COMMENTS TO AMR SEMINAR #50

CASE NO. 1 – CONTRIBUTED BY DAVID BEN-DOR:

Philip Allen: There is an intraepidermal component at the edge of the tumour in my slide and on that the basis, I think it is of epidermal rather than of adnexal origin. I don't think we have enough baseline data to be able to interpret the immunohistochemical results.

Carlos Bacchi: I would also call this tumor as high grade undifferentiated adnexal carcinoma. I would only add one more differential diagnosis poorly differentiated sebaceous carcinoma although the anatomic location is not the best. Thanks David for the case and comprehensive discussion.

Gerald Berry: The vacuolated appearance of the neoplastic cells raised the possibility of sebaceous differentiation but the location is unusual for that. I am left with high grade carcinoma, not otherwise specified; primary versus a metastasis.

Michele Bisceglia: High grade undifferentiated adnexal carcinoma of the skin. Nice case and detailed discussion.

Thomas Colby: Poorly differentiated carcinoma, NOS. consistent with adnexal type. I too wondered about Merkel cell carcinoma on the routine sections.

Kum Cooper: Thanks David for the this interesting case. The Feb issue of AJSP has a paper claiming that D2-40 (podoplanin) distinguishes primary adnexal tumors (+) from metastatic adenocarcinomas (-).

Otto Dietze: I agree, the dysplastic focus in the epidermis is in support of the diagnosis.

Hugo Domínguez-Malagon: Undifferentiated carcinoma, on H&E basis I can not do any better.

Vincenzo Eusebi: Poorly differentiated carcinoma. Metastasis has to be excluded. I would stain the present tumour for chromogranin and synaptophisin. After all, non- Merkel cell neuroendocrine carcinomas primary in the skin do exist.

Giovanni Falconieri: Poorly differentiated carcinoma, not otherwise classifiable. I agree with your assessment, David, and cannot end up with a better definition. I am not sure whether the clear spaces may be either considered evidence of abortive glandular differentiation or artifactual changes.

Cyril Fisher: Undifferentiated carcinoma, consistent with adnexal origin, seems a good diagnosis. Thanks for interesting discussion.

Christopher Fletcher: This lesion certainly looks like a poorly differentiated carcinoma with neuroendocrine features, suggestive of Merkel cell carcinoma – it may be worthwhile to stain the lesion for neurofilament protein and synaptophysin.

Jerónimo Forteza Vila: I had also thought in “Large Merkel Cell Carcinoma” or “Undifferentiated Adnexal Carcinoma”.

Thomas Krausz: I favor a poorly differentiated eccrine porocarcinoma mainly on the basis of the features of the adjacent in situ component.

Janez Lamovec: A solid undifferentiated carcinoma with some basaloid features, perhaps of adnexal origin. I believe that spaces between cells are due to discohesion of cells. On purely morphological ground Merkel cell carcinoma cannot be excluded. In situ lesion at the periphery is in favor of primary tumor.

Thomas Mentzel: In addition to the pleomorphic carcinoma focal bowenoid changes of the epidermis are present, what makes the interpretation even more complicated. Given the lack of obvious squamous, basaloid or neuroendocrine differentiation, the neoplasm is probably best described as pleomorphic carcinoma of adnexal origin.

Markku Miettinen: Agree poorly differentiated carcinoma, c/w primary. Some histologic features raise the possibility of lymphoepithelial carcinoma, although lymphoid background is mild.

Juan Rosai: I agree that the differential diagnosis is between a sweat gland carcinoma and a Merkel cell carcinoma. Although the low power appearance makes you think first of a Merkel, the cytology is not very typical, in the sense that the nuclei have a chromatin pattern which is different from that of the classical Merkel cell carcinoma. Also, this tumor is making focally well-developed glands, which goes along with a sweat gland differentiation.

We should not forget that sometimes these two differentiations go together (Am J Surg Pathol 12: 768, 1998), and the fact that Toker originally interpreted this entity as a form of sweat gland carcinoma, before hitting on the neuroendocrine granules at the EM level.

Dominic Spagnolo: My original thought was Merkel cell carcinoma. I agree with your ultimate interpretation that this is best regarded as an undifferentiated adnexal carcinoma. I have encountered CK7+ Merkel cell CA but never a CK20-CK7+ case.

James Strauchen: Thought of Merkel cell based on the finely dispersed chromatin and numerous mitoses but can't dispute your conclusions.

Saul Suster: Beautiful case, David! I think this is a beautiful example of lymphoepithelioma-like carcinoma of the skin (poorly-differentiated, non-queratinizing squamous cell carcinoma). The nuclear morphology is perfect for this, the syncytial arrangement of the tumor cell islands, and the epidermal compromise all support this diagnosis. There is even some degree of lymphoid infiltration in the stroma, although a significant number of LELCA do not display this feature.

Larry Weiss: Also thought it was a Merkel cell carcinoma, at first look. Nice discussion, and I am okay with the diagnosis of undifferentiated adnexal carcinoma.

CASE NO. 2 – CONTRIBUTED BY OFER BEN-ITZHAK:

Philip Allen: 2A. Probable radiation associated fasciitis (panniculitis) ossificans, left axilla (1997) 2B. Radiation induced osteosarcoma, right pleura (2006), occurring in a patient with nodular sclerosing Hodgkin's disease of retroperitoneum, pelvis and anterior mediastinum (1987), and radiation associated mesenteric fibromatosis (desmoid), 1992. These seem to me to be the most likely diagnoses.

Carlos Bacchi: Fascinating case! In the axillary mass I would favor low-grade malignant mesenchymal neoplasm of unknown histogenesis associated with bone metaplasia. I believe this lesion is very infiltrative, destructive and in some areas the cells are large, epithelioid and somewhat atypical, findings that could justify the possible malignant nature of this lesion. Could the osteosarcoma present in the pleura being arising from ribs or sternum or vertebra with secondary pleura involvement? I can't think about any connection between the pleura and the axillary lesion. It seems to me that they are two different neoplasms.

David Ben-Dor: Interesting confluence of pathologies in this unfortunate patient. The large biopsy (2a from 1997)- at first glance I see long collagen bundles infiltrating the skeletal muscle, which brings to mind fibromatosis. However on higher power one can elucidate a proliferation of plump cells with prominent nucleoli but otherwise not particularly malignant looking. The bone in this specimen looks dystrophic. The second small recent pleural biopsy- agree with the diagnosis of osteosarcoma. This poor fellow has a propensity to develop soft tissue pathologies- whether this tendency is related to the Hodgkin itself or to the treatment is hard to say. Not long ago I saw an article in the New York Times describing the problems faced now by the cohort of children who were treated with modern therapeutic techniques for cancers some twenty years or more ago and have presently come of age.

Gerald Berry: I think that the neoplasms are different, although possibly both related to radiation effect. The osseous component in the axillary soft tissue looks metaplastic while the pleural material looks neoplastic, i.e., malignant tumor bone of osteosarcoma. It is difficult to predict the behavior of the axillary lesion, perhaps recurring potential but unlikely to metastasize unless it were to dedifferentiate. I would expect the pleural lesion to be high grade.

Michele Bisceglia: Postradiation osteosarcoma of the pleura in a patient with previous diagnosis of Hodgkin's disease and probable atypical myofibroblastic cell proliferation with ossification. I would agree on your interpretation of this complex and unfortunate case.

Thomas Colby: I like the axillary lesion as a variant of post-irradiation fibromatosis with ossification. The pleural lesion certainly looks like a sarcoma with bone. This individual's mesenchymal cells did not like radiation.

Kum Cooper: With hindsight and high-grade osteosarcoma of the current pleural biopsy, I think that the axillary mass represents low-grade osteosarcoma (although I initially called it reactive myofibroblastic proliferation with metaplastic bone formation) which has transformed and metastasized to the pleura (given the gross appearance of multiple nodules in the pleura!).

Otto Dietze: I believe that the axillary mass is benign. Myofibroblastic proliferation with ossification is a good interpretation.

Hugo Domínguez-Malagon: Axillary mass: myofibroblastic proliferation with ossification, may call it myositis ossificans. Pleural tumor: osteosarcoma (post-radiation)

Vincenzo Eusebi: A: The pleural lesion is a small fragment of a malignant osteogenic tumour. On the basis of the small tissue sample, it is difficult to be sure if it is a pure osteogenic sarcoma or a fragment of malignant mesothelioma with "sarcomatoid" osteogenic features. B: the axillary lesion is very difficult. The bone material looks atypical to me. In consideration of the fact that the lesion has not recurred for 9 years the proposed name of "atypical myofibroblastic and osteoid proliferation" seems plausible.

Giovanni Falconieri: Rather unusual, I agree. Slide A, fibroproliferative disorder consistent with post radiation fibromatosis and metaplastic bone; slide B suggests osteosarcoma. What the link between, if any?

Cyril Fisher: Axillary tumor appears benign. Might be fibromatosis. Bone is not malignant-looking. Pleural tumor is osteosarcoma.

Christopher Fletcher: I think that I would have called the 1997 left axillary lesion an "atypical myofibroblastic proliferation with osseous metaplasia, best regarded as low grade sarcoma". I believe that the degree of nuclear atypia, at least focally, would necessitate a diagnosis of low grade sarcoma. Having said that, I cannot convince myself that the osseous component shows any convincing features of malignancy. Certainly, however, the more recently identified pleural mass has undoubted features of a chondroblastic osteosarcoma, presumably radiation-induced. Naturally, with the benefit of hindsight, it is tempting to speculate that this represents a metastasis from the axilla, but I do not believe that we have any good evidence to support this possibility.

Jerónimo Forteza Vila: Postradiation mesenteric fibromatosis in independent of pleural lesion; this late lesion is a sarcoma related to radiation, probably a Chondrosarcoma, because we don't see osteoid. We think that it is possible that axilar and pleural lesions were the same process.

Thomas Krausz: On the axillary mass I was considering postirradiation fibromatosis with metaplastic ossification, however focally the cytologic atypia, in my opinion, is too severe, therefore I favor the diagnosis of postirradiation sarcoma. The bone at first sight appears benign/metaplastic, however sometimes bone in soft tissue sarcomas like MPNST with heterologous differentiation may appear benign. Regarding the tumor on the pleura, I favor the diagnosis of postirradiation osteosarcoma of the chest wall. Whether it is a higher grade metastasis from the axillary mass or not, I am not sure. If this neoplasm was a mesothelioma with osteosarcomatous differentiation I would expect at least some keratin expression in the epithelioid cells.

Janez Lamovec: To me axillary tumor looks like fibromatosis. Ossification in fibromatosis was described (J Bone Mineral Res 2005; 20: 1472-7; AJR Am J Roentgenol 2005; 184: 1029-30; Am J Surg Pathol 1987; 11: 66-75). It may well be that both fibromatosis and pleural osteosarcoma are the consequences of radiotherapy.

Thomas Mentzel: That's a very difficult case. Whereas the material from the pleural tumour shows features of osteosarcoma, the axillary mass looks like a low-grade, infiltrating, fibroblastic/myofibroblastic lesion with metaplastic ossification. Did spindled tumour cells stain positively for ß-catenin ?

Markku Miettinen: Osteosarcoma, high grade, probably metastatic in pleura. Consistent with low-grade sarcoma with metaplastic bone. Consistent with being low-grade sarcoma, quite possibly post-radiation tumor. The sampling is small, but there was no convincing osteosarcomatous component in this earlier, axillary tumor. Nevertheless, I think it is fully conveivable that the pleural lesion 2B is metastasis from the axillary one.

Juan Rosai: I think that both lesions represent post-radiation osteosarcomas. The diagnosis is pretty obvious in the pleural specimen but I believe that the axillary mass is too atypical and pleomorphic to be a fibromatosis with calcification. Actually I thought that this was post-radiation osteosarcoma before looking at the pleural sample.

Dominic Spagnolo: Very difficult case. I can't exclude that the axillary and pleural lesions are related (??maybe they were even contiguous with direct growth from axilla to pleura. What happened to the axillary mass over the ensuing 9 years?). On its own, it is difficult to call the axillary lesion malignant but I suspect it was a low grade post-DXT sarcoma all along. In the axillary lesion, the epithelioid cells with neolumina are intriguing - any endothelial markers done?? Hemangioendothelioma with osseous metaplasia can rarely occur, but it seems far-fetched in this context.
I think it most likely that the axillary mass was a low grade post-DXT sarcoma *ab initio*, and there has been progressive high grade transformation of the osseous component to a high grade chondroblastic osteosarcoma in the pleura.

James Strauchen: Pleural osteosarcoma (or sarcomatoid mesothelioma with osteosarcomatous differentiation). Sarcomatoid mesotheliomas don't necessarily stain for cytokeratin or calretinin. There is a literature on mesothelioma following radiation therapy, particularly for testicular germ cell tumors. The axillary lesion strikes me as musculoaponeurotic fibromatosis with osseous metaplasia. I don't believe the two are related.

Larry Weiss: I favor a malignancy for the axillary mass; it is too atypical for benign. I think that the pleural lesion is a high-grade osteosarcoma, and moreover, consider the possibility that it is a metastatasis from the axillary mass. Has this person been evaluated for Li-Fraumeini syndrome?

CASE NO. 3 – CONTRIBUTED BY GERALD BERRY:

Philip Allen: Sarcomatoid variant of anaplastic carcinoma (metaplastic carcinoma) of the left lobe of the thyroid versus primary chondroblastic osteosarcoma. On the basis of the hematoxylin and eosin stain, I would have interpreted the well differentiated glands at the periphery and the few acini inside the tumour as being residual benign thyroid tissue. I suppose that the failure of those cells to stain with TTF1 and thyroglobulin is a point in favor of them being neoplastic. I assume that other sections show less well differentiated, histologically malignant, epithelial components

Carlos Bacchi: Nice example of sarcomatoid variant of carcinoma of the thyroid.

David Ben-Dor: I presume that the slide is from the thyroidectomy specimen (not specifically stated). I assume that the statement about TTF1 being negative refers to the sarcomatoid component and not to the apparently well differentiated glands, or were they also negative? Is this component a residual of the normal thyroid, or was there a pre-existing follicular lesion at the site of the tumor? The glands look rather small and not all of them show colloid clearly. To be honest, before reading the comment with the history and final diagnosis I thought of a malignant mixed tumor of a salivary gland metastatic to a cervical lymph node.

Michele Bisceglia: Sarcomatoid variant of anaplastic carcinoma of the thyroid. Nice example of this tumor. I assume that thyroglobulin and TTF-1 are negative only in the sarcomatoid (mesenchymal) component and would expect that they are positive in the epithelial component, since the differentiation exhibited in these latter peripheral areas is significant.

Thomas Colby: Consistent with sarcomatoid variant of anaplastic carcinoma of the thyroid; the well differentiated epithelial nests are so evenly distributed around the edge that I suspect they are part of the lesion (? well differentiated follicular carcinoma).

Kum Cooper: Thank you for this excellent example of anaplastic carcinoma of the thyroid with heterologous differentiation.

Otto Dietze: Sarcomatoid variant of anaplastic carcinoma; I wonder whether the follicles at the periphery are remnants of a formerly nodular lesion.

Hugo Domínguez-Malagon: Anaplastic carcinoma of thyroid, although is has some unusual features: it looks encapsulated, I do not see infiltration. Apparently is arising from an adenoma.

Vincenzo Eusebi: Sarcomatoid (matrix producing) carcinoma. Are we sure that it is primary in thyroid?

Giovanni Falconieri: Great case, thanks for this extraordinary contribution.

Cyril Fisher: Small carcinomatous component and extensive sarcomatous differentiation, nice case.

Christopher Fletcher: Great example of anaplastic carcinoma of thyroid with heterologous osteosarcomatous differentiation – many thanks. I have not noticed any particular increase in anaplastic thyroid carcinomas at our institution, despite the fact that our thyroid surgery division has been increasing its activity substantially.

Jerónimo Forteza-Vila: Entirely agree with this nice a example of Anaplastic Carcinoma of the thyroid with condroblastic osteosarcoma areas; the perfect delimitation of the lesion suggests the possibility of a metastatic process inside follicular adenoma, but the age and all the data suggest a primary origin. Clinically, the anaplastic carcinoma often arises in the context of a long time nodular hyperplasia even though this information is unknown.

Thomas Krausz: Very nice case. I would have expected thyroglobulin and TTF-1 positivity in the epithelial component, perhaps decalcification explains the negative result.

Janez Lamovec: We see our anaplastic carcinomas of the thyroid mostly in association with longstanding nodular goiter. This, of course, doesn't imply any causal relationship since the latter is quite common in Alpine regions.

Thomas Mentzel: An interesting and I believe rare example of sarcomatoid anaplastic carcinoma with extensive chondrogenic differentiation.

Markku Miettinen: High grade chondroblastic osteosarcoma is a dominant component. This could well represent a metaplastic sarcomatoid component of anaplastic thyroid Ca. Did not see convincing carcinomatous component in the slides. I wondered if the peripheral follicular elements are normal entrapped structures or possible remnants of a follicular neoplasm. Could be difficult to determine.

Juan Rosai: Spectacular case of sarcomatoid thyroid carcinoma with a great prevalence of the osteosarcomatous component. I remember seeing a case many years ago in which the lung metastases were exclusively osteosarcomatous. As usual, this anaplastic carcinoma seems to be arising from a well differentiated follicular tumor.
Most of the anaplastic component actually looks like chondrosarcoma but since there are areas of malignant osteoid being formed directly by the tumor cells, if one were to follow bone tumor guidelines, one would have to think of osteosarcoma rather than chondrosarcoma.

Dominic Spagnolo: Nice example of sarcomatoid anaplastic CA thyroid.

James Strauchen: I would interpret this as a sarcomatoid carcinoma (carcinosarcoma) of the thyroid.

Saul Suster: What we see in the slide is actually a chondroblastic osteosarcoma. Whether this arose from a preexisting thyroid follicular lesion or represents a primary sarcoma arising from thyroid stroma is a matter of opinion. I would have liked to see more convincing areas of transition between atypical follicular elements and the sarcomatous component before accepting this as an example of sarcomatoid anaplastic carcinoma. In other words, I don't see the anaplastic carcinoma in this slide, only osteosarcoma and benign (?entrapped) thyroid follicles.

Larry Weiss: It is interesting that the TTF-1 and the thyroglobulin are negative, when there appear to be some well-differentiated glands at the periphery. Agree with sarcomatoid carcinoma. We are not seeing an increase in anaplastic carcinoma of the thyroid in Southern California—must be your fog.

CASE NO. 4 – CONTRIBUTED BY MICHELE BISCEGLIA:

Philip Allen: Hypoplastic left medullary sponge kidney with intraluminal microlithiasis associated with aneurysms of the splenic artery and left renal artery, abnormal ramifications of the left renal artery and vein and "bilateral dysplasia" of the carotid arteries. Thanks Michele for the encyclopedic discussion.

Carlos Bacchi: Many thanks Michele for this great teaching case of an entity that I was not familiar with.

David Ben-Dor: What is there to add to the exhaustive survey given us?

Gerald Berry: Nice case. We rarely see these except at autopsy.

Thomas Colby: Medullary sponge kidney certainly would fit the histology beautifully in this lovely section.

Kum Cooper: Michele, I had only previously seen gross and radiological photographs of medullary sponge kidney and now I have a slide...thanks to you!

Otto Dietze: Excellent case (like your review from last year), Thank you.

Hugo Domínguez-Malagon: Beautiful case of medullary sponge kidney, nice discussion.

Vincenzo Eusebi: Whatever you say Michele.

Giovanni Falconieri: Thanks Michele for contributing another unusual case of renal pathology and for the accurate historical background of this condition.

Cyril Fisher: Very nice section of medullary sponge kidney. Thanks, Michele, for learned discussion.

Christopher Fletcher: Very convincing case – thanks for the discussion.

Jerónimo Forteza Vila: Thanks. I agree with your diagnosis.

Thomas Krausz: Michele, thank you very much for the superb discussion, I learnt a lot.

Janez Lamovec: As usual, Michele, an erudite discussion on a rare and interesting case. Thank you.

Thomas Mentzel: Thank you very much indeed for the nice case and the excellent comments !

Markku Miettinen: Thank you, excellent case. No further comment.

Dominic Spagnolo: This is as good an example of medullary sponge kidney that I have seen. Thanks for the informative discussion Michele

James Strauchen: Medullary sponge kidney. Very nice case. We rarely see the pathology because it is generally an incidental radiologic finding.

Saul Suster: Very nice example. Thank you for the education.

Larry Weiss: Nice discussion.

CASE NO. 5 – CONTRIBUTED BY THOMAS COLBY:

Philip Allen: Atypical mesothelial proliferation associated with pneumothorax and ruptured giant bulla, right upper lobe, in a patient with malignant mesothelioma of the peritoneum and PET evidence of diaphragmatic involvement. I interpreted this as benign without looking at the history. I showed the sections to Doug Henderson who called it atypical mesothelial proliferation, but by the time he had committed himself, he had read the history. He says he has three cases of unequivocal pleural mesothelioma that appeared to be arising in the region of a giant bulla that presented with spontaneous pneumothoraces. He does not have any like this case with a peritoneal mesothelioma presenting with a spontaneous pneumothorax from a giant bulla.

Carlos Bacchi: In this case Tom, at least in my slide, I had the impression that the tumor cells were present in the lumen of many angiolymphatic structures. Because of this finding I had interpreted that this mesothelioma could be metastatic either from the pleura or from another anatomic location. I was not aware that mesotheliomas could manifest as pneumothorax.

David Ben-Dor: I agree that this is very subtle and likely to be missed by the "average" pathologist. What if one is given a small thoracosscopic biopsy in lieu of the resection specimen provided in this case? There are foci with the lesional cells piling up and forming small papillae, but cytologically they don't look much different from reactive mesothelial cells. The pigmented alveolar macrophages look worse!! Very informative case.

Gerald Berry: I have not seen malignant mesothelioma in the setting of pneumothorax before this case. Nice case that will prompt even closer scrutiny of bleb and bullous resection specimens in the future!

Michele Bisceglia: Malignant mesothelioma (of the pleura) with invasion of the lung, presenting with pneumothorax, in a patient with (concurrent) mesothelioma in the peritoneum. Very subtle diagnosis.

Kum Cooper: At first glance I thought the subtle foci of unusual cells in the lung parenchyma represented type 2 pneumocyte hyperplasia and called the pleural picture one of reactive mesothelial hyperplasia. I have never before seen mesothelioma infiltrate parenchyma with such subtle innocuous foci. So we continue to live and learn! Thanks Tom.

Otto Dietze: Without invasion into the lung I would probably have missed the diagnosis.

Hugo Domínguez-Malagon: Initially I regarded the cuboidal cell proliferation as reactive, but now am convinced that it is a mesothelioma.

Vincenzo Eusebi: Spectacular case. Never seen (actually recognized).

Giovanni Falconieri: Nice case, Tom. The degree of local infiltration is suspicious of malignancy though the diagnostic features are somehow subtle to catch within the inflamed DIP-like background (heavy smoker, no?).

Cyril Fisher: This is a smart diagnosis I don't think I would have made.

Christopher Fletcher: Subtle, but entirely convincing case – I am sure that I would have missed this, too!

Jerónimo Forteza Vila: I agree with your diagnosis. The histologic findings of pulmonary hypertension are remarkable.

Thomas Krausz: I have never seen a case like this before, very educational, probably I also overlooked them.

Janez Lamovec: I had a problem to identify those cells in alveolar septa. On certain moments I think that I see them, but the next minute I am not sure. Very difficult, indeed.

Thomas Mentzel: Whats for a rare and difficult case, many thanks.

Markku Miettinen: Atypical mesothelial proliferation, centered on the pleura. My slide did not show convincing mesothelioma in the lung but I fully believe this could have been a subtle example of one.

Juan Rosai: Very nice case of a malignant mesothelioma. The tumor is so well differentiated as to raise the differential diagnosis with reactive mesothelial proliferation secondary to the pneumothorax. The case is also interesting because of

the intrapulmonary lepidic growth. This case was reported in the Int J Surg Pathol 14:237, 2006. Dr. Rossi had showed me the case when I was visiting his Department: It just happened that somebody else had sent me a very similar case from the United States, so we published them back-to-back in the same journal.

Dominic Spagnolo: How treacherous and disturbing is this subtle invasion by mesothelioma! Off the bat I can't recall a mesothemioma presenting with pneumothorax. I will henceforth pay due respect to those resections for apical bullae.

James Strauchen: Subtle case! Missed this entirely but there is clearly a papillary mesothelial proliferation on the pleural surface. Thank you for this challenging case!

Saul Suster: Very subtle. I would have probably missed it or otherwise banalized it as mesothelial hyperplasia.

Larry Weiss: That is subtle. I will never look at a pneumothorax case quite the same way again.

CASE NO. 6 – CONTRIBUTED BY HUGO DOMINGUEZ-MALAGON:

Philip Allen: Sarcomatoid renal cell carcinoma with chondroid and rhabdomyosarcomatous differentiation, left kidney. I have never seen one of these before, Hugo.

Carlos Bacchi: Thanks for this interesting and rare case Hugo. It is very clear the presence of the two components: clear cell carcinoma and sarcoma (rhabdomyosarcoma).

David Ben-Dor: I use the term sarcomatoid renal cell carcinomas for high grade tumors without verifiying immunohistochemically whether the sarcomatoid areas show true mesenchymal differentiation, so maybe I'm applying the term too loosely. I did see recently a large high grade renal tumor with a focus of what I considered to be rhabdoid cells - maybe these would have been desmin positive if I had made the effort? In the same case I found bundles of benign smooth muscle cells in the stroma- I assume that this is metaplasia of the stroma and not connected to the tumor. Has anyone else seen this? Is the cartilage here malignant? It's hypercellular but not too atypical. If this were in a bone one would of course need recourse to the radiology to decide if it were a chondroma or chondrosarcoma.

Gerald Berry: While we see a number of cases of sarcomatoid carcinoma of the kidney, this is the first I've seen with such florid heterologous elements! Nice case.

Michele Bisceglia: Clear cell carcinoma of the kidney with sarcomatous areas of divergent differentiation (chondrosarcoma, rhabdomyosarcoma). Despite seeing here many renal cancers per year, I have never seen this type of unclassified carcinoma.

Thomas Colby: Agree with diagnosis. I too have not seen rhabdomyosarcomatous elements in a sarcomatoid renal cell carcinoma but I have limited experience, and have not looked very hard.

Kum Cooper: Sarcomatoid carcinoma with heterologous differentiation. I have the rhabdo component in my slide but not the cartilage. Many thanks Hugo.

Otto Dietze: I did not see this phenotype before.

Vincenzo Eusebi: Sarcomatoid carcinoma with clear cell component. I was not able to retrace the rhabdo component. Was it myogenin positive also?

Giovanni Falconieri: Weird case for me Hugo. I also look forward to the renal experts' opinion

Cyril Fisher: Sarcomatoid renal carcinoma, nice case.

Christopher Fletcher: An entirely convincing and quite remarkable case – in my limited experience of sarcomatoid renal cell carcinoma, I cannot recollect seeing heterologous rhabdomyoblastic differentiation in this context in the past.

Jerónimo Forteza Vila: I agree with your diagnosis.

Thomas Krausz: No, I have not seen sarcomatoid renal cell carcinoma with rhabdomyosarcomatous differentiation before. Thank you for submitting it.

Janez Lamovec: I agree with the diagnosis; this tumor must be exceedingly rare.

Thomas Mentzel: Another rare case of sarcomatoid carcinoma with interesting lines of differentiation in the sarcomatoid component.

Michal Michal: The clear cell component looks like it is of urothelial origin (probably arising from the pelvis).

Markku Miettinen: Agree on sarcomatoid carcinoma with high grade spindle cell sarcoma and chondrosarcoma components. Could not pick up rhabdomyosarcoma components, but I believe that they were there.

Juan Rosai: I think that the most likely diagnosis for this renal tumor is that of renal cell carcinoma of clear cell type with sarcomatoid transformation. The hemangiopericytoma-like areas are particularly well developed and made me consider for a second the alternative possibility of hemangiopericytoma/solitary fibrous tumor. However the foci of carcinoma are very convincing and settle the question.

Dominic Spagnolo: Sarcomatoid renal cell carcinoma with heterologous elements. Look forward to the comments of others who see more of these than I do. I don't recall seeing bone and cartilage in a sarcomatoid RCC. Thanks for the case.

James Strauchen: Sarcomatoid RCC with residual clear cell RCC and divergent differentiation. I also considered adult Wilms tumor based on the sarcomatous areas. Very nice case!

Saul Suster: Nice case; don't recall seeing this combination before!

Larry Weiss: Pretty case.

CASE NO. 7 – CONTRIBUTED BY ANDREW FOLPE:

Philip Allen: Multifocal gangliocytic paraganglioma with extensive ganglioneuromatous differentiation, periampullary region, duodenal submucosa, peripancreatic region and in two pancreatic lymph nodes. I concur with your diagnosis, Andrew. Yet another amazing case.

Carlos Bacchi: I was not aware that gangliocytic paraganglioma could be multicentric including involvement of lymph node like in this case. Without reading your discussion I thought the tumor in the lymph nodes was metastatic. Great case, indeed Andrew.

David Ben-Dor: the tumor seems to be very infiltrative, as I see it involving the muscularis (presumably of the duodenum) and percolating amidst the benign glands (ampulla related?). Is this behavior particular to this entity? This lesion can also show areas of carcinoid tumor (according to the description in Weiss) which I didn't see on my examination and weren't mentioned in the comment. Why should this exotic entity have such a limited anatomical distribution compared to regular paragangliomas? Reminds me of reports by zoologists of a certain species of butterfly found in only one tree in Costa Rica. Remarkable case- now that I've seen one I can retire in peace.

Gerald Berry: Agree. Nice case to complement Chris Fletcher's case from a previous AMR submission.

Michele Bisceglia: Multifocal gangliocytic paraganglioma with extensive ganglioneuromatous differentiation with lymph node involvement. I have never seen a similar case in the duodenum (as it also happens with most of the cases contributed in this as well as in many other AMR seminars). I have seen this analogous phenomenon of ganglioneuromatous differentiation only in a few pheochromocytomas (paragangliomas) of the adrenal. The lymph node involvement (multifocal involvement) is intriguing and significant (one has also to think of a frozen section on an involved lymph node). In a certain way the lymph node involvement seems analogous to what we sometimes see in angiomyolipoma of the kidney. And we have to assume that ganglion cells must be present in the (abdominal) lymph node. Moving to a different field of pathology, I take the opportunity to share a recent experience we made here of a primary gastrinoma in a peripancreatic lymph node, which made me aware of the existence of hormonally active neuroendocrine cells in abdominal lymph nodes, an issue (that of primary lymph nodal neuroendocrine tumors) which is well dealt with and referenced in Rosai's textbook of Surgical Pathology.

Thomas Colby: Agree with the diagnosis; amazing!

Kum Cooper: Thank you for this great example Andrew. I have only seen two cases before in seminars but I did not know that they can be multifocal (even in lymph nodes!).

Otto Dietze: Beautiful example of this rare tumor!

Hugo Domínguez-Malagon: The ganglioneuroma component is predominant, the clear cells resemble neurons.

Vincenzo Eusebi: Nice case, but I cannot see the carcinoid-like component.

Giovanni Falconieri: What a case! At a glance this looks a multiphasic neoplasm featuring confluent clear to granular cell cords sitting within organized fascicles of spindle cells. The epithelioid elements have a striking ganglioid appearance.

With the all due respect to the experts' opinion about the benignancy I believe that a long follow up is needed in a case like this, and I would sign this out as a low grade/uncertain biologic potential, at best. In particular, percolating ganglionic cells through the duodenal muscle coat and lymph node location do not speak in favor of a benign lesion. Thanks Andrew for submitting this challenging lesion. I shall look forward to reading the opinion of the other members.

Cyril Fisher: Extraordinary case. I have no experience of this.

Christopher Fletcher: Very convincing example of gangliocytic paraganglioma with lymph node metastasis, which has occasionally been reported in the past – I did not know that these lesions could be multifocal.

Jerónimo Forteza Vila: Agree with gangliocytic paraganglioma. Nice case.

Thomas Krausz: Agree with diagnosis. Very nice case. I think the lymph node involvement is more likely to be direct invasion than metastasis.

Thomas Mentzel: Many thanks for this nice example of gangliocytic paraganglioma with direct extension into an adjacent lymph node.

Michal Michal: Nice case- "gangliocytic paraganglioneuroma".

Markku Miettinen: Fully agree on gangliocytic paraganglioma. I think some wonder if they arise from ectopic pancreatic elements. Seems to invade or push into a lymph node, not a totally typical nodal metastasis.

Juan Rosai: Spectacular case of so-called gangliocytic paraganglioma. The Schwann cell-like areas and the ganglion cell-like areas are more prominent than the neuroendocrine component. The tumor is unusual in the sense of being quite large, invasive, and metastatic to a lymph node, although all of these features have been documented in previous cases. By the way, I have always thought that gangliocytic paraganglioma was a misnomer.

Dominic Spagnolo: Beautiful case of duodenal gangliocytic paraganglioma. Have not seen one involving nodes.

James Strauchen: Gangliocytic paraganglioma, in a lymph node yet!

Larry Weiss: Agree with diagnosis. Holy cow.

CASE NO. 8 – CONTRIBUTED BY GORAN ELMBERGER:

Philip Allen: Malignant basomelanocytic tumour, skin of head. In some areas, the malignant melanoma does not exhibit any basal cell features while in other areas, the basal cell carcinoma component seems to be free of any malignant melanoma. I would interpret these features to suggest a collision between the melanoma and the basal cell carcinoma, with colonization of much of the basal cell carcinoma by melanoma cells. We see lots of basal cell carcinomas and melanomas but I do not think I have seen this appearance before. Thanks for the discussion and the references, which I had not previously read.

Carlos Bacchi: Very nice example of a combined tumor (pigmented basal cell carcinoma and malignant melanoma).

David Ben-Dor: I agree that there are definite areas of basal cell carcinoma and also of melanoma, the latter being seen in the junction and also as a discrete invasive focus. I grant that there are some cellular nests or islands which on H and E look equivocal and can be transitional between the two components; unfortunately I couldn't find the images of the immunostains on the website. There is abundant solar damage (the term "capilitium" is new to me not being a Latin speaker but I assume this refers to the crown or caput) so why can't the sun's rays provoke these two lesions simultaneously? This reminds me of a very nice case presented by Masaharu at one of the AMR meetings, of a melanoma in the toe with an osteosarcoma component.

Gerald Berry: Nice example of a rare lesion in my experience. I wonder if there are collision tumors or tumors of bidirectional differentiation?

Michele Bisceglia: Malignant basomelanocytic tumor of the skin. Thank you for contributing this case. Have never seen one. I also agree on the exhistence of transitional areas. (Parenthetically -speaking of transitional areas- we have quite recently seen here a case of glioblastoma in the brain showing areas of epithelial squamous differentiation).

Thomas Colby: Essentially agree. There appear to be two components (? collision tumor). This looks predominantly like pigmented basal cell carcinoma. I could not access any figures to look at the immunostains.

Kum Cooper: Goran, I have only read about these basomelanocytic tumors. Many thanks for sharing this case. Yes agreed, clearly the melanocytic component will determine the prognosis and outcome.

Otto Dietze: It seems to me that this tumor behaves better than a melanoma of comparable size.

Hugo Domínguez-Malagon: I favor colonization of a BCC by melanoma, there is a BCC nodule adjacent to a recognizable MM in situ.

Vincenzo Eusebi: My section has only a small portion of the tumour with a predominance of BCC and numerous histiocyes loaded with melanin.

Giovanni Falconieri: Another instructive skin! Thanks Goran, for this contribution. I could recognize the 2 distinct lesions, a keratotic basal cell carcinoma and a spindle cell melanoma, arising within an atrophic, sun damaged skin yet I did not know the entity you are mentioning. Hard to say whether this is merely coincidental or, alternatively, a melanoma metastatic to BCC. If the clinicians say that no melanoma elsewhere is (or was) documented, then I would definitely accept this as primary on the scalp.

Cyril Fisher: Basal cell carcinoma/melanoma, striking case, the first I have seen.

Christopher Fletcher: I have seen one previous quite similar, albeit larger, neoplasm and, although I do not usually believe in "collision tumours", nevertheless, it seems to me that, in the setting of such severely sun-damaged skin, then this is simply coincidental colonization of a basal cell carcinoma by malignant melanoma arising in the same site. I do not personally think of these as a single tumour showing bidirectional differentiation but it will be interesting to hear what the skin experts have to say.

Jerónimo Forteza Vila: A collision tumour (Nevus/Basal Cell Carcinoma) must be considered. In any case, morular metaplasia strongly suggests alterations of the Wnt signalling pathway. Nuclear translocation of Beta-Cathenin is probable. Thank your for this nice case.

Thomas Krausz: Beautiful case. Favor collision tumor in view of the extensive radial growth phase of the melanoma.

Janez Lamovec: What a rare tumor! Of course, I have never seen it before but I agree with your line of thought that this is a malignant basomelanocytic tumor. Thank you for giving us the opportunity to see such a rarity!

Thomas Mentzel: An interesting and rare form of a "collision tumour" with focal regression and colonization of the epithelial neoplasm by neoplastic melanocytic cells. We have seen a number of cases of basal cell carcinoma associated with lentigo maligna, lentigo maligna melanoma or superficial spreading melanoma, however, a collision of squamous cell carcinoma with melanoma seems to be very rare.

Michal Michal: The pigmented component of the tumor has an interesting "animal type melanoma" features.

Markku Miettinen: Agree on combined basal cell carcinoma and melanoma. The sections with superficial spreading melanoma component and basalioma was very convincing for the collision tumor; the other section was more difficult and immunohistochemistry would be important to sort out the depth for melanoma.

Juan Rosai: I would go with the term basomelanocytic tumor for this lesion of the scalp, although one could argue for years as to whether the melanocytic component is neoplastic or not. The basal cell carcinoma component is obviously predominant and is so organoid that one could even consider the alternative designation of a skin adnexal tumor.
The areas which are more convincing for a coexistent squamous cell carcinoma are in the basal layer of epidermis and along the base of the pilosebaceous units. The tumor differs from the one we reported a few years ago (Am J Dermatopathol 27: 314, 2005) because the epithelial component is a low-grade lesion, as commented by the contributor.

Dominic Spagnolo: Wow! I have been shown a squamomelanocytic tumor in the last year or so but have never seen a basomelanocytic tumor. I agree with your reasoning and diagnosis. Thanks for the case.

James Strauchen: "Melanocarcinoma"! Arthur Alan (who was married to Sophie Spitz) insisted that malignant melanomas were really derived from keratinocytes and coined the term "melanocarcinoma". Given the divergent embryologic origin of basal cells and melanocytes it seems likely that one proliferation induces the other, akin to the basal cell proliferation and rare examples of basal cell carcinoma associated with dermatofibromas.

Saul Suster: Reminds me of the mixed melanoma/squamous cell carcinoma that was first described by Arkadi Rywlin (Am J Dermatopathol: A malignant neoplasm with features of both squamous cell carcinoma and malignant melanoma; Vol.6 (Supplement):213-219, 1984). The case he reported (for which he coined the term "melanosquamoma") showed true divergent differentiation as demonstrated by simultaneous double labeling with keratin and S-100 in the tumor cells and by demonstration of tonofilaments and premelanosomes within the same cell by electron microscopy. The present tumor I believe is more likely to be a "collision" tumor. Great case!

Larry Weiss: I can't find the immuno figure, and until I see it, I will be skeptical.

CASE NO. 9 – CONTRIBUTED BY GIOVANNI FALCONIERI:

Philip Allen: Russell body gastritis associated with Helicobacter pylori. I too had never heard of it before. A really wonderful case, Falco. Many thanks.

Carlos Bacchi: This is an important case in order for us to be aware that abundant plasma cells with Russell bodies may also be seen in association with chronic inflammation. I believe having some plasma cells with Russell bodies are not an uncommon finding in chronic gastritis. In fact, I have seen cases of chronic gastritis with considerable plasma cells with Russel bodies but not as many as in this endoscopic biopsy. Immunohistochemistry showing polytypic expression for kappa and lambda like in this case is really important as the differential diagnosis with lymphoma including mucosa-associated lymphatic tissue (MALT) with plasma cell differentiation is pertinent.

David Ben-Dor: I had a similar problem a while ago, regarding a man who was diagnosed with large cell lymphoma on gastroscopic biopsies. He subsequently underwent repeated gastroscopic examinations and biopsies which were signed out negative, until I received one which showed groups of these large eosinophilic cells which looked funny until I realized that they were Russell bodies. I then reviewed the earlier biopsies- each one showed a few of these cells which I had overlooked as I assumed they were red blood cells! The conclusion reached (John Chan helped me with this) was that this patient had MALT lymphoma as an underlying condition which was diagnosed only after it had progressed to large cell lymphoma; the MALT persisted in the subsequent biopsies as Russell bodies (which were monotypic) (note for Ofer- this patient apparently has a familial condition and I sent material from this case to your hospital as part of the investigation; maybe you reviewed it). I didn't know that Russell bodies can be seen in the stomach as part of a benign inflammatory condition and certainly not as profusely as here. The problem I had was the converse- they may be difficult to pick up if not numerous. The polytypic nature of the cells here means that they themselves cannot be diagnosed as neoplastic. The slides I got were very nice and amply demonstrative- I think it takes some courage to try and submit a small biopsy case to the group; I wouldn't have dared.

Gerald Berry: I haven't seen this degree of Russell body change in a gastric biopsy. Perhaps I have missed more subtle cases!

Michele Bisceglia: Russel body gastritis. Nice case. Have seen two such cases in the past; one in reactive and one in a lymphomatous (Maltoma) condition.

Thomas Colby: Not sure. Most of the eosinophilic cells don't really look like Russell bodies to this rusty old hematopathologist. I have a case of Sjogren's syndrome in the lung with morphologically similar cells that were clonal. Some of the pink material looks like immunoglobulin crystals. There do appear to be a few separate appearing rounded globules looking more like Russell bodies.

Kum Cooper: Thank you Falco. How does one distinguish this from crystalline histiocytosis? Are these plasma cells in RBG? There are a few that look like Mott cells. What about CD 38 or CD 138 and a CD 68 or CD 163?

Otto Dietze: I remember several cases with a minor degree of Russell bodies but did not use this diagnosis without endoscopic abnormalities.

Hugo Domínguez-Malagon: Fantastic case, I was unaware of the entity "Russell Body Gastritis", thank you.

Vincenzo Eusebi: Very nice case. Never seen such extent of RB in the stomach.

Giovanni Falconieri: My case. The patient received H. Pylori eradicating-therapy and her symptoms improved. A new gastroscopy was basically negative. Examination of a re-biopsy specimen from the antral mucosa was totally negative. This may lend further support to the view that H. Pylori infection might be more than coincidentally associated with RBG.

Cyril Fisher: Another thing I have not seen before! What amazing material we see in this Seminar.

Christopher Fletcher: Remarkable case, the like of which I have not personally seen previously – I would first have thought of crystal-storing histiocytosis, but I suppose that the polytypic staining for immunoglobulins rules this out.

Jerónimo Forteza Vila: I agree with your diagnosis. Thanks for this unusual case.

Thomas Krausz: My differential diagnosis on H&E also included crystal-storing histiocytosis.

Janez Lamovec: I saw once quite a similar accumulation of Russell's bodies in a case of lymphoplasmacytic lymphoma of the stomach presented by Dr. Lennert at a slide seminar on lymphomas.

Thomas Mentzel: I`ve never seen this interesting phenomenon.

Markku Miettinen: Never saw this before. This reminded me of "crystal storing histiocytosis", a lymphoplasmacytoid neoplasm. Clinical correlation and work-up is probably necessary to determine the significance of such lesions; your work-up seemed to show plasma cell polyclonality.

Juan Rosai: Spectacular case of Russell body gastritis. The case is almost identical to the one recently reported by Ricardo Drut, from Argentina (Int J Surg Pathol 14:141, 2006).

Dominic Spagnolo: Thanks Giovanni for this case of Russell body gastritis. A colleague and I wrote up 3 similar cases last year *(J Clin Pathol 2006; 59:851-854. Crystalline plasma cell inclusions in Helicobacter-associated gastritis. Stewart CJ & Spagnolo DV).* These changes can also occur as a much more subtle phenomenon in contrast to this dramatic appearance.

James Strauchen: Very informative case! I assumed (wrongly) that cytologically monotonous Russell bodies implied monoclonality, but apparently it does not. Thank you for this dramatic example!

Saul Suster: Have never seen this before! Great case.

Larry Weiss: I must have gotten one of the good slides, because it is beautiful. If it is polytypic, it is benign for me.

CASE NO. 10 – CONTRIBUTED BY GIOVANNI FALCONIERI:

Philip Allen: Focal nodular hyperplasia of the liver with sarcoid-like epithelioid granulomas. I am no good on livers, Falco, and greatly appreciate seeing this case as a rather old student.

Carlos Bacchi: Great example Falco of focal nodular hyperplasia of liver. I was puzzled by the presence of granulomas including some eosinophils. Could this be associated with parasitic infection where the organism (at least viable) is not present in this material?

David Ben-Dor: nice slide- what's wrong with showing a classic slide of a known entity for a change? Personally I was glad to see this, as not long ago I had a needle biopsy from a liver mass in a youngish woman about which at the beginning I couldn't say much more other than that it wasn't a malignant tumor; it was only when the clinician asked me specifically whether it was fibrolamellar carcinoma that I thought it through and realized that it could be FNH, as the biopsy showed the fibrosis as well as the irregular proliferation of the bile ductules. In this day and age sometimes it's a luxury to have such a nice excisional biopsy sample in which one can see all the diagnostic components of a lesion!! I also recall a different case of a liver mass in a woman the biopsy of which showed only bland liver trabeculae without the fibrosis or bile ductule proliferation which I interpreted as a possible adenoma; the patient went to a different hospital where, according to what her clinician later told me, it was decided that it was FNH. Since it was very large it was decided to leave it be. The needle biopsy presentation of this entity can be confusing since it may not sample all components. I didn't see the granulomas on the slide I got.

Gerald Berry: Was there any other clinical evidence of sarcoidosis? I agree with the diagnosis.

Michele Bisceglia: Focal nodular hyperplasia of the liver with sarcoid-like granulomas. Classic type of FNH. Never seen granulomas in this condition. However speaking of this condition (FNH) I would like to briefly focus on one of the variants you mentioned of FNH, i.e., the telangiectatic FNH. This latter variant was first recognized in December 1999 by a French group led by C. Degott (your ref. Nguyen BN, et al, AJSP 1999). This variant is a special one, and is currently better considered a liver cell adenoma variant ("Paradis V et al. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology. 2004;126:1323-9; Paradis V who is a pathologist is from the same center of C. Degott and is a coauthor in your ref Attal P, et al, Radiology 2003). However, some people call this latter adenoma variant as progressive focal nodular hyperplasia (Sadowski DC, Lee SS, Wanless IR, Kelly JK, Heathcote EJ. Progressive type of focal nodular hyperplasia characterized by multiple tumors and recurrence. Hepatology 1995;21:970-5). The telangectatic variant of liver cell adenoma is not widely known and recognized. Diagnostic criteria of differentiation (FNH vs adenoma, conventional and variant) can also be found in J Hepatol January 2007 (Bioulac-Sage P, Balabaud C, Bedossa P, Scoazec JY, Chiche L, Dhillon AP, et al. Pathological diagnosis of liver cell adenoma and focal nodular hyperplasia: Bordeaux update). I was fully immersed for months in a case of FNH which I simply call FNH in March 1999 before the telangectatic variant was identified: the case came back since the patient after 7 years developed another liver lesion which was recently diagnosed as liver cell (conventional) adenoma with features of multinodular adenomatosis (both liver cell FNH and adenoma can be multiple and can cohexist). It is likely that I will be contributing soon the case I just mentioned here, as a complement of the classical form of FNH you contributed here.

Thomas Colby: Agree with diagnosis. I wonder if this patient actually might have sarcoidosis and the FNH is the incidental finding.

Kum Cooper: Thanks again Falco. Great teaching case: FNH with granulomatous hepatitis. Was the patient on any medication?

Otto Dietze: Interesting "subtype" of FNH, I did not see granulomas limited to the lesion before.

Hugo Domínguez-Malagon: Agree with the diagnosis of focal nodular hyperplasia of the liver, I never seen one with granulomas.

Vincenzo Eusebi: Nice case.

Cyril Fisher: Focal nodular hyperplasia of liver with granulomas, another great case.

Christopher Fletcher: Beautiful example of focal nodular hyperplasia – I have not seen granulomas in these lesions in the past.

Jerónimo Forteza Vila: Thank you very much for this interesting case. I agree with you diagnosis.

Thomas Krausz: Very nice example. As the adjacent liver also shows granulomas I think that the granulomas are relevant. It does not look PBC, but sarcoidosis or infective cause should be excluded clinically.

Thomas Mentzel: Thanks for the "unexplained" association of focal nodular hyperplasia of the liver with multiple granulomas.

Juan Rosai: Spectacular case of focal nodular hyperplasia of liver. It is remarkable how much the lesion resembles cirrhosis. No wonder that an old synonym for it is focal cirrhosis. As far as the granulomas are concerned, I suppose one could call them sarcoid-like, although they are certainly not the typical sarcoid granulomas, which are smaller, more homogeneous and primarily composed of epithelioid histiocytes. They remind me of the granulomas seen in splenectomy specimens in the nebulous condition known as Stengel-Wolbach splenomegaly (which may be a variant of sarcoidosis) (Arch Pathol, 98:261, 1994).

Dominic Spagnolo: I agree with your diagnosis of FNH and non-necrotizing granulomatous hepatitis. Have never seen this association nor seen it mentioned.

James Strauchen: Focal nodular hyperplasia of the liver. One school of thought regarding epithelioid granulomata in association with other disorders (lymphoma, following Hodgkin's, etc.) is that all of these patient's actually have co-existent sarcoid!

Larry Weiss: Classical histologic findings.

CASE NO. 11 – CONTRIBUTED BY MASAHARU FUKUNAGA:

Philip Allen: Perivascular epithelioid cell tumour (PEComa) of the uterus. I looked at the slide "blind" and thought it was a fat-free angiomyolipoma, so it must be a PEComa. Thanks for the contribution, Masa.

Carlos Bacchi: Agree with the diagnosis of PEComa. The close relationship of the tumor cells with the vessel wall is really striking and shows us where the cells are probably coming from. Taking in account the hypercellularity, the presence of coagulative necrosis and the infiltrative growth pattern, I believe this case has malignant potential.

David Ben-Dor: The intimate relationship to the blood vessels is nicely demonstrated here and could be the tip off for the diagnosis, which I presume is clinched by the immuno findings. But if malignancy is judged by the standards applicable to uterine smooth muscle tumors, I don't think this tumor would make the grade.

Gerald Berry: I showed the case to Dr. Kempson who agreed with the diagnosis. He pointed out foci of tumor cells that are closely associated with small arteries as a key diagnostic feature.

Michele Bisceglia: Perivascular epithelioid cell tumor (PEComa) of the uterus. Agree on the diagnosis of Pecoma in this uterine case. Regarding criteria for predicting behaviour I would refer to the paper by Bonetti F on malignant PEComas of the pelvis (Bonetti F, Martignoni G, Colato C, Manfrin E, Gambacorta M, Faleri M, Bacchi C, Sin VC, Wong NL, Coady M, Chan JK.Abdominopelvic sarcoma of perivascular epithelioid cells. Report of four cases in young women, one with tuberous sclerosis. Mod Pathol 2001 Jun;14:563-8). Look forward to Elvio Silva's opinion. Parenthetically, even such (uterine) cases may also occur in the clinical setting of tuberous sclerosis complex.

Thomas Colby: PEComa or reasonable facsimile thereof. The prominence of peculiar vessels made me wonder about a fatty poor angiomyolipoma.

Otto Dietze: I agree with the diagnosis and believe that due to the size and the infiltrative growth it might be of low malignant potential.

Hugo Domínguez-Malagon: PEComa, uncertain malignant potential.

Vincenzo Eusebi: I agree with the diagnosis of PECOMA. Dr. Bonetti tells me that this tumour in the uterine wall, looks like something in between a leio and stromal tumour. The uncertain malignant potential is a good option.

Giovanni Falconieri: I agree with your assessment, Masa. I would also say Pecoma, since both morphology and the immunoprofile fit well. Prognostic predictors of Pecomas are still difficult to understand as long as this tumor category is likely not well defined. We have recently seen a case of "Pecoma" showing an extensive growth over the peritoneal surface simulating a mesothelioma in an elderly woman. Fair nodules were present within the pelvis, including the peritoneal surface of the uterus and the broad ligament. Despite extensive intra-abdominal tumor growth the patient has been fine for > 1 year with no additional therapy.

Cyril Fisher: PEComa seems good!

Christopher Fletcher: Combining your finding of HMB-45 positivity with the strikingly perivascular growth pattern, then I think that the diagnosis of PEComa is entirely justified, albeit the tumour cells have less prominent granular or clear cytoplasm than seen in most cases. In my experience, necrosis alone does not reliably predict malignancy and more convincing features would tend to be the presence of pleomorphism and a high mitotic rate – however, we are all still learning about these lesions.

Jerónimo Forteza Vila: I agree with your diagnosis. Many thanks.

Thomas Krausz: Agree with diagnosis. The relationship of the tumor cells with the vessel wall is very similar to that seen in PEComas at other sites.

Janez Lamovec: PEComa. Nice case.

Thomas Mentzel: A very nice example of atypical/malignant PEComa of the uterus.

Markku Miettinen: Fully agree with PEComa. Perivascular, angiomyolipoma-like pattern, clear cell features and epithelioid cytology are all good for this. Quite likely an ER/PR positive tumor, some seem to consider uterine PEComas just variants of GYN smooth muscle tumors.

Elvio Silva: A uterine tumor with round to polygonal cells forming fascicles, positive for smooth muscle actin and caldesmon is a smooth muscle tumor. There are already several studies, the last one on Am J Surg Pathol 31:95-98,2007, showing that in 30% of uterine smooth muscle tumors the tumor cells can be positive for HMB-45. This is not enough reason to designate the neoplasm as a PEComa. I also believe that we should not call any tumor a PEComa because this term has been created for a group of tumors. In addition, the PE cell has only been recognized in tumors. I believe nobody has reported the presence of normal PE cells (even Dr. Bonetti who proposed this concept). Today we know that in these lesions the cells positive for HMB45 frequently are neither perivascular nor epithelioid. I do not negate the concept of PEComa but I believe it refers to a group of tumors, and smooth muscle tumors are one of these lesions. Most probably even Dr. Fukunaga will report an angiomyolipoma of the kidney as such and not as a PEComa. Uterine smooth muscle tumors should not be different.

Juan Rosai: Good case of PEComa. The presence of necrosis and focal mitotic activity would have been of concern if this had been a smooth muscle tumor, and I think they remain of concern even with the diagnosis of PEComa. Therefore I agree in placing this tumor in an uncertain malignant potential category.

Dominic Spagnolo: I agree with your diagnosis of uterine PEComa, and would also regard this lesion as having uncertain malignant potential.

James Strauchen: PEComa. Very nice case!

Larry Weiss: Without Melan-A staining, I would go with smooth muscle tumor with clear cells.

CASE NO. 12 – CONTRIBUTED BY THOMAS KRAUSZ:

Philip Allen: Undiagnosed, large (7.8 x 2.6 cm), histologically alarming, congenital, spindle and round cell, S100 and EMA positive tumor with focal SMA, MSA, and desmin positivity, melanin containing cells and numerous dilated vessels, subcutis and dermis, scalp. I don't think this tumour has much in common with the published cases of neurocristic cutaneous hamartomas, but I don't know what it is. If any fresh tissue becomes available, cytogenetic studies may help.

It might be a peculiar, undescribed variant of congenital fibrosarcoma. This possibility could also be investigated if a probe for congenital fibrosarcoma is available.

Carlos Bacchi: I have no diagnosis in this case. It seems to me that this is a primitive embryonal-type of malignant neoplasm.

David Ben-Dor: I won't be of much help. The lesion seems to be dominated with large vessels which are surrounded by what looks like undifferentiated stroma. I did find one focus of what looks like a small nerve ganglion, otherwise I have trouble making out the different types of tissues which Thomas says are present based purely on morphology.

Gerald Berry: I was not aware of this lesion. Are they related to the melanotic progonoma?

Michele Bisceglia: Congenital neurocristic cutaneous hamartoma of the scalp. Never seen one. Should be in the spectrum of the entity as you indicated.

Thomas Colby: Sounds good to me; elegant discussion Thomas.

Otto Dietze: I did not see a similar lesion before. The diagnosis and the discussion is impressive.

Hugo Domínguez-Malagon: Difficult case; I was unaware of the entity of neurocristic cutaneous hamartoma. Thank you.

Vincenzo Eusebi: I like the interpretation of neurocristic cutaneous hamartoma. No meningothelial elements are present.

Giovanni Falconieri: Out of my reach!

Christopher Fletcher: This is a very unusual and difficult case and, to me at least, it is hard to know how best it should be classified. It seems more complex and also more atypical-looking than most of the lesions which have previously been reported as neurocristic hamartoma. Was there any positivity for melanocyte antigens in cells other than those which are pigmented? It will be very interesting to learn how this very extraordinary lesion behaves.

Jerónimo Forteza Vila: Many thanks for this nice case. I have no experience about this entity.

Thomas Krausz: Following the submission of the case I received additional histologic material, which focally (in one block) showed also intraepidermal/junctional melanocytic proliferation, therefore congenital nevus with heterologous mesenchymal differentiation is an alternative diagnostic consideration. The referring pathologist still assures me that clinically the lesion, even though it was covered by skin, did not look like a nevus.

Janez Lamovec: To me, certain structures in this strange hamartoma resemble meningothelial nests.

Thomas Mentzel: A biologically very interesting and unusual case, and unfortunately, we have not seen (or missed) an example of this rare entity.

Markku Miettinen: Would favor a designation as a neoplasm, primitive neuroectodermal (non-Ewing). A small pigmented component is also present.

Juan Rosai: I agree that this lesion of the scalp fits the description of neurocristic cutaneous hamartoma, although I must admit I don't quite understand the rationale behind that term. It seems to be one of various kinds of bizarre lesions that develop in giant congenital nevi and which one often is in trouble in deciding how to call. From a biologic standpoint I think it is a borderline/low grade type of tumor.

Dominic Spagnolo: Thomas, I don't know what this is. I don't much like it for cutaneous neurocristic hamartoma. It is cellular, pleomorphic and mitotically active, and I think it is probably malignant. I was considering some form of malignant neuroectodermal tumor. Even atypical teratoid/rhabdoid tumor crossed my mind. But I guess I am way out of my depth.

James Strauchen: Never heard of this one! Seems to be part of the spectrum of congenital melanocytic nevi. Thanks for this informative case.

Saul Suster: This looks more mesenchymal than "neurocristic". The lesion is too cellular and too atypical for a benign condition. I would suspect at least low-malignant potential. How about a totally new entity? The bizarre immunophenotype does not seem to fit for any of the previously described examples of neurocristic hamartoma.

Larry Weiss: I cannot help out with the diagnosis of this tumor; I have never seen anything quite like it.

CASE NO. 13 – CONTRIBUTED BY THOMAS MENTZEL:

Philip Allen: Recurrent polymorphous sweat gland carcinoma, dermis and subcutis, chest wall. I agree with Thomas' diagnosis and anxiously await Saul's verdict. The tumour seems to have been inadequately excised.

Carlos Bacchi: My first impression in this case was of a malignant eccrine spiradenoma but I would rather wait to hear Saul's and other member's opinion in this case.

David Ben-Dor: The overall architecture with the dispersal into the fat does make this suspicious for malignancy, but on high power it looks rather bland. Most of it looks like a spiradenoma.

Gerald Berry: Agree with the diagnosis of polymorphic sweat gland carcinoma but defer to Saul on this one!

Michele Bisceglia: Polimorphous sweat gland carcinoma of the skin. Agree.

Thomas Colby: Favor low grade carcinoma, polymorphous sweat gland type sounds good.

Otto Dietze: Good case & diagnosis.

Hugo Domínguez-Malagon: Fascinating case, it even resembles PLGA of salivary gland.

Vincenzo Eusebi: Polymorphous (for what it means) sweat gland carcinoma is an honorable compromise. Usually this group of lesions in salivary glands and breast are BCL2 positive.

Giovanni Falconieri: History indicates a low grade, recurrent adnexal tumor of skin, yet no idea about the name.

Cyril Fisher: Consistent with polymorphous sweat gland carcinoma, very nice case, thank you, Thomas.

Christopher Fletcher: To me, sweat gland carcinomas show such remarkably variable morphology and such different proportions of often different components, that I find their reproducible classification very difficult and I find that the associated published literature is very confusing. It seems to me that there is very little consensus regarding the best classification of many skin adnexal neoplasms and I have always dreamed that dermatopathologists might get together to solve this problem – however, the problem of lesional heterogeneity may simply be too large.

Jerónimo Forteza Vila: I agree with your diagnosis. Nice case.

Thomas Krausz: It is difficult to classify. I have no better diagnosis to offer.

Thomas Mentzel: My case.

Markku Miettinen: Agree on low-grade carcinoma, these might sometimes go under "malignant mixed tumor". Thank you for updating me on this.

Juan Rosai: I agree that this is a spectacular example of sweat gland carcinoma combining a variety of patterns, one of them been adenocystic (not to be confused with adenoid cystic carcinoma).

Dominic Spagnolo: Polymorphous sweat gland carcinoma seems to be appropriate. Have never seen this before.

James Strauchen: I recognized the appendage nature of this case but got no further. I must admit it looked benign to me, but I will defer to the experts. What has the follow-up been?

Saul Suster: I agree with the diagnosis of polymorphous low-grade carcinoma. It shows the variegation of patterns that we reported in our study with T-Y Wong, including adenoid cystic-like areas, carcinoid-like ribbon areas, and solid areas.

Larry Weiss: It would be very interesting to see the histology of the lesion from 12 years ago.

CASE NO. 14 – CONTRIBUTED BY ELIZABETH MONTGOMERY:

Philip Allen: Post colonoscopy perforation of ascending colon in collagenous colitis. I initially missed the collagenous colitis, but there is no doubt it is present. Thanks for this excellent case, Elizabeth.

Carlos Bacchi: This is a hard one! I had great difficult in finding the thickening of the subepithelial collagen in my slide.

David Ben-Dor: Of course this begs the question as to why the perforation occurred in a totally different part of the colon? Is this related to what the chaos theoreticians talk about, a butterfly flapping its wings causing a volcano to erupt halfway around the world?

Gerald Berry: I was not aware of the risk of perforation in collagenous colitis. Nice example and discussion.

Michele Bisceglia: Mucosal tear / "fractured colon" in collagenous colitis with perforation. Was not aware of this risk in this condition. Further, it is likely I would miss the diagnosis in this case. Will be alerted about this diagnosis any (luckily rarely) time a perforated colon following colonoscopy arrives.

Thomas Colby: Very interesting case. I initially missed the features of collagenous colitis at the surface and thought that the ischemic change was likely secondary. A very instructive case. It reminds us that fractures of all types occur in individuals of this age (93 years).

Otto Dietze: I was not aware of this complication before, thank you.

Hugo Domínguez-Malagon: Extraordinary case, I was unaware of the entity "mucosal tear/fractured colon" in collagenous colitis. Thank you

Vincenzo Eusebi: Interesting case.

Giovanni Falconieri: Nice case. Thanks for this unusual contribution and the references.

Cyril Fisher: Collagenous colitis. Thanks for interesting discussion.

Jerónimo Forteza Vila: I agree with your diagnosis. I have not had any similar case, although this is a relatively common diagnosis in our hospital.

Thomas Krausz: I was not aware of this association. Highly educational case. Thank you.

Thomas Mentzel: I`ve found it very difficult to establish the diagnosis of collagenous colitis on the submitted slide.

Markku Miettinen: Necrotizing acute inflammation. Your explanation on pathogenesis sounds interesting. Could not see perforation point in the slide, but perforation is a logical reason for this process.

Juan Rosai: I'm afraid I would have missed the collagenous component in this colonic specimen. I would have probably naively thought of an abscess possibly secondary to a ruptured diverticulum.

Dominic Spagnolo: What a dramatic case of perforation in collagenous colitis. The histology looks like a severe phlegmonous colitis that occurs in patients with chronic liver disease.

James Strauchen: I totally missed the collagenous colitis with all the surrounding abscess formation! "Fractured" colon has a very nice ring to it!

Saul Suster: I would have missed the collagenous colitis (you can tell I'm no GI pathologist!). Thanks for this interesting contribution.

Larry Weiss: The subepithelial collagen table was about the last place I thought of looking at in this case. Thanks for bringing this phenomenon to my attention.

CASE NO. 15 – CONTRIBUTED BY CESAR A. MORAN:

Philip Allen: Mixed epithelial and stromal tumour, right kidney. Just as well you circulated this case Cesar. I keep on forgetting it.

Carlos Bacchi: Nice example of mixed epithelial and stromal tumor (MESTK).

David Ben-Dor: Thanks!! The membership of the AMR contains a rare concentration of academic firepower expert on this entity (since Michal was the first to propose it). The seeming simplicity of the structure (whose components including the ovarian stroma are nicely demonstrated) seems to belie the complexity of its genesis and accords it a place in the firmament of renal stromal-epithelial malformations/tumors. Michal and Michele deserve great credit for their contributions in elucidating and reviewing this topic.

Gerald Berry: Agree. There are probably more cases in the AMR series than in the literature!

Michele Bisceglia: Mixed epithelial and stromal tumor of the kidney. Agree. There is currently a debate regarding the fact whether MESTK is the same of cystic nephroma in adults. MESTK has been included as a nosologic entity in the new WHO book of classification of renal tumors where cystic nephroma (of adults) is also present. In the same book it appears clear that the socalled cystic nephroma of the adults has many (if not all) identical features of MESTK. In the literature (in my opinion), even recently, typical MESTK are described as cystic nephroma (Mukhopadhyay S, Valente AL, de la Roza G. Cystic nephroma: a histologic and immunohistochemical study of 10 cases. Arch Pathol Lab Med. 2004 Dec;128:1404-11). Thus the 2 entities should be one and the same (this issue is well discussed in Antic T, Perry KT, Harrison K, Zaytsev P, Pins M, Campbell SC, Picken MM.Mixed epithelial and stromal tumor of the kidney and cystic nephroma share overlapping features: reappraisal of 15 lesions. Arch Pathol Lab Med. 2006 Jan;130:80-5). I wonder why not to term all these cases in adults as MESTK (as a spectrum) and leave the term cystic nephroma (or multilocular cyst of very young children) only to those pediatric cases (taken out from the cystic partially differentiated nephroblastoma group) in which no nephroblastomatous elements are found?

Thomas Colby: Agree with diagnosis.

Otto Dietze: Thank you for reminding us of this entity, I thought it was cystic nephroma.

Hugo Domínguez-Malagon: Beautiful case of MESTK, thank you.

Vincenzo Eusebi: MESTK. I hope Michal agrees.

Giovanni Falconieri: Thanks Cesar. At a snail rate it seems that I am becoming aware of the entity.

Cyril Fisher: Mixed epithelial-stromal tumor, nice case, thanks, Cesar.

Christopher Fletcher: The overlap between mixed epithelial and stromal tumour and cystic nephroma is very striking, as was recently nicely pointed out by Turbiner et al in *Am J Surg Pathol* 2007;31:489-500. Is it justified to continue separating these lesions?

Jerónimo Forteza Vila: I have never seen any similar case.

Thomas Krausz: Nice example. We also had one recently.

Thomas Mentzel: Many thanks for this nice example.

Michal Michal: Mixed epithelial and stromal tumor of the kidney. I am surprised that many pathologists still would classify this tumor with ovarian stroma as cystic nephroma.

Juan Rosai: I have to confess I would have called this case a multilocular cystic nephroma, not being yet too acquainted with the alleged differences with mixed epithelial and stromal tumor.

Dominic Spagnolo: Very nice mixed epithelial and stromal tumor of kidney.

James Strauchen: Very nice case with ovarian-like stroma. There seems to be a spectrum with multilocular cyst/cystic nephroma.

Saul Suster: Another great example of this entity first described by Michal Michal. I also believe that MESTK and cystic nephroma are one and the same and simply represents two extremes of the same condition.

Larry Weiss: Nice case.

CASE NO. 16 – CONTRIBUTED BY SANTIAGO RAMON Y CAJAL:

Philip Allen: Multinodular sarcomatoid malignant mesothelioma, diaphragm and pleura with noncontiguous tumour masses in the pleura of the right lower lobe and the pericardium. I showed this case to Doug Henderson. He says this is one of the most common mesothelioma problems referred to him in consultation. It is not widely recognized that most sarcomatoid mesotheliomas are calretinin negative. He regards all pleural based sarcomatoid tumors that stain for keratins, even if only weakly, as malignant mesotheliomas. In addition, some tumors he interprets as sarcomatoid mesotheliomas are completely negative for keratins. In the absence of any reliable or convincing immunohistochemical staining, he regards sarcomatoid tumors with a pleural base as mesotheliomas, even if they are nodular and non contiguous rather than diffuse.

Carlos Bacchi: High-grade malignant pleomorphic tumor!

David Ben-Dor: The option of mesothelioma would be difficult to prove given the negativity for mesothelial markers. Too bad that the EM didn't work out.

Michele Bisceglia: High grade malignant pleomorphic tumor of the pleura. Agree. I think that in situations like this it might be impossible to say more.

Thomas Colby: Pleomorphic sarcomatoid malignant neoplasm. For this sort of histology I would tend to favor sarcomatoid carcinoma of lung origin rather than mesothelioma. For me even focal staining for epithelial markers supports epithelial origin in this type of situation. Doubt sarcoma.

Otto Dietze: Some features would be consistent with the MFH type but I agree that pleomorphic tumor is the better diagnosis.

Hugo Domínguez-Malagon: I still consider mesothelioma the best option. At the periphery there are slit-like spaces lined by atypical polygonal cells.

Giovanni Falconieri: Great case Ramon. I would favor a pleomorphic spindle cell sarcoma NOS over mesothelioma, since in my experience sarcomatoid mesotheliomas are diffusely and often strongly positive for keratins, especially if low-molecular-weight-keratins are tested. The immunostaining pattern would be also consistent with monophasic spindle cell sarcoma, yet morphology does not fit very well.

Cyril Fisher: Given the location and immunophenotype, I'd favor sarcomatoid mesothelioma.

Christopher Fletcher: I think that it is quite unusual to see such marked pleomorphism even in the sarcomatoid variant of mesothelioma. The fact that this patient had multiple separate nodules raises the possibility that these might be metastases from a primary tumour elsewhere – for example something like dedifferentiated liposarcoma. Only ongoing clinical correlation will help to determine the true nature of this difficult case.

Jerónimo Forteza Vila: Very interesting case. I think that the best possibility is a sarcomatoid mesothelioma.

Thomas Krausz: Difficult case. I am also against the diagnosis of mesothelioma. I would like to suggest some kind of dendritic reticulum cell sarcoma, perhaps follicular dendritic variety.

Janez Lamovec.: Spindle cell and pleomorphic malignant tumor, probably sarcoma. I am not able to suggest any specific name.

Thomas Mentzel: For me the neoplasm shows features of high-grade pleomorphic sarcoma NOS.

Markku Miettinen: Malignant sarcomatoid neoplasm, cannot fully determine origin. Possibilities include sarcomatoid Ca/mesothelioma, and sarcoma. Some dedifferentiated liposarcomas can look like this. Clinical and clinicoradiologic correlation plus extensive sampling might be helpful on these cases.

Juan Rosai: I don't think that one can be more specific than saying that this is a high-grade malignant pleomorphic tumor. In addition to pleomorphic sarcomatoid mesothelioma and high grade pleomorphic sarcoma, I would add the consideration of sarcomatoid carcinoma.

Dominic Spagnolo: I think this is a sarcomatoid mesothelioma most likely. The surface mesothelial cells also look atypical and some of the tubules look infiltrative on my section.

James Strauchen: I would favor a malignant solitary fibrous tumor of the pleura, but can't rule out sarcomatoid malignant mesothelioma.

Saul Suster: I favor an epithelioid variant of malignant solitary fibrous tumor. The immunohistochemical results in this case don't make any sense and I would tend to disregard them rather than try to over interpret results and end up with an "immunohistochemical" diagnosis. H&E and common sense should still prevail in cases such as this. We would greatly appreciate getting clinical follow-up on this case; I suspect this is not going to behave in an indolent fashion.

Larry Weiss: I prefer a diagnosis of sarcoma.

CASE NO. 17 – CONTRIBUTED BY JOSHUA SICKEL:

Philip Allen: Metastatic pancreatic adenocarcinoma in the ovary simulating a primary mucinous ovarian tumour. A very instructive case. Thanks for the contribution and reference, Josh.

Carlos Bacchi: Great case of a metastatic pancreatic adenocarcinoma simulating a primary mucinous tumor of the ovary.

David Ben-Dor: One must always be on the lookout for a primary elsewhere when dealing with ovarian mucinous neoplasms, especially when bilateral and with signet ring cells (as in this case- though I looked through a recent review article by Young on ovarian metastases which appeared a few months ago in Advances: there he claims that signet ring cells can be seen in a primary ovarian mucinous tumor, but "rarely in great number". This of course begs the question as to how to define "rarely" and "great number" and how to apply these guidelines to a concrete case). The metastasis can be extremely bland and even look benign (the "maturation phenomenon" described by Young). This scenario of the ovarian tumors appearing before the primary is discovered has been described in the literature. I agree that this can be most confusing and impossible to diagnose. In this case the epithelium lining the smaller cystic glands is bland almost to the point of looking benign (in my slide the lining of the large cysts is slightly atypical) and I'm not sure if on its own merits it could be considered borderline. The incongruous juxtaposition of this with the adjacent high grade invasive tumor is something that only a metastasis could explain.

Michele Bisceglia: Metastatic pancreatic adenocarcinoma simulating a primary mucinous tumor of the ovary. Without knowing clinical history, I would have been extremely difficult to think to mets from pancreas. Thank you for focusing on this amazing event. Speaking of CDX-2 positivity in (occasional) pancreatic tumors, and moving to a different tumor, but relevant to the same embryogenetic area of the pancreas, I would like to say that recently have seen 2 cases of extrahepatic cholangiocarcinomas, which showed CDX-2 positivity in over 20% and 60% of cells each one respectively.

Thomas Colby: Agree with diagnosis. Have not encountered this before.

Otto Dietze: I hope that I did not miss a similar case in the past!

Hugo Domínguez-Malagon: I should confess that I would not consider the diagnosis of mucinous tumor of the pancreas, metastatic to the ovary if I was unaware of a previous history.

Vincenzo Eusebi: Impressive case.

Giovanni Falconieri: Quite distressing. I would have hard time with this since this would fit reasonably within the category or a primary mucinous tumor.

Christopher Fletcher: I am sure that I would have failed to recognize this as a metastasis from the pancreas. Interestingly, I recently uncovered a mistake which I made 8 years ago of the converse type – I saw a biopsy of a cutaneous scalp lesion in 1999 which I called metastatic poorly differentiated carcinoma, being unable to narrow down the primary site. I recently (8 years later) received a needle biopsy from one of this patient's newly discovered lung metastases which now has bland meningothelial morphology and, by backwards clinical correlation, we were able to discover that the lesion which I had originally diagnosed as carcinoma ultimately turned out to be an atypical meningioma which had invaded through the full thickness of the skull, a fact which had not been detected at the time the original biopsy was sent to me. This job can make fools of us in forever unexpected ways!

Jerónimo Forteza Vila: I entirely agree with your diagnosis.

Thomas Krausz: Instructive case. I have seen it before.

Janez Lamovec: One would expect that pancreatic primary would be somewhat similar to this ovarian metastasis. The degree of tumor "maturation" is striking; the possibility of two different tumors still exists.

Thomas Mentzel: Many thanks for this example of a bland-looking metastasizing lesion.

Markku Miettinen: Mucinous neoplasm, could not have been able to predict its pancreatic origin. Apparently, this is difficult even with markers. So, clinical work-up of abdomen (and follow-up) seem to be important. Thank you for this nice challenge.

Juan Rosai: I think that the arguments presented by Dr. Sickel are very reasonable and convincing, although from a purely morphologic standpoint I don't see how one can rule out a primary ovarian tumor.

Dominic Spagnolo: Agree with metastatic pancreatic adenocarcinoma simulating primary ovarian mucinous neoplasm. Have seen this before but very uncommonly.

James Strauchen: I was fooled on this one! I also thought of a cystic mucinous tumor and didn't consider a metastasis. The bilaterality should have been a clue!

Saul Suster: Great case Josh! It would have been impossible for me to make that diagnosis without the clinical history and knowledge of a pancreatic tumor.

Larry Weiss: I don't think that it is so unusual for mets to the ovary to look like this, especially given the focally poorly differentiated area. The bilaterality is often the tip-off.

CASE NO. 18 – CONTRIBUTED BY DOMINIC SPAGNOLO:

Philip Allen: Indeterminate (histiocytic/follicular dendritic) cell sarcoma arising in a scar in the abdominal wall skin in a patient with follicular lymphoma showing marginal zone differentiation, and subsequent death from progressive, widespread and apparently non biopsied tumor, four years after the lymphoma diagnosis and one year after excision of the indeterminate cell sarcoma. I remain determined to be indeterminate in this situation, but I am mightily impressed by Dominic's learned discussion.

Carlos Bacchi: I think I would just call this a histiocytic sarcoma.

David Ben-Dor: I think the association with multiple cutaneous epithelial tumors is very interesting- is this a reflection of defective immune surveillance connected to these hemato-lymphoid proliferations? Of course the criteria for diagnosing proliferations of "indeterminate" cells suffer from the same lack of specific features which are the properties of the parent cell, and thus becomes a diagnosis of exclusion which by the nature of things is not always intellectually satisfying.

Gerald Berry: I agree with the designation of indeterminate cell histiocytosis/dendritic cell sarcoma. In light of the prior history of lymphoma I wonder if they are related (? example of transdifferentiation).

Michele Bisceglia: Indeterminate cell tumor / sarcoma; indeterminate cell histiocytosis; dendritic cell sarcoma, not otherwise specified (WHO). What a difficult, but very well studied case!. Very instructive as well. Thank you very much, Dom.

Thomas Colby: I like the designation of "indeterminate cell tumor." How can we go wrong with that sort of designation? To me this is definitely of histiocytic lineage and the issue is simply trying to find the right name to put on it. I would favor this being malignant.

Otto Dietze: Dendritic cell sarcoma (NOS), the few cases I have seen before were not associated with lymphoma.

Hugo Domínguez-Malagon: Dendritic cell sarcoma NOS would be the best uncommitted term. No experience with its association with lymphomas.

Vincenzo Eusebi: I do not know.

Giovanni Falconieri: Simply impossible case, Dom. I shall look forward to the other people opinions.

Cyril Fisher: Interesting case outside my experience but great discussion including EM findings which are contributory in this context.

Christopher Fletcher: I think that I would have labeled this as an unspecified dendritic cell sarcoma, although it would be interesting to see if the tumour stained for langerin (I believe that antibody would not have been available in 1999). I find the concepts of indeterminate cell tumour and dendritic cell sarcoma NOS very difficult, since the morphologic appearances in reported examples of these lesions, as well as their immunophenotype, seems to be quite inconsistent and the diagnostic criteria are really not well defined.

Jerónimo Forteza Vila: If there are not Birbeck granules, I think the most appropriate option is interdigitating cell sarcoma.

Thomas Krausz: It lacks eosinophils and Birbeck granules for a diagnosis of typical Langerhans cell histiocytosis, however the patient received chemotherapy. Is it possible that the therapy interfered with the "maturation" process of the tumor cells? I still prefer a diagnosis of a variant of Langerhans cell histiocytosis than indeterminate cell histiocytosis.

Thomas Mentzel: The neoplasm looks like a malignant histiocytoid dermal lesion, and in addition to the discussed lesions I was thinking on an unusual example of extranodal histiocytic sarcoma as well.

Markku Miettinen: Histiocytic/Langerhans cell neoplasm, cannot rule our malignant behavior. Complete excision, follow-up and clinical work-up. It is conceivable that some of these tumors may lose CD1a. How about langerin (CD207)?

Juan Rosai: I'm pretty sure that this lesion is malignant and I'm attracted to the idea of a tumor of dendritic/reticulum cells by putting together the history, the morphology and the strong positivity for S100 protein. The obvious differential diagnosis is malignant melanoma, and I was surprised not to see melanoma stains such as HMB-45, Melan-A and Mart-1.

James Strauchen: Indeterminate cell tumor/sarcoma seems a reasonable classification. I saw a similar case some years ago, which had been misdiagnosed elsewhere as malignant melanoma, based on the S100 positivity. I think these are biologically indolent. I was unaware of the association with low-grade lymphoma. Rosai-Dorfman has also been reported in association with low-grade B-cell lymphoma.

Saul Suster: I looked at the slide first without reading Dom's description, and my first impression was that of a melanocytic tumor, malignant (there are numerous mitoses in depth). I think this could fit for "minimal deviation melanoma" or simply an amelanotic malignant melanoma. Did you try HMB45 and Melan-A?

Larry Weiss: I agree that this is a well-worked up case of an indeterminate tumor. The almost uniform skin location suggests a veil-cell origin. I tried to include the entity in the 2001 WHO classification but was overruled. We have seen these tumors associated with B-cell lymphoma, including Vasef et al. (which was from City of Hope). By the way, I do not believe that the M-PIRE concept strictly holds anymore with what we now know about dendritic cell origin and differentiation.