent meningeal hemangiopericytoma (HPC). HPC of the meninges has a local recurrence rate of about 80-85% and a rate of extra cranial metastases of 20% according to the collective experience of several large series from various sources, reported over the last 2 decades (Mena H et al Hum Pathol. 1991;22:84-91; Vuorinen V et al. Acta Neurochir (Wien). 1996;138:1399-408; Tihan T et al. Arch Pathol Lab Med. 2003;127:432-439). Eusebi et al (in the ref. he quoted which included the case he contributed in this Seminar) and Hayashi et al (Clin Neurol Neurosurg. 2009;111:34-38) have found an even higher rate of local recurrence of 92% and 87.5%, respectively. In the study of Hayashi et al the rate of extracranial metastases was 50% and that of tumor-related deaths was > 60%. Parenthetically all these data are in favour of keeping separate HPC of meninges from meningeal solitary fibrous tumor, despite the controversy surrounding its (HPC's) histogenesis.
Another metastatic meningeal HPC was contributed by Ira Bleiweiss in Seminar 4 (this Bleiweiss' case metastasized to pleura, paravertebral area and leg) 18 years after primary surgery.

Ira Bleiweiss: Wow. How weird. I've never heard of this happening before.

Thomas Colby: Agree with diagnosis. Remarkable case.

Kum Cooper: Vincenzo...another man from Istanbul!

Ivan Damjanov: Hemangiopericytoma.

Otto Dietze: I agree, however, it would be difficult to argue for metastatic disease without the intracranial recurrences and a second primary tumor would be the first differential diagnosis, esp. with no lung involvement.

Hugo Dominguez-Malagon: Differential diagnosis includes monophasic synovial sarcoma that also fits with this immunophenotype, I would add immuno for TLE-1 and FISH for SYT.

Göran Elmberger: Great case. In a high grade (WHO III; anaplastic) HPC such as this I am not surprised that metastasis eventually did take place. Slides from recurrent meningeal location !?

Giovanni Falconieri: Beautiful example of meningeal HPC. I have seen a similar case many years ago here and it was histologically similar. That case was characterized by metastatic spread to spinal cord but not distant metastases.

Franco Fedeli: Subcutaneous nodular metastasis from intracranial recurrent meningeal hemangiopericytoma. This case confirms that a proportion (15%) of meningeal hemangiopericytomas can give rise to extracranial metastases.

Cyril Fisher: I suppose one might think of malignant SFT also in this context.

Christopher Fletcher: I have to be honest and admit that I believe that meningeal hemangiopericytomas represent cellular or malignant examples of solitary fibrous tumour. I have not seen any convincing evidence that allows one to separate meningeal HPC from SFT – but I am no neuropathologist.

Andrew Folpe: Metastatic meningeal HPC. Kind of impossible to tell from a mitotically active primary soft tissue HPC/SFT without the history. Thanks for submitting this.

Jerónimo Forteza Vila: Crack-like vascular architectural pattern and nucleus morphology supports the diagnosis.

Masaharu Fukunaga: Thank you very much for the beautiful case. I had a similar case of meningeal hemangiopericytoma with lung metastases recently. I had difficulties of making a diagnosis without previous history of meningeal tumor excised 25 years ago.

Allen Gown: Thank you, Vincenzo, for this pretty example of an HPC.

Thomas Krausz: Agree that in this clinical context this "hemangiopericytoma" is best regarded as metastatic.

Janez Lamovec: It looks like hemangiopericytoma but in soft tissue or skin/subcutaneous tissue one shouldn't expect it without information of a previous meningeal tumor.

Thomas Mentzel: A very nice example of recurring meningeal "hemangiopericytoma" (meningeal solitary fibrous tumour).

Markku Miettinen: Consistent with metastatic hemangiopericytoma. Synovial sarcoma would be in the differential (FISH?).

Liz Montgomery: Thanks for sharing this metastatic CNS hemangiopericytoma. What a lovely lesion with perfect "hemangiopericytoma" vessels and no chunky collagen! These things can really create diagnostic havoc when they metastasize years hence as did this one and no one actually bothers to tell the pathologist the history.

Santiago Ramon y Cajal: Very interesting case of meningeal hemangiopericytoma.

Juan Rosai: Great case of hemangiopericytoma/solitary fibrous tumor of meninges metastatic to soft tissue. This tumor has a greater tendency to metastasize outside the CNS than most intracranial tumors. Kris Unni told me once that if you have a tumor with the appearance of hemangiopericytoma inside a bone, it is more likely to be a bone metastasis from a meningeal tumor than a primary bone neoplasm. Nice pearl, if true !

Dominic Spagnolo: Agree, metastatic hemangiopericytoma from meninges. I was nearly torched with the reverse scenario recently – patient with history of multiply recurrent soft tissue SFT (eventually called malignant SFT), strikingly hemangiopericytomatous in appearance, then presents with cerebellar lesion for frozen section – looks for all the world similar, but of course is an incidental hemangioblastoma.

James Strauchen: Metastatic meningeal HPC.

Saul Suster: Agree, although I believe neuropathologists are behind the curve in persisting to call this "hemangiopericytoma". The tumor is morphologically and immunohistochemically indistinguishable from SFT, except than when located in the meninges it almost invariably behaves in a malignant fashion with distant metastases. Perhaps "aggressive meningeal SFT" would be more appropriate?

Lawrence Weiss: Classic histology even if not in ordinary location.

Eduardo Zambrano: Besides this case, I have only seen 2 cases of metastatic meningeal HPC, both metastasizing to bone. Similar to this case, both metastasized several years after the initial presentation in the CNS.

CASE NO. 12 – CONTRIBUTED BY CYRIL FISHER:

Phil Allen: Anastomosing hemangioma of the kidney with extra-medullary hematopoiesis. Thanks for this case, Cyril. I fear I would have called it an angiosarcoma because of the vascular invasion and would have been forced to trot out the pathologist's excuse for an overdiagnosis, "it must have been a low grade tumor" when it did not recur.

Carlos Bacchi: Thanks for the nice example of anastomosing hemangioma of the kidney.

David Ben-Dor: The classical teaching is that anastomosing vascular channels indicate angiosarcoma but as in the grammar I suppose of all languages there are rules and there are exceptions to the rules. It's better to speak a language you learned from your mother than one you learned by reading a grammar book since in the former situation you learn in context rather than artificially. It's propitious for the discovery of new entities if an accomplished soft tissue pathologist and urological pathologist are in the same place.

Michele Bisceglia: Anastomosing hemangioma of kidney. This tumor (of which I have never seen one) is interesting, not only per se as a separate entity or variant, but also for the heterotopic hematopoiesis. As to the context of vascular tumors or richly vascularized tumors presenting heterotopic hematopoiesis I have seen it in the past in 2-3 cases of hemangioblastomas of CNS only (just using "hematopoiesis AND hemangioblastoma" as search terms in PubMed, then 14 references came out on this issue). Another possible point of interest in regard to vascular or vascularized tumors of the kidney (such as the case in point) is the potential "perirenal hemorrhage" such tumors can give rise, which by chance I learnt just few

days ago is called “Wunderlich syndrome”. Wunderlich syndrome is represented by the perirenal hemorrhage associated with an underlying tumoral renal pathology and is usually reported in association with RCC and AML of the kidney).

Gerald Berry: Another unusual renal neoplasm from members of the group!

Ira Bleiweiss: I would have called this angiosarcoma, particularly with the invasion of fat.

Thomas Colby: Agree with diagnosis. A new entity for me although I vaguely remember seeing the reference.

Kum Cooper: Thank you, Cyril, for this fine example. I never thought that I would see a case after reading the reported 6 cases from Liz.

Ivan Damjanov: Thanks. I made up my mind that it was benign, but you provided the correct diagnosis. Was extramedullary hematopoiesis described in any other previously reported cases?

Otto Dietze: Thank you for the contribution of this most recent tumor entity, I know it only from the literature.

Hugo Dominguez-Malagon: Interesting entity, I wonder if the lipomatous component and large vessels are part of the lesion.

Göran Elmberger: Important concept. Wonder if lesion occurs in other organs as well. Certainly difficult mimicker of AS but truly no cellular atypia. Thanks.

Vincenzo Eusebi: Haemangioma of kidney.

Giovanni Falconieri: Very difficult and concerning. I did not know the entity, I am sure that I would missed the point were it a real-life case. Thanks for this highly educational contribution.

Franco Fedeli: Anastomosing hemangioma of kidney with heterotopic hematopoiesis. Interesting case. This is the first time I see it. Agree this is benign.

Christopher Fletcher: This is a very nice example of anastomosing hemangioma – thanks Cyril ! We have seen quite a number of these occurring in perirenal soft tissue but I have less experience with those that actually involve renal parenchyma.

Andrew Folpe: Terrific example of this distinctive renal vascular tumor. Before we knew about Liz and Jon's paper, Mahul Amin and I were calling these "splenoid hemangiomas", since they reminded us a bit of the spleen. Their name is better.

Jerónimo Forteza Vila: On the one hand it points to angiosarcomas, on the other reminds Masson’s intravascular hemangioma, despite that the kidney is not a typical location for this entity.

Masaharu Fukunaga: I would like to call it angiosarcoma because of infiltrative growth and cellular atypia.

Thomas Krausz: Superb example. I saw a similar case (consult) a year ago.

Thomas Mentzel: Thanks for this partly intravascular haemangioma. Are vascular structures surrounded by actin-positive cells and did endothelial cells stain positively for WT-1 ?

Markku Miettinen: Agree on hemangioma. Has some resemblance to cellular angiolipoma, with lobulation, fibrin thrombi, and possible integral fatty component.

Liz Montgomery: What a fun case! Thanks, for sharing it, Cyril. My slide has tons of extra-medullary hematopoiesis. We have seen more such cases and quite a few have been in the female genital tract – one case with several lesions so maybe the gender ratio will even out over time as more cases are noted.

Santiago Ramon y Cajal: Beautiful case.

Juan Rosai: This anastomosing hemangioma of the kidney looks well-differentiated cytologically but pretty complex to me at the architectural level. I would have called it a hemangioendothelioma, and I will not be too surprised if one of these tumors were to recur.

Dominic Spagnolo: Pretty much the "full house" in this beautiful example of anastomosing hemangioma. Thanks, Cyril.

James Strauchen: Thank you! The extramedullary hematopoiesis is a striking feature. Do they make erythropoietin or other growth factors?

Saul Suster: I had never seen a tumor like this in the kidney before – thank you Cyril for contributing this case. To my eye it is somewhat reminiscent of Kaposiform hemangioendothelioma seen in association with Kassabach-Merrit syndrome. This has been an education for me!

Lawrence Weiss: Missed (or forgot about) the paper and missed it as a hemangioendothelioma. Thanks for educating me.

Eduardo Zambrano: Nice case. I recognized it as some kind of benign vascular proliferation involving kidney, but I was sadly unaware of the existence of the entity published by Drs. Montgomery and Epstein.

CASE NO. 13 – CONTRIBUTED BY CHRISTOPHER FLETCHER:

Phil Allen: Sclerosing PECOMA, retroperitoneal perirenal fat. Thanks for the contribution Chris. I have never recognized one of these before. It certainly bears a vague resemblance to fat free angiomyolipoma of the kidney.

Carlos Bacchi: Incredible example of sclerosing PECOma.

David Ben-Dor: The cell groups looked squamoid (or maybe meningothelial?) to me to be honest.

Gerald Berry: Agree. Nice example of PEComa.

Michele Bisceglia: Indeed, a very sclerotic PEComa. The sclerotic stroma can be misleading. This variant indeed expands the morphological spectrum of PEComas, which (either spindled or epithelioid) we are prone to think as more often appearing as clear cell tumors. In addition to this sclerosing PEComa, Chris contributed in previous Seminar # 35 a case of sclerosing paraganglioma: it would be interesting to make a review of all tumors which can present in the form of a sclerosing variant. I refer to tumors other than soft tissue tumors, of which sclerosing variants are well known and of which previous reviews have been already made (Adv Anat Pathol 10: 179-199; 2003; Pathologica: 98:239-298;2006 (Table 1; page 245)

Thomas Colby: Agree with diagnosis. Thanks for sharing the case. Have not seen one of these before.

Kum Cooper: Thanks, Chris, for sharing this "newly described" entity. I did not recognize it as a PEComa (although a weird AML was in my differential!).

Ivan Damjanov: Thanks for reminding me of your 2008 paper. Location, location ,location, like real estate.

Otto Dietze: I have not seen a sclerosing variant of PEComa before.

Hugo Dominguez-Malagon: Beautiful case of sclerosing PEComa, thank you.

Göran Elmberger: Wonderful case. Its amazing how these PECOMAS can take various forms and shapes. I believe it must have been difficult initially to recognize that these tumors actually belonged to the spectrum of PECOMAS. I am also fascinated by the concept of PECOMAS lacking a normal recognized histological counterpart. It is really the rule of all translocation sarcomas to be very broadly distributed and loosely connected to a defined tissue of origin. Tumors like DSRCT t(11;22), PECOMAS t(3;10), SS t(X;18), CCS t(12;22) and ASPS t(X;17) all occur in more and more locations often loosely related to the originally described distribution pattern of the entity. Thanks for sharing!

Vincenzo Eusebi: Very nice case. I was aware of the paper, but never seen in real life.

Giovanni Falconieri: Impossible case to comment on. Thanks, Chris, for this extraordinary contribution.

Franco Fedeli: Sclerosing PEComa. Another first for me. It is impressive to note how high is the frequency with which people see cases or entities for the first time, even cases of which he has not even heard before!

Cyril Fisher: Sclerosing PEComa, great slide.

Masaharu Fukunaga: Thank you very much for sharing the beautiful case of sclerosing PEComa. It looks like glomus tumor.

Allen Gown: Lovely example of this tumor variant, Chris.

Thomas Krausz: Highly educational case, thank you Chris.

Janez Lamovec: The first I've seen. Thank you.

Thomas Mentzel: A wonderful example of a rare morphological variant of PEComa !

Markku Miettinen: Have to agree on PEComa based on markers. However, histologically has more smooth muscle tumor-like look than many other PEComas, but the kidney associated-ones might be of this type.

Liz Montgomery: This is a beautiful case and a nice complement to the other PEComa family member in case 9. The sclerosis is a real fooler.

Santiago Ramon y Cajal: Great case. Sclerosing PEComa. Thank you very much!

Juan Rosai: Pretty striking case. I would have considered a sclerosing glomangiopericytoma in the differential diagnosis, but since this tumor is said to be positive for both SMA and HMB-45 I don't see how one can escape from making a diagnosis of PEComa. I am concerned, however, at the speed with which this entity is expanding. All too often this is followed by a big crash.

Dominic Spagnolo: Beautiful retroperitoneal sclerosing PEComa. Have not seen this before. Thanks.

James Strauchen: A most unusual PEComa! Thank you!

Saul Suster: Spectacular case! Thank you, Chris, for sharing this with us. I don't recall having seen this before (or most likely have simply missed them....)

Lawrence Weiss: First one I have seen on glass. Really looks like it's coming off the vessels.

Eduardo Zambrano: Great case. I had never seen an example of this variant of PEComa before.

CASE NO. 14 – CONTRIBUTED BY ANDREW FOLPE:

Phil Allen: Subclinical acute inflammation in severe degenerative arthritis, right knee. Thanks Andrew, for this most instructive case and the reference. Most of the orthopaedic surgeons here believe that polymorphs in bone indicate bacterial infection. This case and the quoted paper should work as a powerful antidote to such a poisonous idea.

David Ben-Dor: I don't know what prosaic is anymore. I'm not sure I would have even paid attention to the neutrophils and if I did, might not have ascribed much importance to them. In any case it's good to have one's attention drawn to what seem simplistic at first glance. Not everything needs to be molecular genetics.

Gerald Berry: Agree.

Michele Bisceglia: Subchondral acute inflammation in severe arthritis. Andrew, you did well in pointing to this finding. Thank you. Had previously seen this finding before and also interpreted it as related to osteoarthritis but did not know it was the subject of more in-depth investigation.

Ira Bleiweiss: Agree and thanks for the non-esoterica -and to quote the orthopods "but did you count the polys?"

Tom Colby: Agree with diagnosis. This case points out the value of only doing gross examination on certain specimens.

Kum Cooper: Andrew, I am still scratching my head since I did not even pick up the neutrophils on the first go!

Ivan Damjanov: Point well taken. Thanks.

Hugo Dominguez-Malagon: All is new information for me, thank you.

Göran Elmberger: New and educative to me. We don't see these kinds of specimens any more here. Surgeons save their bucks... Thanks.

Vincenzo Eusebi: Thanks for this case.

Giovanni Falconieri: A distinctly challenging case. I did not know the entity. Thanks for this contribution and the reference.

Franco Fedeli: Subchondral acute inflammation in severe arthritis. One can easily understand why the original pathologist thought of acute osteomyelitis in seeing the microabscess-like neutrophilic subchondral infiltrations.

Cyril Fisher: Fits for this diagnosis. This is new to me too!

Christopher Fletcher: Thanks for this educational case.

Andrew Folpe: My case. Hope it wasn't too mundane.

Jerónimo Forteza Vila: Agree with the diagnosis.

Masaharu Fukunaga: I did not know the entity of subchondral acute inflammation in severe arthritis, thank you, Andrew.

Thomas Krausz: Agree with interpretation. I was not aware of the helpful reference either.

Thomas Mentzel: Many thanks and I was unaware of this interesting phenomenon. How frequent is it?

Markku Miettinen: Agree on degenerative joint disease associated inflammatory reaction. Lack of acute inflammation in marrow spaces takes also out osteomyelitis from consideration.

Liz Montgomery: Thanks for educating me about a quirk of arthritic bone. Luckily I probably would have missed the acute inflammation in the first place and would not have had a problem with the case thereby getting the right answer for the wrong reason. Seems that this could be a real problem on frozens.

Santiago Ramon y Cajal: It may be a prosaic case but a very important diagnostic dilemma.

Juan Rosai: As Dr. Lauren Ackerman would have said, the case is not very "romantic", but it sure seems significant from a clinical standpoint.

Dominic Spagnolo: It certainly makes the point that acute inflammation can be quite prominent in these OA lesions with subchondral cyst formation. In the context of know severe OA, I'm pretty sure I have ignored this feature in the past.

James Strauchen: DJD with acute inflammation. Very informative case!

Saul Suster: This is actually not a "prosaic" but a very educational and valuable contribution, Andrew. There are even clusters of plasma cells in my slide – quite easy to mistake this for osteomyelitis if you are not aware of this condition.

Lawrence Weiss: Seen it and ignored it in the past. Now it has a name.

Eduardo Zambrano: I must admit that after I saw the foci of acute inflammation within the subarticular bone, I started examining the blood vessels looking for sickle cells that would point to a potential Salmonella etiology. I am not sure I have noticed this acute inflammatory reaction in these types of specimens before, but I was also unaware of the study describing this phenomenon.

CASE NO. 15 – CONTRIBUTED BY JERÓNIMO FORTEZA VILA:

Phil Allen: Sclerosing variant of benign metastasizing leiomyoma with 57 bilateral pulmonary nodules appearing two years after a hysterectomy for a histologically similar uterine tumor. As I have previously mentioned when commenting on earlier club cases, I believe this condition is in a different neoplastic category from sarcomas and belongs to a group of endometriosis-like tumors with a good prognosis, a dependency on oestrogen and some sensitivity to progestogens. Lung-conserving multiple metatasectomies is excellent treatment.

Carlos Bacchi: Agree with the diagnosis of leiomyomatosis. I would favor primary by the number of lesions but not sure.

David Ben-Dor: Just to make sure that I got things straight: the uterine mass was an endometrial stromal sarcoma, as typified by the photos- histologically it makes sense. At the time no uterine smooth muscle tumor was diagnosed. The lesion on the glass slide showing one of the recently discovered lung nodules looks to me like leiomyoma. If I understood correctly the possibility of primary pulmonary leiomyomatosis is suggested. I didn't succeed in finding a description of this in the reference books I have access to (AFIP fascicle, WHO book, Rosai). I would assume that these nodules are related to the original uterine endometrial stromal sarcoma and represent a metaplastic phenomenon. That it can be very difficult at times to separate uterine endometrial stromal and smooth muscle lesions as primary lesion (let alone disseminated) and the degree of immunohistochemical overlap between them can attest to a biological relatedness brought out here. Fascinating case.

Gerald Berry: The prominent hyalinization was reported in some of the cases of metastatic ESS to the lung reported by Tom Colby. I would defer to him on this.

Michele Bisceglia: Pulmonary leiomyomatosis in patient diagnosed with sarcoma of the endometrial stroma with low level of malignancy. I would favor pulmonary metastasis of the endometrial stromal sarcoma undergoing changes in the morphological and immunohistochemical features. Genetic hits can occur at various stages of oncogenesis. Maybe molecular analyses could demonstrate if the lung tumor is a submodal clone of the uterine tumor and if the two tumors share the same initiating genetic changes.

Ira Bleiweiss: Agree with pulmonary leiomyomatosis.

Thomas Colby: An interesting problem. I am not sure I have seen a case in the lung with multiple smooth muscle nodules in which there was not a current or previous uterine lesion that was documented to be myomatous. I agree that the uterine lesion looks different than the lung nodules but to me this is almost too much of a coincidence: multiple pulmonary nodules of this type (most of which fit the scenario of benign metastasizing leiomyoma) and a concurrent uterine lesion, although with a different histology. It is not clear to me why the pulmonary nodules were resected. In the limited available literature, patients with metastatic endometrial stromal sarcoma do not go on to die of their pulmonary disease and patients with benign metastasizing leiomyoma have a very indolent slowly progressive course.

Kum Cooper: My morphological impression was that of metastatic endometrial stromal sarcoma.

Ivan Damjanov: I think that the dilemma cannot be resolved but unless firmly proven otherwise I would link the pulmonary lesions to the uterus.

Otto Dietze: I agree that pulmonary leiomyomatosis is the more correct diagnosis, depending on the clinicians one might be influenced to favor metastatic disease unless there is a second or third opinion confirming this diagnosis.

Hugo Dominguez-Malagon: Pulmonary leiomyomatosis seems reasonable.

Göran Elmberger: Challenging case. Looking at slides from lung I agree on leiomyoma. Photomicrographs submitted from uterine tumor looks slightly different with prominent vessels. One of the uterine micrographs suggests intravenous spread. However, in my experience differential diagnosis between endometrial low-grade sarcoma with iv spread and intravenous leiomyomatosis can be utterly challenging basically coming down to the performance and interpretation of IHC. Furthermore mixed endometrial stromal and smooth muscle tumors are also accepted WHO entities. Molecular diagnosis could possibly be of some help with the t(7;17) marker translocation being present in most low-grade ESS. When it comes to the interpretation of the multiple lung nodules I am somewhat sceptical against leiomyomatosis interpretation since time has taught us that a diagnosis of primary leiomyomatous tumors should be advanced only with strong caution. Thus in my mind this probably represents the entity of "benign metastasising leiomyomas" in itself probably a misnomer for what rightfully should be considered and called as metastasising low-grade uterine leiomyosarcoma. In an individual case the relationship between the multiple pulmonary nodules and the uterine tumor (possibly heterogenous) can be difficult to prove but reports have been published utilizing various more or less sophisticated molecular techniques that could be of help even in an individual case (Tieze L, Gunther K, Hörbe A, et al, Human Pathol, 2000 Jan, 31 (1): 126-8.) Follow-up is of interest but not always decisive for interpretation since regression after oophorectomy has been reported even in bona fide cases of "benign metastasising leiomyomas". Thanks.

Vincenzo Eusebi: Remarkable case of what I think to be a metastasis from the uterine tumour. Metastases can be very "benign-looking" especially after treatment.

Giovanni Falconieri: I agree with your interpretation, don't see how we can consider this primary also based on this particular clinical history.

Franco Fedeli: Pulmonary leiomyomatosis in patient diagnosed with sarcoma of the endometrial stroma with low level of malignancy. I am concerned with pulmonary metastases in this case. However I agree that on morphology the lung nodule in the section seems different from the classical endometrial stromal sarcoma so beautifully pictured in the images posted on website.

Cyril Fisher: Pulmonary leiomyomatosis.

Christopher Fletcher: The appearances here could also represent benign metastasizing leiomyoma. Were there also any myomas in the hysterectomy specimen, along with the stromal sarcoma?

Andrew Folpe: Interesting problem. I think in this clinical setting I would inclined to regard these as metastases from the endometrial stromal tumor, showing smooth muscle differentiation. Curious to hear other opinions.

Masaharu Fukunaga: It is a very tough case. I prefer metastatic uterine endometrial stromal sarcoma, low grade.

Allen Gown: In some respects this is reminiscent of so-called "benign metastasizing leiomyoma".

Thomas Krausz: I favor the diagnosis of metastatic endometrial stromal sarcoma.

Janez Lamovec: This is leiomyoma to me but I don't know whether a transformation of endometrial sarcoma into leiomyomatous tumor in a metastasis is possible or not.

Thomas Mentzel: Given the clinical findings and the morphological description pulmonary leiomyomatosis seems the most likely diagnosis, very interesting case!

Michal Michal: It would be interesting to know the t(7;17) in both the uterine and pulmonary tumors.

Markku Miettinen: Smooth muscle tumor, good for "benign metastasizing leiomyoma". Can's see stromal sarcoma features here. Still somewhat mystic entity.

Liz Montgomery: I found this difficult but perhaps did not completely understand the case. It seems that the uterine lesion was an ESS with vascular space invasion and that there was no smooth muscle lesion in the uterus (or there was and I missed this in the write-up). The images on the web of the uterine lesion look like an ESS and there was CD10 labeling but no desmin labeling. The lung lesions are less cellular than the uterine one but not 100% perfect for "benign metastasizing leiomyoma" and a bit on the cellular side for pulmonary leiomyomatosis but they have desmin labeling and the uterine ESS did not. I missed whether the lung lesions had CD10. The good news is that whether the lung lesions are *de novo* pulmonary leiomyomatosis or reflect a peculiar pattern of spread from the endometrial lesion that bypasses the abdomen and pelvis, there is a therapeutic target in the form of the ER expression.

Santiago Ramon y Cajal: Difficult case. I suppose that in the lung, tumor cells were negative for CD10.

Juan Rosai: To me the appearance of these nodules is that of so-called benign metastasizing leiomyomas, the question being how they relate to the uterine endometrial stromal tumor.

Elvio Silva: I enjoyed the case and your discussion. In my opinion, WT1 is a little better than ER to determine if a smooth muscle tumor is of müllerian origin or not. The combination of both it would be better. In our experience, if the smooth muscle tumor looks benign all cases related to müllerian origin are + for WT1, if it looks malignant only 50% are +.

Dominic Spagnolo: I find it difficult to accept that these numerous pulmonary lesions are not related to the intrauterine growth (with intravascular growth). How thoroughly was the uterine lesion sampled? The CD10 positivity is more a feature of highly cellular leiomyomas, which may have intravascular growth and may resemble stromal tumors though I do note your desmin and HHF35 stains were negative. So I'm not sure about this intriguing case. Look forward to everyone's opinions.

James Strauchen: I am impressed you examined all 57! Conventional wisdom is that these cases are all metastatic!

Saul Suster: What would make more sense in this setting is for this to be "benign metastasizing leiomyomas". The discrepancy with the histology of the uterine lesion, however, is hard to explain (unless we want to resort to "transdifferentiation", "meta-differentiation", "proto-differentiation" and "ectoplasmic juxtadifferentiation"). Maybe the tumor simply underwent "progressive differentiation" or "reverse-dedifferentiation" and now looks more like conventional leiomyoma? (Maybe I should not include "word salad" in my diet anymore - this one gave me indigestion!)

Lawrence Weiss: I favor the possibility that this is a metastasis from the uterine neoplasm, despite the disparate features.

CASE NO. 16 – CONTRIBUTED BY ALLEN GOWN:

Phil Allen: Sarcoma, possibly epithelioid leiomyosarcoma, uterus. I doubt that this is a desmoplastic small round cell tumor. The patient is a middle-aged female, the tumor is primary in the uterus and the sections don't look like a desmoplastic small round cell tumor. I suspect that "the fiend that lies like truth" is now assuming the guise of RT-PCR results.

Carlos Bacchi: Great case! It is a rare location (uterus) for DSRCT indeed.

David Ben-Dor: This is a very thorough work-up and scientific evaluation of an unusual case by two leading authorities in molecular tumor analysis, so the conclusion should be treated with great deference. As someone in the bleachers in this respect, the only comment I can make concerns the nosological role the cytokeratin plays in DRSCT. Even if cytokeratin positivity is intrinsic to the definition one can argue that in a straightforward classical case meeting all the other criteria the diagnosis can still be maintained even when the cytokeratin is negative; however it might be debatable whether this logic can hold in a case such as this in which the location and age are not characteristic for the entity. But if the genetics are incontrovertible then what can I say. I'm sure that this case will give rise to a lively debate. It's certainly not metastatic ductal carcinoma from the breast.

Gerald Berry: What an unusual site! Nice discussion.

Michele Bisceglia: Desmoplastic small round cell tumor confined to uterus. Allen, this is indeed a unique case in that location.

Ira Bleiweiss: I never would have even considered this diagnosis.

Thomas Colby: I would favor some sort of sarcoma here with muscle differentiation. This case illustrates the problem of changing gold standards in our diagnoses from morphology, to immunohistochemistry, to molecular and the inter-method concordance may not be that great.

Kum Cooper: The molecular profile triumphs!

Ivan Damjanov: There is no point arguing with the genetics, but otherwise I would have called it ESS.

Otto Dietze: I have not seen DSRCT in this location before!

Hugo Dominguez-Malagon: Excellent case and discussion, it seems that the spectrum of DSRCT is expanding, or perhaps the "typical" translocation *EWS-WT1* corresponds to more than one entity as often happens.

Göran Elmberger: Great case that brings some philosophical questions to mind. Undoubtedly, this represent a "translocation sarcoma" with t(11;22) – "marker translocation" for DSRCT. The morphology is at its best compatible with DSRCT even if my section largely shows a clear cell tumor and desmoplasia is not very pronounced. Clinically, the case is unusual in its uterine location (only case described), the comparatively old age and the female sex of the patient. Immunohistochemistry fails to detect "definitional" polyphenotypic markers such as CK and synaptophysin. Following the argumentation of Alaggio et al (Spindle cell tumor with EWS-WT1 transcript and a favourable clinical course: a variant of DSCT a variant of leiomyosarcoma, or a new entity? Report of 2 pediatric cases; Am J Surg Path 2007) this tumor could represent an unusual manifestation of a bona fide translocation verified case of DSRCT, an unusual poorly differentiated ESS with an EWS-WT1 transcript or an hitherto unrecognized subgroup of uterine mesenchymal neoplasms bearing the same translocation as DSRCT. Unfortunately, in my opinion more cases need top be identified and those cases need long time observation to define prognosis and response to targeted therapy before strong conclusions are justified. However, being overly philosophic sofar someone always has to make the first observation and spread the word. Thanks for stimulating and unique case.

Vincenzo Eusebi: Small cell undifferentiated sarcoma consistent with desmoplastic small cell round tumour.

Giovanni Falconieri: Thanks for contributing another phenomenal case! I shall look forward to reading the soft tissue gurus' comment.

Franco Fedeli: Desmoplastic small round cell tumor confined to uterus. I agree this is (an exceptionally rare) example of DSRCT. This case should be considered as an "extraabdominal" example of intraabdominal DSRCT, due to the fact that I believe the qualifier intraabdominal that the original authors coined for this tumor was referring to the serosal-subserosal location and did not intend to refer to visceral location too.

Cyril Fisher: Non-typical morphology, incomplete immunophenotype and unexpected location – very difficult case! Nice demonstration of diagnostic use of both FISH and RT-PCR.

Christopher Fletcher: This is yet another truly unique case – I imagine that the diagnosis would be essentially impossible without the molecular genetic support.

Andrew Folpe: This was (and remains) a spectacular case.

Jerónimo Forteza Vila: Agree with diagnosis. Although it is true that suggests the study of the diagnosis of the sarcoma of endometrial stroma, already the immunohistochemistry points a different way, and the molecular study of the EWSR1-WT1 quimerism confirms the diagnosis.

Masaharu Fukunaga: Great case, thank you very much sharing it and detailed discussion.

Thomas Krausz: Before reading the discussion my main differential diagnosis was between high grade uterine sarcoma NOS and an unusually aggressive looking endometrial stromal sarcoma. Histologically it is

not the classic desmoplastic small round cell tumor but knowing how the morphologic spectrum of this tumor type expanded and having the typical translocation, I have no better diagnosis to offer.

Janez Lamovec: The tumor is definitely not desmoplastic and without cytogenetic studies most difficult to properly diagnose. I thought of rhabdomyosarcoma as my first option.

Thomas Mentzel: What a wonderful case, many thanks indeed.

Michal Michal: I would prefer the diagnosis of low-grade endometrioid stromal sarcoma.

Markku Miettinen: All evidence points to desmoplastic small round cell tumor, although difficult to recognize histologically. Of course, uterine location and keratin-negativity are unusual. There are some reports of "myoid variety of DSRCT", may be this is related.

Elizabeth Montgomery: Gracious! This is really hard with the negative keratin although a WT1 immuno might have helped "up front". The morphology is reasonable for DSRCT "up front" but with the negative keratin it is reassuring that the genetics support DSRCT.

Juan Rosai: I should be able to recognize this entity at the H&E level, but I'm ashamed to admit that in this case I didn't. On the other hand, it is difficult to think of desmoplastic small round cell tumor for a lesion which is not occurring in a young male, which is involving the uterus, which is not very desmoplastic, and in which the tumor cells are not that small. However, it is hard to argue with the molecular genetic findings, although I wonder whether it is right to take entities that were identified on morphologic grounds and redefine them on the basis of some molecular genetic findings regardless of their morphology. Incidentally I have seen another case of "desmoplastic small cell tumor" involving the uterus. That case was even more pleomorphic than the present one (including multinucleated giant cells) and was located in the uterus of an elderly lady! As I remember, the case was from Hopkins and had the right gene fusion.

Dominic Spagnolo: Very clever work-up of what you rightly call an extraordinary case of a unique uterine DSRCT. I have to say I did not consider this at all.

James Strauchen: Desmoplastic round cell! Didn't think of it!

Saul Suster: Histologically does not fit into my concept of DSRCT. Being a skeptic by nature, I would wait until we learn more about the "specificity" of the molecular genetic translocations in these tumors before we start taking them as an article of faith and reinvent the gold standard. We are, after all, starting to discover that some gene fusion partnerships appear to be more promiscuous than previously appreciated.

Lawrence Weiss: I congratulate you guys for getting the diagnosis.

CASE NO. 17 – CONTRIBUTED BY JANEZ LAMOVEC:

Phil Allen: SETTLE metastatic to lung. I initially thought it was a primary or secondary synovial sarcoma but in this case, I believe both the history and the immunohistochemistry are telling the truth.

Carlos Bacchi: I agree with the diagnosis of SETTLE, metastatic to lung. It would be very hard to make this diagnosis without any previous history. I guess that with no history the differential diagnoses would be metastatic sarcomatoid carcinoma and synovial sarcoma. Thanks for the case!

Gerald Berry: Metastatic SETTLE.

David Ben-Dor: Beautiful slide of a great case. The diagnosis was facilitated by this lung tumor presenting not too long after the primary was diagnosed, since from what I just read the tumor can spread after many years, and then a situation can arise similar to what we've seen in these seminars in cases of middle aged or elderly women who present with mysterious lung lesions and only after careful detective work the fact that the patient had for example an ovarian granulosa cell tumor removed becomes apparent. It's interesting the way the tumor insinuates itself between the elements of the host lung tissue without destroying them, as one would expect of a metastasis, thus making the diagnosis more of a challenge.

Michele Bisceglia: SETTLE, metastatic to lung. Never seen one, either SETTLE or a congener of it, either primary or metastatic, except for 2-3 cases from AMR Seminars (a case of SETTLE by Thomas Mentzel in Seminar # 44; a case of ectopic hamartomatous thymoma by Phil Allen in Seminar # 13 which is believed to be probably the possibly benign counterpart of Settle; and a case of ectopic hamartomatous thymoma with carcinoma in Seminar # 17 by Michal Michal). Notice to all members: we do not have a case of CASTLE in our Registry, except for 1 case by Bruce Wenig (Seminar # 23) in which he just included the possibility of CASTLE as one of the differential diagnoses he listed for his case in that seminar. Thank you, Janez for contributing this very rare tumor. I do not express any opinion or comment on this case of yours, since you was "curious to hear from experts in the field" [only].

Thomas Colby: Agree with diagnosis. Have not seen a case like this before. Thank you for sharing it.

Kum Cooper: Thank you, Janez, for this fascinating case. I have seen SETTLE in the thyroid but never in the metastatic context.

Ivan Damjanov: It all fits—good diagnosis.

Otto Dietze: I cannot remember a case of SETTLE in our files and I hope that we did not miss this diagnosis previously.

Hugo Dominguez-Malagon: SETTLE, exceptional presentation with lung metastasis.

Göran Elmberger: That's a diagnosis I certainly need the history to make. Given SETTLE I believe it's quite characteristic. Firstly, the pattern puts the lesion in the group of "biphasic" pulmonary tumors. The challenge here is to realize that this really is a pseudo biphasic tumor with a component of reactive benign alveolar epithelium. This metastatic lesion really invades interstitially compressing remnant structures. IHC is often necessary to reveal this pattern. The differential without the knowledge of primary SETTLE would be broad and include some primary pulmonary tumors such as pulmonary blastoma, carcinosarcoma and SS as well as many metastatic tumors such as LG ESS, benign metastasising leiomyoma and cellular DF. In this case interpretation might be even more difficult noting the isolated focus of atypical adenomatous hyperplasia (AAH) next to the metastasis. The finding of AAH in a young patient like this always makes me wonder. Smoking history? In Sweden we have the world's probably lowest rate of smoking (11 %) in the general population but one problem is young females. What about Slovenia? Thanks.

Vincenzo Eusebi: Case is very remarkable. Glandular mucous producing cells intermingled with spindle cells reminiscent of synovial sarcomas. These features are consistent with SETTLE. Just for fan I would ask for the chromosomal translocation seen in synovial sarcomas.

Giovanni Falconieri: Great case, Janez. We may add synovial sarcoma to the differential diagnosis of SETTLE **.**

Franco Fedeli: SETTLE, metastatic to lung. I have seen a case in its primary (intrathyroidal) site in an Italian slide seminar.

Cyril Fisher: Another amazing case – metastatic SETTLE, pretty rare event.

Andrew Folpe: Very convincing example of SETTLE metastatic to the lung.

Jerónimo Forteza Vila: With the SETTLE diagnosis, it sets out a different diagnosis with the synovial sarcoma.

Masaharu Fukunaga: It is also a tough case, spindle epithelioid tumor with thymus-like differentiation. Thank you for sharing, Janez.

Allen Gown: Interesting case; I wonder if anyone has studied SETTLE tumors with markers such as PAX8.

Thomas Krausz: Before reading the discussion I was considering synovial sarcoma monophasic or biphasic (primary versus metastatic). Jan, thank you very much for treating us to a metastatic SETTLE.

Thomas Mentzel: Again a very rare and exotic neoplasm, thank you very much.

Markku Miettinen: Agree, although not having much experience on this entity.

Liz Montgomery: What a beautiful case. I have very little experience with SETTLE but have not seen a metastasis. The entrapped lung tissue makes it very tough and could have been a real pitfall with the history of a thyroid disease.

Santiago Ramon y Cajal: Very unusual and remarkable case.

Juan Rosai: Here is another case that I should have recognized immediately but I did not. However I would accept the diagnosis offered by Janez, although with a little bit of reluctance.

Dominic Spagnolo: Great case, Janez. I'm convinced!

James Strauchen: Metastatic SETTLE! Didn't think of it!

Saul Suster: Convincing case; had no idea these could metastasize to the lung. Thank you, Janez, for this excellent contribution.

Lawrence Weiss: Wow. I was thinking synovial sarcoma.

Eduardo Zambrano: A few years ago, I saw a case with very similar histology in an 11 year-old boy who showed lymph node metastasis from a SETTLE at initial presentation. He shortly thereafter developed pulmonary metastatic disease, which is rather unusual since, when these tumors metastasize, they do so late in the course of disease.

CASE NO. 18 – CONTRIBUTED BY MICHAL MICHAL:

Phil Allen: Mammary analogue secretory carcinoma of parotid gland containing the ETV6-NTRK3 fusion gene. Amazing. A brilliant piece of work by Dr. Skalova and associates, including Michal.

Carlos Bacchi: Thanks for the case.

David Ben-Dor: A brilliant conjecture proven at the end by genetics. We've all heard the old saw that the breast is nothing but a very big sweat gland, now the salivary gland can be included in this partnership. It will make me wonder the next time I think of an oncocytic lesion of the salivary gland.

Gerald Berry: The resemblance to secretory breast carcinoma is striking.

Michele Bisceglia: Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene. Thank you, Michal. Fine observation. Salivary glands, breast and skin share several tumor entities (adenoid cystic carcinoma, acinic cell carcinoma, oncocytic carcinoma, and lymphoepithelial carcinoma of salivary glands in the breast, cylindroma of the skin or basal cell adenoma of salivary glands in the breast, sebaceous carcinoma of the skin in both salivary glands and breast, ...); this secretory carcinoma you showed us, along with others (e.g., mucinous carcinoma, apocrine carcinoma, ...) are classically seen in the breast, but may also occur in the skin and salivary glands.

Ira Bleiweiss: Agree. Looks exactly like secretory carcinoma of breast.

Thomas Colby: Agree with diagnosis. New entity for me.

Kum Cooper: Thank you, Michal. I read the paper, saw Alena's presentation in Brazil and now I have my own slide!

Ivan Damjanov: I thought this is an acinic cell carcinoma, but I will accept your fancy diagnosis, of course. Maybe it is time for me to hang the cleats and forget about the fusion genes. I was impressed.

Otto Dietze: I will check our acinic cell carcinomas of the last decades ...

Hugo Dominguez-Malagon: Thank you Michal for sharing this case of MASC, a newly described entity described by your group that now can be separated from acinar cell carcinoma.

Göran Elmberger: Michael. Just want to congratulate you and Alena to this fantastic work. Clearly, the event of the year when you presented this at the Florence meeting. When Alena and I gave our salivary gland course in Stockholm last autumn your lab was able to molecularly confirm one of my previous cases. I think it is like with your beautiful description of CAT – once one read your work one start recognizing the entity. I believe there was a Swedish pathologist, Carl Blanck who also recognized this tumor long time ago. I inherited his collection from 100 years of Stockholm salivary gland pathology and he put aside quite a few tumors looking like the MASC tumors in the box of "atypical ACC's". He did not publish the entity and was "before his time". Thanks for showing this beautiful case – a member of a rapidly growing family of translocation carcinomas.

Vincenzo Eusebi: Mammary analogue secretory carcinoma.

Giovanni Falconieri: Difficult case to comment on, Michal. Thanks for contributing another weird salivary gland lesion.

Franco Fedeli: Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene. Indeed it is identical to the (more frequent) mammary counterpart.

Christopher Fletcher: Very convincing secretory carcinoma with the promiscuous fusion gene. I have never personally encountered such a case in this location.

Cyril Fisher: Michal, thanks for the opportunity to have a slide of this remarkable new entity within the ETV6-NTRK3 fusion gene family.

Andrew Folpe: Amazing case. I also gave this one away to one of the junior H/N people. They're going to be big fans of this slide club.

Jerónimo Forteza Vila: Agree with the diagnosis.

Masaharu Fukunaga: It is a great case. Mammary analogue secretory carcinoma of salivary gland. Thank you for sharing it with you, Michal.

Thomas Krausz: Great work. Thank you very much for sharing this case with us. Before reading the discussion I was also considering a variant of acinic cell carcinoma.

Janez Lamovec: It is indeed similar to mammary tumor. I wonder if alpha-lactalbumin was also positive.

Thomas Mentzel: A very interesting neoplasm extending the group of lesions showing a *ETV6-NTRK3* fusion, many thanks.

Markku Miettinen: Nice study, again, difficult to connect with secretory carcinoma, seems to be low-grade.

Liz Montgomery: Beautiful case as is your style. I would have misdiagnosed it as a weird acinic cell carcinoma. Very cool that you have detected the *ETV6-NTRK3* fusion in salivary gland secretory carcinomas.

Juan Rosai: Very nice example of what truly seems a newly recognized entity.

Dominic Spagnolo: A beautiful case Michal, and very instructive – it prompted me to re-read your paper. I don't think I have encountered such a case routinely, or if I have, I misdiagnosed it!

James Strauchen: Fascinating! Salivary mammary analogue secretory carcinoma. Why do they occur in the parotid?

Saul Suster: Excellent pick-up, Michal, and a beautiful paper – congratulations! Thank you for sharing the case with us.

Lawrence Weiss: Thanks for your "glass" illustration of your paper. Congratulations.

CASE NO. 19 – CONTRIBUTED BY MARKKU MIETTINEN:

Phil Allen: Fibrous umbilical polyp. Yet another lesion I probably have missed in the past. It doesn't look much like fasciitis or a desmoid to me. Looking at the slide "blind," I thought it would be a digital fibrous tumor (Reye) without inclusions. Thanks for the enlightenment, Markku.

Carlos Bacchi: It is the first time I see this lesion (fibrous umbilical polyp). Thanks for teaching me.

David Ben-Dor: Another seemingly straightforward entity (or at least something with a straightforward name) for a change.

Gerald Berry: Agree. I do not recall seeing this lesion before.

Michele Bisceglia: Fibrous umbilical polyp. Did not know this could represent a specific entity. Thanks, Markku.

Thomas Colby: Agree with diagnosis. I guess this is a bellybutton button.

Kum Cooper: I recently saw an identical case and did not know what to call it. I may have called it an FEP. Thank you for the education Markku.

Ivan Damjanov: Markku, very good teaching case, thanks. Could I ever be forgiven for not having read the classical paper of Vargas?

Otto Dietze: Sorry, I did not realize this entity before.

Hugo Dominguez-Malagon: Fibrous umbilical polyp, nice case.

Göran Elmberger: Interesting case. God fit with original description 2001. Thanks.

Vincenzo Eusebi: Fibrous umbilical polyp.

Giovanni Falconieri: Agree with the total benignancy of the lesion, although I did not know the entity alluded to. Thanks for this contribution.

Franco Fedeli: Fibrous umbilical polyp. Maybe I have seen a couple of cases which I signed out by instinct and almost in a correct manner, that is as "fibrous polyp", but unaware I was dealing with a true entity.

Cyril Fisher: Fibrous umbilical polyp in infancy, I have rarely seen this.

Christopher Fletcher: Convincing example of fibrous umbilical polyp. The few examples which I have seen have tended to be somewhat more cellular and fasciitis-like but there seems to be a spectrum of cellularity.

Andrew Folpe: Fascinating. I hadn't heard of this entity. Thanks for educating me.

Jerónimo Forteza Vila: Agree with the diagnosis. I didn't know the entity.

Masaharu Fukunaga: I have never seen this lesion, fibrous umbilical polyp. Thank you, Markku. 20. Typical case of sclerosing angiomatous nodular transformation.

Thomas Krausz: This is as new entity for me.

Janez Lamovec: Fibrous umbilical polyp. New to me.

Thomas Mentzel: An interesting organoid looking fibroma-like lesion.

Liz Montgomery: A very cute fibrous umbilical polyp.

Santiago Ramon y Cajal: Curious entity.

Juan Rosai: Another interesting case, which (like case 5) is more impressive clinically and grossly than microscopically. I'm sure that Dr. W D Steck, the famous omphalopathologist (see Cancer 18:907,1965; S.G.O.120:1043,1965), and Dr. Bill Button, the equally famous clinical omphalologist/aspiring omphalopathologist, (see Foraker A G: Job Plodd, Pathologist: His trials and tribulations, Medical Economics Company, 1975) would have enjoyed it.

Dominic Spagnolo: Nice example of a fibrous umbilical polyp. Thanks.

James Strauchen: Thank you! I was not aware of this entity!

Saul Suster: Was not aware this had a name! Thank you for the education.

Lawrence Weiss: Nice case. I had never seen this before.

Eduardo Zambrano: I did my Pediatric Pathology fellowship at Children's Hospital in Boston, not too long after Sara Vargas published her paper, so I was able to review some examples of these intriguing fasciitis-like cases with her at the time.

CASE NO. 20 – CONTRIBUTED BY JAMES STRAUCHEN:

Phil Allen: Sclerosing angiomatoid nodular transformation (SANT) of the spleen. What a magnificent case! Many thanks.

Carlos Bacchi: Great case for a collection. Thanks.

David Ben-Dor: The question is whether it's wise or fair for a surgeon to morcellate when he has no idea what he's morcellating and still expect a diagnosis- but who says life has to be fair?

Michele Bisceglia: Sclerosing angiomatoid nodular transformation (SANT) of the spleen. Beautiful case. Kum (Cooper) also presented a case of SANT in the AMR conference in Istanbul in June 2010.

Thomas Colby: Agree with diagnosis.

Kum Cooper: I like the "how do you recognize your grandmother" connotation! I presented a similar case at the Istanbul AMR meeting. The gross is also fairly distinctive

Ivan Damjanov: Nice, thanks.

Otto Dietze: I have recognized the lesion only in lymph nodes but not in the spleen, thank you.

Hugo Dominguez-Malagon: Spectacular example of SANT, reminds me of intravascular fasciitis.

Göran Elmberger: Thanks for introducing me to grandmother. She is a beauty. Good fit with original description. Mostly nodular but focally also reversed nodular pattern. In the spectrum of IgG4?? Thanks.

Vincenzo Eusebi: Nice case (SANT). Thank you.

Giovanni Falconieri: Thanks for contributing this. To me this is challenging, although I have seen an example circulating through the Ljubljana slide seminars. Lesion fragmentation adds further level of difficulty.

Franco Fedeli: Sclerosing angiomatoid nodular transformation (SANT) of the spleen. A similar case was presented at the 4th Intl AMR Symposium in Istanbul by Kum and I showed the same lesion in Italian slide seminar last year.

Cyril Fisher: SANT, a lovely example and one for the collection!

Christopher Fletcher: Indeed a perfect example of SANT ! I think that the previously suggested association with other significant disease is more likely coincidental and it will be interesting to know how John Chan feels in this regard.

Andrew Folpe: We have seen a number of these here over the past several years. They're really very distinctive.

Jerónimo Forteza Vila: Nice case.

Allen Gown: Thanks for the lovely example of this process.

Thomas Krausz: I agree, this is a very nice example of SANT. Associated calcifying fibrous tumor has been described in some of the cases. Also there is a suggestion about the pathogenetic role of IgG4 plasma cells.

Janez Lamovec: Most characteristic example of SANT! Thank you for this case.

Thomas Mentzel: Many thanks for this wonderful example of SANT (and of course for the funny explanation to your resident). What is the exact relationship to IgG4-related sclerosing disease ?

Michal Michal: Practically identical nodular transformation of the red pulp of the spleen can be sometimes seen in metastatic lobular carcinoma of the breast to the spleen- *Fakan F, Michal M. Nodular transformation of splenic red pulp due to carcinomatous infiltration. A diagnostic pitfall. Histopathology, 1994:25:175-178***.**

Markku Miettinen: Agree on sclerosing angiomatoid tumor of the spleen.

Liz Montgomery: SANT is very nice to see in the spleen. Thanks for sharing this case.

Santiago Ramon y Cajal: Great for the teaching set. Thank you.

Juan Rosai: This one I had no problems in recognizing. It is the kind of process that once you know it, it becomes an instant pattern recognition. I still have some questions about its nature. Originally I thought it was a vascular tumor and called it multinodular hemangioma in the Surgical pathology book (9th Ed., Fig 22-33), but then John Chan convinced me that the lesion is not neoplastic but rather reactive. He is always right, but I would still like to keep the neoplastic pathogenesis option.

Dominic Spagnolo: Beautiful example of sclerosing adenomatoid nodular transformation of the spleen - thanks. There is recent discussion on its relationship to inflammatory myofibroblastic tumors and also to IgG4 sclerosing disease.

Saul Suster: Beautiful example. We must be having an epidemic of SANT in Milwaukee because we have seen several cases here in the past 3 years.

Lawrence Weiss: Classic case. I will use this case to illustrate the entity.

CASE NO. 21 – CONTRIBUTED BY SAUL SUSTER:

Phil Allen: Poorly differentiated carcinoma, anterior mediastinum and large (15 cm), histologically similar tumor, left adrenal discovered five years after the initial mediastinal core biopsy. I think review of the clinical and organ imaging findings are likely to be more helpful than the immunohistochemistry. If the mediastinal tumor was not treated, how big is it now? Is it anatomically centered in the thymic region or could it be a metastasis in a mediastinal lymph node? How did they discover the current adrenal tumor? Are there any other metastases? Et cetera.

Carlos Bacchi: Could this be a thymic carcinoma?

David Ben-Dor: Morphologically it reminds me of a juvenile granulosa cell tumor. It's interesting that you state that negativity for p63 in the new material rules out thymoma so I can only deduce that at the time of the first biopsy this marker wasn't available?

Michele Bisceglia: Poorly-differentiated malignant neoplasm with evidence of epithelial differentiation, NOS. Poorly differentiated carcinoma. Saul, if you consider p63 positivity as a mainstay/prerequisite for considering this tumor as of thymic origin, why don't you consider that the primary tumor (which was p63

negative in a core biopsy) could be p63 positive in other areas (other than the core biopsy)? Any tumor which expresses certain markers as a primary can lose some markers in metastatic deposits.

Ira Bleiweiss: Carcinoma. Unknown primary. I'm no help.

Thomas Colby: Saul, I don't have any problem in some cases just professing my ignorance and I think this is one such case. It appears to be a distinctive example of something.

Kum Cooper: Thanks, Saul. You certainly know how to pick them! I like your thought of a YST. AFP is not very sensitive. Could try glypican-3 which is useful for YST. I would also try OCT3/4 and SALL-4 for germ cell tumor.

Ivan Damjanov: No idea- to me it looks like an endocrine tumor.

Otto Dietze: Sorry, no idea. I presume that TTF 1 was also negative and a low differentiated (retrosternal) thyroid carcinoma has been excluded.

Hugo Dominguez-Malagon: I can´t do better than undifferentiated neoplasm with immunohistochemical evidence of epithelial differentiation. A germ cell origin should be considered because of the age and mediastinal location.

Göran Elmberger: Saul, I don't know what it is. Could it be some odd kind of GCT? Germ cell markers could be added including FISH for i(12p) and tissue id testing using microsatellites. Was also blindly considering some of the renal translocation carcinomas but the localization seems not to be right.

Giovanni Falconieri: Obviously this is quite difficult for me as well, Saul. Phenotypically, this is just a poorly differentiated carcinoma. Remarkable cystic changes are present which, as you mentioned, do not help us to narrow a broad differential diagnosis. Yet, I feel that thymic carcinoma might receive some consideration here, especially based on the clinical history.

Franco Fedeli: Poorly-differentiated malignant neoplasm with evidence of epithelial differentiation, I cannot be more precise. I agree with your considerations.

Christopher Fletcher: I do not recognize this unusual tumour as any specific entity and, like you, Saul, I think that it is best to be descriptive. The fact remains that, among consultation material in particular, there is a substantial subset of tumors which I suspect none of us can meaningfully classify.

Andrew Folpe: Very interesting. If I could invent a pleomorphic, high-grade variant of SETTLE, it might look a lot like this case...

Jerónimo Forteza Vila: Morphology reminds an embryonic tumour, ranging from a carcinoma to a polyembryoma, but there are no criteria to make this diagnosis.

Masaharu Fukunaga: It looks like a poorly differentiated adrenal carcinoma. It is a challenging case.

Allen Gown: Saul, I wonder if a germ cell marker such as SALL4 would be helpful in this case.

Thomas Krausz: I also don't know what this is, but would consider "malignant" SFT with some keratin expression. I assume endothelial markers were negative?

Janez Lamovec: Since I am not an adrenal maven and as I examined this case blindly I thought of some kind of germ cell tumor and even more far-fetched possibility of male juvenile granulosa cell tumor but given the immuno results this is probably not a case.

Markku Miettinen: If not thymoma, then it must be some kind of thymic carcinoma, one of microcystic variety. Cannot believe it is from adrenal origin. Thymic carcinoma markers, such as KIT, CD5 and CD70 and perhaps also mesothelial markers, would be of interest.

Liz Montgomery: I am clueless about a nicer classification for this horrible tumor.

Santiago Ramon y Cajal: I do not know either. My first thought was of tumors mimicking ovarian tumors….. Then I read the patients is a man with a peculiar clinical history. Moreover, inhibin is negative. I have a "déjà vu" but still is not clear for me. Thank you.

Juan Rosai: I don't know what this case is, but I would not discard completely the original hypothesis of a malignant thymic epithelial tumor, as proposed by Saul.

Dominic Spagnolo: I had pretty similar thoughts, Saul – mesothelioma and unclassified sex cord-stromal tumors were high on my list. Too weird for a NUT carcinoma and p63 negative. It doesn't look like an adrenal primary to me. I have no idea what this is.

James Strauchen: No idea! Some of the spaces look vaguely vascular but I assume endothelial markers were negative.

Lawrence Weiss: This does not look like any primary adrenal tumor that I have ever seen. The only wild suggestion of a primary tumor is a malignant transformation of an adenomatoid tumor. I favor that it is a metastasis—of a carcinosarcoma or a funny component of a germ cell tumor. I would handle the case by recommending it be sent to someone else.

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

Phil Allen: Repeatedly recurrent psammomatous meningioma starting at age 15, skull base, infratemporal fossa and temporal bone treated with radiotherapy, and colonic angiosarcoma with pulmonary metastases, female now aged 33. Sorry Paul. Like you, I cannot find any publications describing this odd association and I certainly have never seen it before.

Carlos Bacchi: Nice example of meningioma, psammomatous variant. I am not aware of any relationship between this tumor and angiosarcoma.

Gerald Berry: I saw an identical lesion at frozen section a few weeks ago.

Michele Bisceglia: Indeed this meningioma belongs to the psammomatous variant. I recall only one case of meningioma which was associated with a malignant visceral organ tumor (i.e., renal cell carcinoma). That patient was also affected by littoral cell angioma of the spleen and was contributed in the Club in AMR seminar # 20 (case # 3).

Kum Cooper: Paul, I agree with your assessment. It appears to be WHO Grade I. Not sure of the behavior. She clearly has a problem in her genes

Ivan Damjanov: Psammomatous meningioma.

Otto Dietze: I have no similar personal observation and don't know about this association from the literature.

Hugo Dominguez-Malagon: Completely agree with psammomatous meningioma. The air under de slide cover and the cracking artifacts are a constant feature of psammomatous tumors including diffuse sclerosing PTC.

Göran Elmberger: Haven't heard of that combination. One of a kind? Some unique germline mutation could still be present. Next generation sequencing… Thanks.

Vincenzo Eusebi: Psammomatous meningioma. These cases induce desperation in our technicians as they are difficult to cut with microtome. To remove the calcium they use a drop of citric acid on the surface of the block for a while before using the microtome.

Giovanni Falconieri: My section is not so bad, Paul, and I think I can recognize the lesion. I totally agree with you. We see a number of meningeal neoplasms here, however I cannot recall association with colonic angiosarcoma.

Franco Fedeli: Meningioma, psammomatous variant. I assume the association with colonic angiosarcoma in this case is casual.

Cyril Fisher: Excellent example of (highly) psammomatous meningioma. Not aware of association with angiosarcoma.

Christopher Fletcher: Truly a perfect example of psammomatous meningioma. I have never personally encountered a case in which the patient had developed meningioma and angiosarcoma but such odd combinations are bound to turn up now and again.

Andrew Folpe: Meningioma.

Jerónimo Forteza Vila: I hadn't seen the combination before.

Masaharu Fukunaga: Thank you for sharing the beautiful case, Paul. I have not seen this combination of meningioma and angiosarcoma of the colon.

Allen Gown: Thank you for the nice example.

Thomas Krausz: Nice case. I am not aware of association with angiosarcoma either.

Janez Lamovec: I am not aware of any association of meningioma and angiosarcoma.

Thomas Mentzel: A nice example of a typical psammomatous meningioma, but I have no idea about any relationship to angiosarcoma arising in the GI-tract.

Markku Miettinen: Agree on psammomatous meningioma.

Liz Montgomery: What a pretty meningioma – a nice contrast to the metastatic GIST in case 7.

Juan Rosai: Very typical case. Don't know of any association between colonic angiosarcoma and meningioma.

Dominic Spagnolo: Agree psammomatous meningioma. Am not aware of this particular clinical scenario you describe. The young age of the patient certainly suggests some underlying cancer predisposition. Is there any family history? Li-Fraumeni would not seem to be a candidate – am not aware of angiosarcoma being described in this. But maybe worth looking at p53 gene germline status.

James Strauchen: Very psammomatous!

Saul Suster: Agree with the diagnosis. Am not aware of any association with angiosarcoma. Also, patient must have some unusual genetic makeup because angiosarcoma of the bowel must be an extremely rare tumor. I, at least, have never seen one before.

CASE NO. 23 – CONTRIBUTED BY PAUL WAKELY, JR.:

Phil Allen: Papillary thyroid carcinoma metastatic to the kidney in a male aged 62 with widespread bony metastases. I don't know how one would tell the difference between papillary thyroid carcinoma and papillary renal cell carcinoma on the hematoxylin and eosin stained slide alone. This case illustrates another danger of immunohistochemistry. I too have seen several cases in which the referring laboratory's immunohistochemical results were totally unreliable.

Carlos Bacchi: First time I see a case of PTC metastatic to the kidney.

David Ben-Dor: There are cases of primary carcinoma of the kidney which morphologically mimic thyroid tumor. This case would be the diametrical opposite. When I picked up the slide and before reading the description I did think of thyroid but the nuclear clearing was missing. Obviously knowing the location of the tumor would make one think in the first place of a papillary tumor of the kidney unless one had the history and even then I would think of a kidney tumor. It would also be helpful to have the slides of the thyroid primary on hand.

Michele Bisceglia: Papillary thyroid carcinoma metastatic to the kidney mimicking a primary papillary renal cell carcinoma. I do not have a clue for differentiating papillary thyroid metastatic carcinoma to kidney from primary papillary renal cell carcinoma morphologically. Psammoma bodies are not missing, however papillary renal cell carcinoma (some of them) can show psammoma bodies. I did not find nuclear pseudoinclusions to support thyroid origin, although I did not search carefully for them (but nuclear pseudoinclusions can be seen even in papillary tumors of diverse origin). In conclusion I thin we have to immunostain for TTF1 and/or thyroglobulin in any papillary tumor to make us sure to exclude thyroid. Regarding the frequency of renal metastases from thyroid carcinomas had the opportunity to review the literature up to 2008 and found that about 20 cases, detected clinically, had been reported at that time of both follicular and papillary type thyroid carcinomas, of which only 5 appeared as isolated deposits (Virchows Archiv 2008).

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis.

Kum Cooper: Interesting case Paul. On a pure morphology interpretation the presence of entrapped glomeruli had me favor a metastases. Secondly this appears to be a tall cell variant. The differential would include the eosinophilic variant of papillary renal cell carcinoma (type II) . p504S is also a useful primary papillary renal marker.

Ivan Damjanov: No experience with this problem. Without your additional data I favored a renal papillary carcinoma—just showing you how much of a guessing game this might be.

Otto Dietze: The lack of foam cell to my opinion is suspicious for the diagnosis of a papillary RCC of this size. On the other hand I agree that pap. RCC´s often gives the impression of nuclear morphology like PTC and I remember a case several years ago in our institute, where the other error (metastatic PTC vs. pap.RCC) occurred.

Hugo Dominguez-Malagon: I saw the slide before reading the information, my diagnosis was PTC, one more histological feature that could help in the differential diagnosis is the presence of apocrine (decapitation) secretion that is evident in this case.

Göran Elmberger: History. History. History. Controlled IHC. As long as I'm the lab director at Karolinska we will keep on using multi tissue controls stained with all cases on same slide as well as participating in several external QA programs. Bad IHC is worse than none at all! The case is particularly challenging considering that the cytological features of the tumor are not very typical of classic PTC. More like the columnar cell variant with considerable cytological atypia. Tough differential dx without IHC. Believe you mentioned possible hints. Might add that type II PRCC shows more of hobnailing. Thanks.

Vincenzo Eusebi: Nice case. This is a metastatic papillary carcinoma from thyroid in view of TTF-1 positivity. Primary thyroid-like carcinomas of the kidney are well known. Recently we have seen a metastatic papillary carcinoma to the scalp identical to papillary carcinoma of thyroid. The lesion was TTF1 negative. Then I was told that the patient had a primary renal cell (papillary) carcinoma. What I am saying is that some tumours (especially thyroid & kidney) share similar structure (and hence cytology) but are of different origin.

Giovanni Falconieri: Challenging case, Paul. I agree totally with your assessment. In fact, my first idea was of a primary papillary cancer of the kidney as long as I could not recognize convincing clues for a PTC. The nuclear morphology of this particular case does not reflect the changes we normally expect to see in PTC including grooves or pseudonuclear inclusion.

Franco Fedeli: Papillary thyroid carcinoma metastatic to the kidney mimicking a primary papillary renal cell carcinoma. On morphology I cannot see anything specific that allows me to ascertain the thyroid as the organ of origin in this tumor as well as on the contrary no sign which can let me exclude a renal primary.

Cyril Fisher: Difficult. The nuclear features are good for PTC but as you say not wholly specific.

Christopher Fletcher: I think that it would be extremely difficult to make the correct diagnosis in a case such as this, in the absence of the prior history of a thyroid tumour.

Andrew Folpe: There's no kidney on my slide, so it just looked like a papillary thyroid CA. Don't think I've ever seen one go to the kidney. Interesting.

Jerónimo Forteza Vila: Without previous immunohistochemistry, with the papillary cancer before the tumour of the kidney it is logical to diagnose a renal papillar cancer. It is also understandable that, given the oddity of a thyroid cancer metastatic to a renal cancer, to have done the usual methodology of wide IHQ studies previously to any diagnosis of renal cancer, besides the existence of image techniques, these logic diagnosis will become less habitual.

Masaharu Fukunaga: I prefer papillary renal cell carcinoma only on histology. It is very interesting, Paul.

Allen Gown: IHC using antibodies to PAX8 would not help elucidate this case!

Thomas Krausz: Was the original papillary thyroid carcinoma tall columnar cell variant?

Janez Lamovec: This appears to be an oxyphilic variant of PTC. On H&E, I wouldn't be able to differentiate it from PRCC. Thank you for this case.

Thomas Mentzel: What's for a pitfall!

Markku Miettinen: Agree on metastatic papillary thyroid carcinoma, never saw this in the kidney.

Liz Montgomery: Wow! This metastatic thyroid tumor would be very easy to misdiagnose as renal carcinoma.

Santiago Ramon y Cajal: Very unusual case. Thank you very much!

Juan Rosai: Very cute case. The positivity for thyroglobulin and TTF-1 clinches the diagnosis, which otherwise might have been controversial.

Dominic Spagnolo: How could the immunos have been so discrepant for all the thyroid markers?? Just goes to show one should always verify the brown stains in one's own lab. I don't think on morphologic grounds one could distinguish between PTC and renal papillary carcinoma. In fact, the nuclear features for PTC are completely underwhelming.

James Strauchen: Difficult differential without the immuno!

Saul Suster: Morphologically looks good for PTC, and this is nicely supported by the results of your IHC stains. But in all honesty, would have not been able to recognize it as coming from the thyroid or avoided a diagnosis of papillary RCC if I had not had the history.

Lawrence Weiss: I depend on the history and the immunos, if necessary. Hopefully, they won't let me down (like in this case).

CASE NO. 24 – CONTRIBUTED BY LAWRENCE WEISS:

Phil Allen: Indeterminate cell tumor of the spleen. I hope Dominic Spagnolo agrees with the diagnosis, Larry!!

Carlos Bacchi: Great case of ICT; it is always difficult to diagnose.

David Ben-Dor: These cells do look "indeterminate" in the generic sense, in that it's hard to say in what direction they're going just by looking at them. It's interesting that this tumor is defined as much (or maybe more) by what it *doesn't* stain for immunohistochemically as it is by what it does.

Michele Bisceglia: Indeterminate cell tumor of the spleen. The absence of eosinophils is a clue in differentiating this tumor from Langerhans cell histiocytosis in lymph node (as well as elsewhere) especially if you do not have the antibody for Langerin. Thank you for contributing this nice and unique case in the seminar.

Thomas Colby: Agree with diagnosis. I suspect there are many clinicians out there that think that we make too many diagnoses of "indeterminate cell tumors."

Kum Cooper: Thank you Larry. Read the paper, now see and possess the glass slide.

Ivan Damjanov: You might be right—the IHC supports your view. Low grade malignancy—that is how far I came.

Otto Dietze: Convincing morphology and IHC, congratulation to this first description of a spleen involvement.

Hugo Dominguez-Malagon: Very nice case of undetermined cell tumor with unusual spleen location.

Göran Elmberger: Great case. Seems logical to find the tumor in the spleen. Nuclear morphology not unlike LCH but as you say no eos. An ancestor cell without physiological function or a specific actor in the immune system? Given a skin case I could think of an even more serious mistake than calling it LCH namely calling it malignant melanoma (S100+!). Broad panels important with redundant info as well as broad diagnostic knowledge generating the differential diagnostic list to consider. Thanks.

Giovanni Falconieri: Terribly difficult case. Phenotypically there are barely perceivable features of endothelial differentiation. Never seen something like this. Thanks for this extraordinary contribution.

Franco Fedeli: Indeterminate cell tumor of the spleen. Educational case. Many thanks for sharing this terrific case.

Andrew Folpe: Wow. Glad that was your case.

Jerónimo Forteza Vila: Spleen histiocytic sarcoma. I would label it as a splenic histiocitic tumor, resembling the tumors of interdigitating cells.

Masaharu Fukunaga: It is quite new to me. Thank you very much for the unique tumor.

Allen Gown: Thanks for this interesting case, Larry.

Thomas Krausz: I found this tumor diagnostically challenging. Before reading the diagnosis/discussion I was considering vasoformative and hamartomatous tumors of the spleen. I agree some kind of dendritic cell tumor is also a key possibility. In the light of the comprehensive workout I agree with the diagnosis.

Thomas Mentzel: A rare lesion in an extraordinary rare location, many thanks.

Markku Miettinen: I'm afraid have been calling these hemangioma variants before. Difficult to connect with dendritic cell tumor. Of course, immunophenotype, especially CD1a, suggests otherwise.

Liz Montgomery: Thanks for teaching me about this peculiar lesion that immunohistochemically (but not histologically) resembles Langerhans' cell histiocytosis.

Juan Rosai: I think that Larry has presented a very convincing argument in favor of this tumor of the spleen being of reticular/dendritic cell origin. Perhaps it is the first of this kind in this organ, but better check the first ten issues of the Virchows Archiv (allegedly, everything was already described there).

Dominic Spagnolo: I've not encountered an indeterminate dendritic cell neoplasm in spleen either. Nice case Larry.

James Strauchen: Very nice case! Haven't seen one in the spleen but not surprising if it's the first case!

Saul Suster: Larry – thank you for the education and for sharing this case that you have published previously. Was not familiar with the 'indeterminate" category.

QUIZ CASE #1 – CONTRIBUTED BY BRUCE WENIG:

Phil Allen: Looks like a myofibroma in a 59-year-old to me, but I am troubled by the moderate nuclear pleomorphism. I don't think there is enough in the histology for a diagnosis of myofibroblastic sarcoma, but I would follow the patient carefully.

Reference:
Foss RD; Ellis GL. Myofibromas and myofibromatosis of the oral region: A clinicopathologic analysis of 79 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod (United States), Jan 2000, 89(1) p57-65.
ABSTRACT: The clinicopathologic features of 79 myofibromas or myofibromatosis of the oral and maxillofacial region were studied. The case studies were taken from the files of the Armed Forces Institute of Pathology. The tumors affected 44 males and 33 females (gender was unknown in 2 cases). The patients' ages at diagnosis ranged from birth to 84 years, with mean and median ages of 26.6 and 22 years, respectively. Four patients had infantile myofibromatosis; 2 had extraoral bone lesions and 2 had multiple subcutaneous tumors. In descending order, tumors involved the mandible, tongue, lips, cheek or buccal area, maxilla or palate, pterygomandibular raphae, floor of mouth, and submandibular gland. One third of the tumors affected the bones of the jaws; 12 were central and 15 were cortical or periosteal. All medullary tumors occurred in patients under age 18. On gross examination, the lesions were firm, homogeneous or whorled, white-grey fibrous masses that ranged in size from 0.5 to 5.0 cm. Microscopically, all tumors demonstrated a pattern of nodules or bundles of spindle cells separated by areas of greater cellularity and crescent-shaped vascular spaces. Distinct hemangiopericytoma-like areas were present in 22 cases. Despite apparent circumscription, the tumors commonly infiltrated and entrapped adjacent muscle, nerve, or salivary tissue. Immunohistochemically, 37 of 37 and 39 of 39 tumors stained positively for alpha-smooth muscle actin and muscle-specific actin, respectively, with the former eliciting a more intense reaction. Eight of 8 tumors were weakly positive for CD68, and one case stained focally with S-100 protein. No desmin staining was present in 36 tumors examined. Diagnostic interpretations by the pathologists seeking consultation were malignant or aggressive tumors in 31 cases and other benign conditions in 26. Nine were interpreted as myofibromatosis and 13 offered no interpretation. Thirty-two patients were alive and free of tumor an average of 42 months after initial diagnosis. Four patients had one recurrence each, and 2 had lesions recur twice. Myofibromas are relatively common soft tissue tumors of the maxillofacial region, which have been misinterpreted as malignant or aggressive lesions.

David Ben-Dor: This is a well circumscribed nodular proliferation of spindle cells that I assume are smooth muscle fibers with interspersed irregular vascular spaces. The smooth muscle fibers are in part bland but there are areas of hypercellularity and pleomorphism. However I didn't see any mitoses or necrosis. It looks like a vascular malformation or smooth muscle tumor of vascular origin but the atypia would need to be explained – I wouldn't call it malignant off the bat but how about the ultimate cop-out of STUMP?

Michele Bisceglia: 59-year-old male presented with an enlarging sublingual mass. I think this tumor has myoepithelial differentiation and is malignant. The circumscription, partial encapsulation, focal stromal myxoid changes and hyaline plaques, all suggest the pre-existence of a pleomorphic adenoma. My suggested diagnosis is "myoepithelial carcinoma ex pleomorphic adenoma".

Thomas Colby: ? myoepithelioma, probably malignant; rule out PECOMA.

Kum Cooper: Malignant myopericytoma.

Otto Dietze: Angioleiomyoma.

Hugo Dominguez-Malagon: Looks like a myofibroma with atypia.

Göran Elmberger: I would do IHC! Bizarre fasciculated spindle-epithelioid tumor. First impression is malignant but I have hard time finding mitoses and necrosis. Symplastic? MIB1? Vessel involved? Primary epithelioid smooth muscle tumor uncertain malignant potential? EBV? Possibly SG tumor atypical variant???. Curious.

Giovanni Falconieri: Tough case. It looks like a myoid tumor with focal incomplete capsular infiltration. I have noted bizarre cells but not a terrific mitotic activity. ? Smooth muscle tumor of uncertain biologic potential.

Franco Fedeli: 59-year-old male presented with an enlarging sublingual mass. On morphology and to my eyes this highly atypical tumor shows myoepithelial/myoid differentiation (malignant myoepithelioma?, leiomyosarcoma?).

Christopher Fletcher: Slide labelled case 25 – this appears to be a truly exceptional myofibroma which shows multifocally striking nuclear atypia. I do not recollect seeing a similar case in the past but, since

myofibroma is part of the spectrum of myopericytic neoplasms and since there are undoubtedly malignant myopericytomas, then presumably this might fall somewhere along that same spectrum. However, I think that I would personally be very cautious about predicting the biologic potential of this lesion, since at least some of the atypia may well be degenerative in nature.

Andrew Folpe: Malignant myopericytoma, in areas resembling leiomyosarcoma.

Jerónimo Forteza Vila: Hemangiopericytoma with marked atypical nucleus and sclerosis.

Masaharu Fukunaga: Bizarre vascular leiomyoma. Mitotic figures are rarely observed.

Janez Lamovec: ?Myofibroma.

Thomas Mentzel: The neoplasm looks like a partly intravascular myofibroblastic neoplasm with similarities to myofibroma but with the presence of enlarged and irregular shaped tumour cell nuclei.

Markku Miettinen: Atypical vascular smooth muscle tumor, favor benign. Cannot find mitoses. Complete excision and follow-up would be generally indicated.

Liz Montgomery: Clearly a member of the myofibroma/myopericytoma family of tumors. There is negligible (or no) mitotic activity despite the big nuclei; to me the nuclei are like the big ugly ones in schwannomas and believe this will behave in a benign fashion.

Dominic Spagnolo: Solitary myofibroma, sublingual.

James Strauchen: Oral angiomyoma.

Eduardo Zambrano: This lesion looks myofibromatous to me. There are some scattered large atypical cells, of which I don't know the significance, but I think it otherwise looks like a possible myofibroma.

Bruce Wenig: STUMP. See comment below:

Histology*:* The tumor is submucosal in location (even though surface epithelium is not present) and characterized by the presence of interlacing bundles or fascicles of cells composed of blunt-ended or "cigar-shaped" nuclei with abundant eosinophilic cytoplasm. Marked nuclear pleomorphism is present as are scattered mitotic figures but there is not a marked increase in mitotic activity, atypical mitoses are not present and there is an absence of necrosis. The tumor is nodular and there is no definitive evidence of invasive growth.

Immunohistochemical staining:

- positive for vimentin, smooth muscle actin, muscle specific actin;
- negative for cytokeratins (AE1/AE3, CAM5.2) EMA, S100 protein, CD31, CD34, desmin, caldesmon;
- S100 protein failed to show evidence of neurotropism
- Ki67 (MIB1) – low proliferation rate (approximately 1%).

Differential Diagnosis*:* Smooth muscle tumor of uncertain malignant potential (SMTUMP) versus low-grade leiomyosarcoma.

Discussion: I favored a diagnosis of SMTUMP. SMTUMP is a recognized category among head and neck smooth muscle tumors predominantly identified in the sinonasal tract and less often in other sites (e.g., oral cavity) that in comparison to leimoyomas show increased cellularity, moderate nuclear pleomorphism and the presence of no more than 4 mitoses per 10 high power fields; SMTUMP may be locally infiltrative. Histochemistry:

- cytoplasmic myofibrils can be demonstrated by special stains appearing red with Masson trichrome and blue with phosphotungstic acid-hematoxylin (PTAH).

Immunohistochemistry:

- actin (smooth muscle and muscle-specific), vimentin and desmin positive;
- S100 protein, CD34, CD31 negative;
- MIB-1 index for both leiomyoma and SMTUMP is low (less than or equal to 5%).

Treatment and Prognosis: The treatment for SMTUMP is complete surgical excision which is usually curative. Recurrences rarely occur and likely correlate to inadequate excision.

References:

Fu YS, Perzin KH. Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx: a clinicopathologic study. IV. Smooth-muscle tumors (leiomyoma, leiomyosarcoma). Cancer 1976;35: 1300–8.

Huang HY, Antonescu CR. Sinonasal smooth muscle cell tumors: a clinicopathologic and immunohistochemical analysis of 12 cases with emphasis on the low-grade end of the spectrum. Arch Pathol Lab Med 2003;127:297-304.