COMMENTS TO AMR SEMINAR #77

CASE NO. 1 – CONTRIBUTED BY CYRIL FISHER:

Phil Allen: Histiocyte rich rhabdomyoblastic tumor (inflammatory leiomyosarcoma) with ALK gene rearrangement, posterior pharyngeal wall. This extraordinary tumor defies all the old histogenetic attempts to classify it. Is it rhabdomyoblastic, leiomyosarcomatous, myofibroblastic, histiocytic or a peculiar mixture off all kinds of differentiation? It has bamboozled the old reliable H and E, although it is "obviously" a histiocytic tumor. The oracular brown stains confirm the histiocytic differentiation but add some muscle features while the ALK gene sometimes suggests an inflammatory myofibroblastic variant. It looks malignant to me but so far, none have metastasized. It is so distinctive that it must be a definite entity, the likes of which I cannot find anywhere in my out-of-date memory bank. Let us give thanks to Cyril for showing it to us and for summarizing the present state of play.

Gerald Berry; Agree. In my experience, the xanthomatous component can nearly completely obscure the neoplastic elements. Having a broad differential diagnosis is essential. In this case the clustered areas of neoplastic smooth muscle cells are helpful.

Ira Bleiweiss: Very rhabdoid, indeed.

Alberto Cavazza: A strength of this seminar is seen in the first 4 cases, showing the morphologic spectrum and the latest immunohistochemical and molecular advances of 2 couples of rare entities. For a general pathologist like me, a fantastic way to remain updated. Thanks for sharing these fascinating cases!

Kum Cooper: Thank you for sharing this newly described entity Cyril. I've been following the literature and was hoping to catch a case. Now you've provided me with a glass slide. Thank you.

Goran Elmberger: Interesting and difficult case. Histiocyte-rich or histiocyte-like?

Franco Fedeli: Recently a group of studies from Stanford and from Mayo Clinic proposed the reclassification of this tumor as "Inflammatory rhabdomyoblastic tumor".

Masaharu Fukunaga: Thank you very much for the interesting and impressive case, which I have never seen before. The comments and differential diagnoses are very informative.

Brandon Larsen: I have not encountered one of these tumors before, at least one that I recognized. A beautiful case. Thanks for sharing, Cyril.

Jesse McKinney: Interesting case. More epithelioid than case #4. ALK is odd.

Thomas Mentzel: Many thanks for the included case and the discussion of a new entity!

Markku Miettinen: By histology only I was considering tenosynovial giant cell tumor, diffuse type, but agree on histiocytic rhabdomyoblastic tumor, based on diffuse desmin and positivity for myogenic transcription factors.

Michael Michal: This is an amazing case! I was very lucky to have a chance to see it "live" when I visited Dr. Fisher's department at Birmingham some time ago as he had just received the case. It is an interesting feature of these tumors that desmin is commonly positive in many of the histiocyte-like foam cells (it is a diagnostically quite helpful feature, actually). In this particular case, these cells were also

diffusely ALK-1 positive further suggesting they might be neoplastic as well. I would like to know whether this case had the same near-haploid karyotype in addition to the ALK gene break.

Fred Petersson: Nice case, thanks. Widespread foamy cytoplasmic changes indeed! I am not sure I see that many macrophages/histocytes (CD163 ?). The inflammatory cells appear lymphocytic.

Delia Perez-Montiel: I have never seen a case like this before and I was hoping to see one. Michal's work destroyed the concept of smooth muscle differentiation when they described this tumor.

David Suster: Similar cases were reported by Michael Michal in Virchows Arch in 2020, as was properly acknowledged by Dr. Fisher. They were the first to recognize the primitive myogenic phenotype in this tumor and they aptly proposed the term "low-grade inflammatory myogenic tumor".

Saul Suster: Spectacular case, Cyril! Thank you for sharing it with us. I wonder how many of these I've seen previously and misdiagnosed. One comment: I'm afraid this is going to turn into another game in which vying parties are jockeying to get credit by changing the name of the tumor. We see this time and again in surgical pathology and it's exhausting for the rest of us who have to follow the circumvolutions of the game. There should be a law that the first description of an entity should be honored and the originally proposed name retained (unless it was far-off base), but playing word-games by changing "low-grade myogenic tumor" into "myogenic sarcoma of low-grade malignancy" or something along those lines is childish and shameful. We should go back to maintaining some standards and having some honor in our specialty. I'm afraid we have "normalized" (i.e., passively accepted) this behavior in academic pathology the same way that lying and misinformation has been normalized in world politics.

CASE NO. 2 – CONTRIBUTED BY ONDRA HES:

Phil Allen: Ectopic translocation TFE3 (Xp11) renal cell carcinoma, right suprarenal retroperitoneum, possibly arising in a small right upper duplex kidney of a female aged 21. I agree that it is a renal cell carcinoma, but it does not seem to have arisen in the apparently intact kidney. Would it be worth re-examining the gross specimen looking for an inconspicuous duplex ureter running into the massive tumor?

Gerald Berry: Agree. I have very limited experience with these tumors.

Ira Bleiweiss: Agree. Never seen this before, at last not that I can remember.

Alberto Cavazza: Great case and comments. I thought of a peculiar papillary carcinoma of the kidney, and I considered the possibility of a translocation carcinoma because of the histologic complexity and the age, but I was not able to go further than that!

Kum Cooper: Thanks to Ondra for sharing this educational case. I guess this one did not read the books, but the age is a giveaway to perform the relevant molecular analysis.

Goran Elmberger: Great case and discussion. When not to genotype??

Franco Fedeli: Translocation TFE3 (Xp11) renal cell carcinoma. Our thanks to Ondrej for showing us this rare tumor. I have appreciated the Am J Surg Pathol 2020 paper of his about a review on molecular pathology of kidney cancer.

Masaharu Fukunaga: Translocation TFE3(xp11) renal cell carcinoma. It is very difficult to make a diagnosis histologically.

Brandon Larsen: Interesting case and very helpful discussion, particularly regarding false negative FISH results and sensitivity of NGS.

Jesse McKinney: Nice example that highlights the extreme histologic heterogeneity of the TFE3 translocation-associated RCCs.

Thomas Mentzel: Great case but these interesting renal neoplasms are completely out of my knowledge….

Markku Miettinen: Renal carcinoma, ISUP/ WHO grade 3, adjacent to or involving adrenal gland. I certainly agree on translocation carcinoma based on results, hard to make it on histology.

Fred Petersson: Convincing diagnosis despite puzzling radiology. IHC negativity for CKs – good "triage-test" for translocation RCC.

Delia Perez-Montiel: The unusual thing about this case is that it is extrarenal and in areas resembles and alveolar soft part sarcoma.

Saul Suster: A wonderful contribution by our dear late friend Ondra. We all mourn his loss and miss him. He will forever be a part of this Club.

CASE NO. 3 – CONTRIBUTED BY JESSE McKINNEY:

Phil Allen: MIT family translocation type renal cell carcinoma, side not stated. I have survived epidemics of histochemistry, electron microscopy, immunohistochemistry and even Covid but am now entering the infectious world of genomic pathology without adequate educational protection. In the absence of long-term follow-up and correlation of a tumor's clinical features with the molecular abnormalities, the practical significance of the multiplying genetic changes may remain uncertain.

Gerald Berry: Agree.

Ira Bleiweiss: Agree, but not sure I see cilia.

Alberto Cavazza: Great example of a rare case. I would have also considered the possibility of PEComa.

Kum Cooper: There are scattered foci in my slide that show a subtle biphasic morphology. Thank you for this example.

Goran Elmberger: Educative case. Good to know that morphological spectrum now is wider. Nothing like description in present WHO. Only entrapment of native renal tubules is in description but that is probably rather non-specific. Wonder what would make me consider it? Any tips from morphology? IHC? Molecular work up for all kidney tumors? Is there presently any reason to try make this diagnosis? Hereditary? Specific therapy? My present molecular pathologist always asks me for a reason and does not accept diagnosis!

Franco Fedeli: Another MIT family translocation renal cell carcinoma. The morphology of this tumor is variable depending on fusion partners. I think that it is impossible to classify correctly renal tumors now without molecular study.

Masaharu Fukunaga: Welcome Jesse. RCC, MiT family translocation type (TFEB re-arranged). I have never seen this type of RCC. Thank you very much.

Brandon Larsen: This case is a great reminder of the variability seen in translocation-associated RCCs, and reminds me why I have a low threshold for sharing renal tumors with my GU colleagues and testing for translocations before signing out.

Markku Miettinen: Renal carcinoma, with some resemblance to Birth-Hogg-Dube carcinoma, but agree on TFEB translocation carcinoma although never saw one.

Fred Petersson: Protean histologic appearance of translocation RCC. What about the IHC? Was CK negative? Large tumor – sampling? The rosettes with smaller neoplastic cells and bm-like material may be a very focal finding.

Delia Perez-Montiel: Very illustrative case – in some areas it looks oncocytic.

Saul Suster: Impossible to diagnose without the molecular studies. It is getting so that I am second-guessing every diagnosis of renal tumors and sending everything out for sequencing.

CASE NO. 4 – CONTRIBUTED BY MICHAEL MICHAL:

Phil Allen: Inflammatory leiomyosarcoma (histiocyte rich rhabdomyoblastic tumor), skeletal muscle, site not known. Michael is certainly a chip off the old block. Was it the Father or the Son who wised Cyril up to this exciting "new" entity? Fancy the same tumor appearing twice in the same AMR!! Michael (and Michal) are to be congratulated on the 2020 Virchows Arch paper and on the informative notes to the Club. On the basis of these two cases, the features that might suggest the diagnosis on the H and E could be the foamy macrophages associated with the inflammatory myofibroblastic pattern. I always like to use the first describer's preferred name and can see no reason why inflammatory rhabdomyoblastic tumor is in any way superior to Merchant's inflammatory leiomyosarcoma. This tumor is just as leiomyoblastic as it is rhabdomyoblastic. Unfortunately, the WHO now doth bestride the tumor world like a colossus, while we puny pathologists must conform lest we be condemned by editorial inquisitors. I must confess that I still defy such people with the grammatically correct "Hodgkin's" disease. Perhaps we should demonstrate or twitter for the apostrophe S which is missing from our late colleagues' Rosai-Dorfman disease. Fancy turning Juan and Ron into adjectives.

Gerald Berry: Agree. This is the pattern of inflammatory leiomyosarcoma that I have more commonly encountered.

Alberto Cavazza: Great case and comments.

Kum Cooper: Thank you Michael for sharing this case which complements Cyril's case (Case #1). Thank you also for reviewing this exciting evolution of this now "over 25yr old tumor". And as you say the story is likely not yet completed!

Goran Elmberger: Great case. In the old H&E days I would have had no problems in accepting designation as inflammatory LMS. Given IHC results and today's knowledge I think the suggested future name sounds good. Thanks for summarizing the scientific progress so elegantly and instructively.

Franco Fedeli: Another "Inflammatory rhabdomyoblastic tumor" with a spindle cell morphology.

Masaharu Fukunaga: Welcome, Michael. The case is very beautiful, and the comments are excellent.

Brandon Larsen: A beautiful case. Thanks for sharing, Michael. I must admit that I've been confused by the various and changing names for these tumors over the years and rapid developments in the literature in recent years, and I haven't kept up. Your summary discussion was very helpful to me.

Jesse McKinney: Thanks for the historical review. It will be interesting to see how this evolves…

Thomas Mentzel: Wonderful case and together with Case 1 it shows a broad morphological spectrum of these fascinating neoplasms!

Markku Miettinen: Agree on inflammatory/ histiocytic rhadomyoblastic tumor. Without stains could go as an atypical nerve sheath tumor.

Fred Petersson: Another case of this enigmatic tumor! Great summary.

Delia Perez-Montiel: Agree with the diagnosis. The name of this tumor needs to be changed. There are some very characteristic foamy cells.

David Suster: Great example of this tumor and much easier to diagnose than Case No.1.

Saul Suster: I agree with Phil Allen's comment that the WHO now "doth bestride the tumor world like a colossus, while we puny pathologists must conform lest we be condemned by editorial inquisitors". Given that the tumor is clearly showing both smooth *and* skeletal muscle differentiation, the term "inflammatory rhabdomyoblastic tumor" is incomplete and erroneous. Perhaps we should come back to the original designation of "myogenic" here, which is more accurate and correct.

CASE NO. 5 – CONTRIBUTED BY MARKKU MIETTINEN:

Phil Allen: Massive primary sarcomatoid malignancy, right visceral pleura in a patient with recurrent / residual moderately differentiated squamous carcinoma of the vocal cord, side not stated. In the absence of multiple sarcomatoid metastases in the regional neck nodes neck and other sites, I think this solitary, massive, sarcomatoid pleural tumor is unlikely to be a metastasis from the moderately differentiated vocal cord carcinoma. I believe it is either a primary pleural surface sarcomatoid carcinoma or a biphasic sarcomatoid malignant solitary fibrous tumor with epithelial differentiation, if such an entity is known to exist. I can't be confident that the epithelial component is squamous.

Gerald Berry: Agree. The lesion is variously biphasic with primarily a spindled component but with scattered islands of squamous cell carcinoma. Given the clinical history and the squamous component I think this is best placed in the sarcomatoid squamous cell carcinoma category.

Ira Bleiweiss: Agree.

Alberto Cavazza: I agree with the diagnosis and with the difficulty to be sure if this is primary or metastatic. If molecular data are not definitive, I would calibrate the probability based on the clinical scenario, particularly on the characteristics of the previous vocal cord tumor: if it was large/clinically aggressive, histologically similar/high grade etc, I would favor a metastasis, otherwise my probability of a second primary would increase.

Kum Cooper: Thank you Markku for sharing this instructive/interesting case. With the history of vocal cord carcinoma, I also wondered about synovial sarcoma. But your genetic were exclusionary of the latter!

Goran Elmberger: Challenging case! Molecular findings in pleural and laryngeal tumors not very reminiscent – two synchronous independent malignancies? You asked for ideas, so I'll be a bit wild. Since we are in the pleura why not an odd malignant mesothelioma? Biphasic? Epithelial structures sometimes glandular/acinar/rosetting and sometimes more squamoid. BAP1 commonly mutated in MM in combination with LOH. Squamoid differentiation described in MM. Not sure off course!

Franco Fedeli: Very bland morphology for this tumor. It seems to me one of the varieties of spindle cell sarcomatoid carcinoma fasciitis-like that can occur in the breast.

Masaharu Fukunaga: Histologically it seems to be sarcomatoid mesothelioma, but the histology and immunoprofile indicates sarcomatoid SCC. Thank you for the interesting case.

Brandon Larsen: Fascinating case, Markku. I have to admit that the tumor really doesn't strike me as a sarcomatoid squamous cell carcinoma, although I'm not sure what it would be instead. The massive size of the tumor and clinical behavior would also be exceedingly unusual for sarcomatoid squamous cell carcinoma. The cytologic monotony is striking to me. If this were my case, I would've performed our NGS panel for gene fusion events in sarcomas and mesenchymal neoplasms. The abrupt keratinization reminds me of squamous elements in adamantinoma-like Ewing sarcoma or other translocated sarcomas.

Jesse McKinney: Very odd case. I also considered a tumor in the malignant mixed tumor/myoepithelioma family or thymic sarcomatoid carcinoma. Curious about stage of prior vocal cord tumor? I guess the XPO1 mutation would not change classification.

Thomas Mentzel: Despite the clinical features I was thinking on H&E staining also on a partly myxoid biphasic synovial sarcoma, but this seems to be unlikely.

Fred Petersson: Difficult case. Any spindle cell changes in the laryngeal tumor? Is the diagnosis based on the probability of the comparative molecular signatures? My experience with spindle cell (squamous) laryngeal carcinomas is that they are most often cytologically more pleomorphic than the slide from the pleural tumor. Looking forward to "thoracic pathology input".

Delia Perez-Montiel: I would first rule out synovial sarcoma.

David Suster: This is a very difficult case. Most sarcomatoid squamous cell carcinomas I've seen do not show well-differentiated squamous cell carcinoma components within the tumor and myxoid stroma – this seems different. Also, there are glandular elements in the tumor. Could this be a carcinosarcoma primary at this site?

Saul Suster: I don't know what this is. The history of previous vocal cord squamous cell carcinoma is certainly suggestive of this being a metastasis, but it would be highly unusual for a small tumor in the vocal cord to have metastasized this way – they usually go to regional lymph nodes first and I have never seen a pleural metastasis from vocal cord SCCA. It would be of interest here to review the vocal cord tumor to see what it looked like. I once saw a similar tumor that had been diagnosed as sarcomatoid mesothelioma, but it contained glandular and squamous elements and was later proven to be a malignant mixed tumor arising in the mediastinum. Other possibilities I would seriously consider here include a synovial sarcoma and a sarcomatoid mesothelioma. Not all tumors associated with translocations always exhibit the translocation.

CASE NO. 6 – CONTRIBUTED BY VANIA NOSE:

Phil Allen: Multiple metachronous carotid body tumors, base of skull, neck, mediastinum and periaortic region observed over 30 years. What a nice textbook case! Approximately 10% of paragangliomas are multiple. When familial, nearly half are likely to be multiple.

Gerald Berry: Agree. The clinical history and multifocal distribution of disease suggests a syndromic tumor. Has genetic testing been performed?

Ira Bleiweiss: Wow! Very concerning for malignancy but no mitoses.

Alberto Cavazza: I think morphology is fine for paraganglioma. The clinical history suggests a sort of genetic problem, and I would perform an immunohistochemical analysis for Succinate Dehydrogenase subtypes.

Kum Cooper: Thank you Vania. Sounds like this belongs to the hereditary SDH mutated PGs.

Goran Elmberger: Sure looks like a zellballen tumor. Case description seems bit truncated. Maybe some part missed out? Syndromic case? Mets??

Franco Fedeli: Classic multiple paraganglioma. What about the immunostaining for Succinate dehydrogenase (SDH)? Is amyloid the eosinophilic material into the tumor?

Masaharu Fukunaga: A wonderful and interesting case of multiple paragangliomas, thank you, Vania.

Brandon Larsen: Looks like an odd paraganglioma to me. The patient's presentation sure sounds like some type of syndromic condition.

Thomas Mentzel: The lesion shows features of a paraganglioma with scattered enlarged cells containing enlarged nuclei. It is known that paragangliomas tend to occur multifocally, and a number of cases are familial.

Markku Miettinen: Agree, paraganglioma.

Fred Petersson: Seems like the patient is suffering from "multiple paraganglioma syndrome". Germ line mutation SDH-complex? MEN 1, RET? VHL? NF1?

Delia Perez-Montiel: Very illustrative case. Thank you very much.

David Suster: Hereditary paraganglioma/pheochromocytoma syndrome. Nice Case!

Saul Suster: The clinical history provided was short and a discussion and diagnosis were not given, but since the case was contributed by Vania, who is the ruling queen of syndromic tumors, I'm assuming this must be part of a syndrome of hereditary paragangliomas.

CASE NO. 7 – CONTRIBUTED BY KYLE PERRY:

Phil Allen: Fibrous dysplasia with areas of cartilaginous differentiation (fibrocartilaginous dysplasia) proximal femur, side not stated. Thanks for that Kyle. I reckon I would have been caught out with a core needle biopsy on such a case. Of the original describers, Dave Dahlin died of West Nile Fever which he caught when fishing near the great lakes several years ago. Franco Bertoni still sends me a Christmas card. He is going strong but may not now be interested in sparring with members of the AMR club. I never knew Beabout.

Gerald Berry: Agree. I have seen cases of fibrous dysplasia with focal cartilaginous differentiation but not as the predominant pattern.

Alberto Cavazza: Interesting case. I agree with the diagnosis, and I have no specific comments.

Kum Cooper: Thank you Kyle for sharing this rare variant of FD. Agree the storiform cellularity is more than the reparative changes of callus formation. Also wondered about NOF in the storiform cellular areas but clearly not metaphyseal in radiology.

Goran Elmberger: Thanks, a second bone case is definitively appreciated. Looks a bit scary to me lacking experience in bone pathology.

Franco Fedeli: Cartilaginous differentiation in a fibrous dysplasia can simulate a low-grade cartilaginous tumor. It is important to know if it is monostotic or polyostotic because in the polyostotic form there may be abundant cartilage present.

Masaharu Fukunaga: Fibrous dysplasia with areas of cartilaginous differentiation, fibrocartilaginous dysplasia. I have never seen this type of bone tumor. Thank you very much for the detailed imaging study and comments.

Brandon Larsen: This is a great case. I was not a member of the AMR Club for Seminar #20… so I appreciate you sharing another case. The areas of classic FD make it easy to recognize, but a core biopsy could lead to confusion!

Jesse McKinney: Very nice case!

Thomas Mentzel: A nice case of fibrous dysplasia with a prominent cartilaginous component.

Markku Miettinen: Fibromyxoid neoplasm, favor benign. Fibrous dysplasia can have areas of almost no bone (this has some minimal spheroid ossicles).

Fred Petersson: No cartilage on my section only non-mitotically active, cytologically bland FD-type lesional tissue.

Delia Perez-Montiel: It could be called fibrocartilaginous dysplasia, except that in this entity, the chondrocytes are arranged in columns like the growing cartilage.

David Suster: Nice case. The differential diagnosis includes a collision tumor between fibrous dysplasia and enchondroma, but I think this case is very convincing for fibrocartilaginous dysplasia.

CASE NO. 8 – CONTRIBUTED BY FREDRIK PETERSSON:

Phil Allen: Primary neuroendocrine tumor grade 1 (carcinoid), right kidney in a patient with previous breast carcinoma. Thanks Fred. I haven't seen one before nor could I find any published association between breast carcinoma and renal neuroendocrine tumors.

Gerald Berry: Agree, nice case.

Ira Bleiweiss: Agree.

Alberto Cavazza: As you say, the diagnosis is not particularly difficult, but the location is really rare: another example of the Istanbul man.

Kum Cooper: Thank you Fred for this interesting case. Nice write up and DD.

Goran Elmberger: Rare and beautiful case!

Franco Fedeli: Thank you, Fredrik, to share with us this very rare case. I have never seen a carcinoid of the kidney. Based on morphology I would have suspected a metanephric adenoma.

Masaharu Fukunaga: Agree with primary renal neuroendocrine tumor, grade 1 (carcinoid). Thank you very much for the excellent slide and comments. GI neuroendocrine tumor is really rare.

Brandon Larsen: I don't believe I've ever encountered a NET arising in the kidney before. Looks just like I'd expect it to look! Thanks for sharing.

Jesse McKinney: Nice example. We see about one primary WD-NET of the kidney a year, usually as a consultation case.

Thomas Mentzel: Great case, many thanks for the nice and clear discussion!

Markku Miettinen: Well-differentiated neuroendocrine tumor (carcinoid) apparently from kidney.

Delia Perez-Montiel: I missed the diagnosis; I thought I saw squamous morules. But I agree with the diagnosis.

David Suster: Agree. Very rare.

Saul Suster: Nice case – than you for sharing it!

CASE NO. 9 – CONTRIBUTED BY SHIRA RONEN:

Phil Allen: Histologically malignant but biologically benign proliferative nodule arising in a neonatal giant congenital nevus on the back, with 40 years follow-up. I have always resolved that I would never make a diagnosis of malignant melanoma in a child, let alone a neonate. As I have not handled many melanocytic skin tumors in children, I have never got one wrong. If I could have seen this case 40 years ago and stuck to my dictum, I would have also apparently got it right. However, if I could see enough of these rare cases with proliferative nodules, I fear I would eventually see one that metastasized, even if the Ki index was less than 20%. Still, I would be right most of the time and many patients would be spared radical surgery and a falsely gloomy prognosis. On the other hand, what if one of these can metastasize after 40 years? A colleague of mine who trained in Adelaide in the 70s developed a "halo nevus" on her calf which she watched for some months. She eventually had it excised but unfortunately, the halo did not indicate saintly behavior. It was a malignant melanoma that had by then invaded the subcutis and had placed her into both Clarke's and Beslow's worst outlook category. She ignored their prognostications and became a well-known liver pathologist who belonged to either the Gnomes or the Elves, those two delightfully named but mutually competing international groups of liver pathologists. Thirty years after the excision, she developed metastases and died of melanoma a year or so after the first metastasis became evident. Should melanoma be regarded as one of those tumors that occasionally breaks all agreed rules?

Gerald Berry: Agree.

Ira Bleiweiss: Agree. Beautiful case.

Alberto Cavazza: I agree with the diagnosis: interesting example of a worrisome but benign lesion.

Kum Cooper: Thank you Shira for reviewing the features and updated literature for giant congenital nevi.

Goran Elmberger: Interesting case one does not see often in general pathology. Good follow-up! Any molecular findings??

Franco Fedeli: Difficult case because the number of mitosis in this case is very high.

Masaharu Fukunaga: Welcome, Dr. Ronen. I have never seen proliferative nodule arising in congenital giant nevus. Your comments are very informative, thank you very much.

Brandon Larsen: Nice case. This case makes me glad that I have dermatopathology colleagues.

Jesse McKinney: Nice case. I never get to see these…

Thomas Mentzel: A very nice and convincing case! To be honest I´ve never understood the "concept" of "minimal deviation melanoma"… In some cases, it might be very difficult to distinguish between large or even multiple proliferating nodules in a congenital melanoma and malignant melanoma arising in a congenital naevus. It has been reported that reduced H3K25me3 expression in malignant melanomas may be of help (Am J Surg Pathol 2017; 41: 396-404).

Markku Miettinen: Congenital nevus with an atypical component potentially concerning melanoma evolution. Also neurotized nevus-like components deeper.

Fred Petersson: Proliferative nodule in a congenital nevus – always scary. Reassuring message in the Comments. Thanks.

Delia Perez-Montiel: Impossible for me! Congenital nevus is an obscure topic for me.

Saul Suster: Welcome Shira and thank you for this great case!

CASE NO. 10 – CONTRIBUTED BY DAVID SUSTER:

Phil Allen: Epithelioid osteoblastoma, segmentally resected metaphysis, right femur of a male aged 22. The histology certainly looks malignant, but the radiology ought to save the day. I think we may have one of these cases about to come under review at Flinders Medical Centre in the near future. I have never previously recognized a case. What a nice entry into the Club!

Gerald Berry: Agree. This bone forming neoplasm has cellular areas, but I didn't find sufficient pleomorphism or mitotic figures to reach a diagnosis of osteosarcoma. Radiologic correlation with an experienced bone radiologist would be essential, as you indicate.

Ira Bleiweiss: Agree. Nice case.

Alberto Cavazza: A diagnosis particularly difficult for me. Interesting comments. In the lumen of some vessels there is a peculiar basophilic material: does the tumor has been embolized?

Kum Cooper: Thank you David for this lovely example of osteoblastoma with secondary ABC-like changes. Nice write up too. Best kc.

Goran Elmberger: Interesting case and great study! Obviously important for those brave ones engaged in bone pathology.

Franco Fedeli: Epithelioid osteoblastoma with so-called secondary ABC.

Masaharu Fukunaga: Welcome, David. Thank you very much for the beautiful case of epithelioid osteoblastoma, resembling ABC.

Brandon Larsen: Great case David. Thanks for sharing.

Jesse McKinney: Another nice bone case!

Thomas Mentzel: Many thanks for this nice and rare variant of osteoblastoma!

Markku Miettinen: Although has the looks of an aneurysmal bone cyst, there are osteoblastoma-like components. Fusion studies or USP6 could also help.

Michael Michal: We recently had a resection specimen of osteoblastoma-like osteosarcoma and found it quite difficult to diagnose even in the resection (radiology was unhelpful). In many parts the tumor looked very similar to this case. I am really glad we did not have to deal with such a case on core needle biopsy!

Fred Petersson: Great case. Benign (epithelioid) osteoblast-rich tumor with secondary ABC-type changes. As always, critical to have the radiologist on "your side".

Delia Perez-Montiel: Agree with the diagnosis.

David Suster: This cased was part of a series that we recently published in Human Pathol, Vol. 125:68-79, 2022 (PMID: 35337839).

CASE NO. 11 – CONTRIBUTED BY ADY YOSEPOVICH:

Phil Allen: Triple negative invasive apocrine carcinoma, left breast. I have no experience with this tumor and indeed, at Flinders Medical Centre, breast tumors have been handled by breast experts for at least two decades. As a result, my opinions are generally unfashionable. Still, as a stick in the mud, I would be unwilling to argue against post-operative chemotherapy for apocrine carcinoma without good evidence that such treatment is unnecessary. What if she were to die of tumor without the attempted protection of chemotherapy?

Gerald Berry: Agree. This case shows very convincing apocrine differentiation.

Ira Bleiweiss: Agree. Quite a collision between a rare tumor and a common tumor.

Alberto Cavazza: Interesting case. Probably I would add a GCDFP-15 and an androgen receptor to further support the apocrine features, but I agree with the diagnosis. Your comments on triple negative carcinomas with low proliferative index seems correct to me, but I have not enough experience to give an opinion on this topic.

Kum Cooper: Thanks Ady. Ill have to defer your questions to my neighbor Ira who lives a few doors down the corridor!

Goran Elmberger: Good case. Your thinking on the therapy here as triple negative is very interesting since I believe apocrine breast tumors would rate as triple negative more or less by definition, Probably one needs to take Ki67 in greater consideration. Perhaps molecular profiling could be of help? Maybe a study needs to be done if not yet performed.

Franco Fedeli: What about androgen receptor in this case? Triple negative with AR positive?

Masaharu Fukunaga: It is a very interesting case of invasive apocrine carcinoma. I guess patients with invasive apocrine carcinoma with triple negative need chemotherapy.

Brandon Larsen: I have very little experience with apocrine carcinomas of the breast, but it seems reasonable to treat this particular case more conservatively given the lack of mitotic activity.

Jesse McKinney: Good point… I look forward to the discussion.

Thomas Mentzel: As far as I know there are no prognostic differences between apocrine and non-apocrine carcinoma of the breast. In the skin, where apocrine carcinoma occurs predominantly in the axillary region, the prognosis is not like that of a low-grade carcinoma (40% develop lymph node metastases).

Markku Miettinen: Apocrine carcinoma, low-grade.

Fred Petersson: I agree with the diagnosis. The in-situ component looks ductal. Was e-cadherin membranous or cytoplasmic? Of note, some invasive pleomorphic lobular carcinomas may be triple negative and express AR, i.e, apocrine features. The infiltrative pattern is in part discohesive – aggressive. My intuition is that this is a dangerous tumor. Looking forward to the input from more seasoned breast pathologists.

Delia Perez-Montiel: Very representative case; thank you.

David Suster: Nice case – agree! These are rare tumors.

CASE NO. 12 – CONTRIBUTED BY SAUL SUSTER:

Phil Allen: Erdheim-Chester disease, skin and subcutis, right shoulder region. I have never previously seen it in the skin. I would have called this an unusual variant of benign cutaneous histiocytoma. Could cutaneous histiocytomas be the benign counterpart of Erdheim-Chester disease? I note that diabetes insipidus is a well-recognized feature of Erdheim-Chester.

Gerald Berry: Agree. We have seen ECD in the bone, lung, and heart but I have not seen in the soft tissues. Having bone involvement makes this xanthogranulomatous lesion more convincing for ECD. The BRAF status would be interesting to know.

Alberto Cavazza: I have seen some examples of Erdheim-Chester presenting in the skin, but I do not remember previous cases in subcutis or soft tissues. Spectacular case!

Kum Cooper: Thanks Saul for sharing this bone fide soft tissue example of ECD. Like you I've seen it in the lung, pleura and the omentum, but not in soft tissue.

Goran Elmberger: Wow. I have now on my desk a challenging case with xanthelasma-like lesion in eyelid where I consider hereditary ECD or rather L-histiocytosis according to recent classification. NGS pending. They can have many different genetic changes even if BRAF mutation is the most common one. Eyelid is the most common cutaneous manifestation in ECD according to literature. My case was in two monozygous male twins early adult with eyelid changes, infiltrates in lymph nodes, salivary glands and lungs. Twin brothers have resected lung lesions looking more like LCD-eosinophilic granulomas. I anxiously await our NGS studies, but we lack experience in detecting histiocytosis molecular findings. Anyone more experienced? It is said that these diseases are not familiar/hereditary, but these twins must

have a germline mutation. In case I am able to find significant genetic findings I will probably share cases with you later on.

Franco Fedeli: Erdheim-Chester disease is a real exotic disease. My experience is based only on chest tumors.

Masaharu Fukunaga: Xanthogranulomatous process consistent with Erdheim-Chester disease, this is the first time I see this type in the skin. Thank you, Saul for the interesting case.

Brandon Larsen: Fascinating. Like you, I've seen a number of cases of ECD in the lungs, retroperitoneum, and bone. However, I did see a unique case about 5 years ago that presented as a soft tissue mass in the thigh, clinically suspected to represent an ALT. It looked more like classic ECD in retroperitoneal fat, though, and not so fibrohistiocytic like in your case. I don't recall what the BRAF status was in that case, but the patient had a known history of ECD involving other anatomic sites which made it easier to recognize.

Jesse McKinney: I have seen only rare cases presenting with retroperitoneal masses, but not subcutaneous. Our rheumatologists always want us to comment on the possibility of E-C disease (as a pertinent negative) in "idiopathic retroperitoneal fibrosis" biopsies… but it never is.

Thomas Mentzel: I haven´t seen (or I missed it) a case of cutaneous involvement of Erdheim-Chester disease, but it is mentioned in the textbooks and the literature. BRAFV600 is supposed to be positive.

Markku Miettinen: Agree on histiocytosis, such as Erdheim-Chester disease, but looking at this without history went as a benign fibrous histiocytoma variant.

Michael Michal: This is a very tough case. We recently had a case of ECH in bone with typical radiology and clinical suspicion – then the diagnosis is quite obvious. I have found 2/13 cases in our registry from abdominal/retroperitoneal soft tissue but no case in superficial soft tissues or skin. The rarity of these tumors in this location might be partially explained by their relatively unspecific morphology and immunophenotype and many cases are likely misdiagnosed as xanthogranuloma, reticulohistiocytoma or "xanthoma NOS" (such as pretty much in this case). At least now there are some molecular markers that we can look for! Of note, there is a recent great paper on the topic – out of 42 cases, only 2 had an involvement of superficial soft tissues. However, cutaneous involvement was relatively common (8/42 cases), often being present around the eyelids. Some cases also resembled xanthelasma or dermatofibroma. Ref.: Ozkaya N, Rosenblum MK, Durham BH, et al. The histopathology of Erdheim-Chester disease: a comprehensive review of a molecularly characterized cohort. Mod Pathol. 2018 Apr;31(4):581-597.

Fred Petersson: Wow! I was thinking along the lines of a heavily xanthomatized fibrous histiocytoma (collagen entrapment in the periphery) or plexiform xanthomatous tumor (some nodular "packeting"). The overall clinical scenario very suggestive of ECD. Please share the BRAF results when out. The few cases we have had have been in bone – some with very subtle presence of foam cells on biopsy.

Delia Perez-Montiel: The differential diagnosis involves Rosai-Dorfman; let's see the results of BRAF V600E.

Saul Suster: My case. The results of BRAF V600e were negative in this case. Given that the patient has bone lesions typical of ECD, I still believe this is subcutaneous involvement by the disease. BRAF V600e is positive in only half of the cases of CED. S100 and CD1a stains were negative.

QUIZ CASE 1 – CONTRIBUTED BY SAUL SUSTER:

Phil Allen: Elastofibroma, parietal pleura, right lower lobe region. Was this mass in continuity with an overlying elastofibroma in the usual subscapular location?

Gerald Berry: I'm not sure what to call this paucicellular collagenous lesion but it looks like some post-inflammatory scarring process. I don't see the cellular composition for SFT or fibromatosis. The broad panel of immunostains don't seem to point in any particular direction.

Alberto Cavazza: I vote for elastofibroma. Pleura is clearly a rare location, and I do not remember having seen previous examples of elastofibroma in the pleura.

Kum Cooper: Elastofibroma involving pleura. Was this in proximity to the scapula?

Goran Elmberger: Elastofibroma? Pre-calcifying tumor of the thorax?

Franco Fedeli: I think that this tumor is an elastofibroma of the pleura. Rarely it was described in this location. Did you perform elastic stain?

Masaharu Fukunaga: Histologically typical case of elastofibroma, unusual location.

Brandon Larsen: Looks like elastofibroma to me but presenting in a really strange way! Was this involving her posterior chest wall?

Jesse McKinney: Fibrosis related to neuroendocrine tumor ("carcinoid syndrome" fibrosis)???

Thomas Mentzel: The lesion looks like a benign fibroblastic lesion with some resemblance to (calcifying) fibrous tumour, but I haven´t seen any calcification.

Markku Miettinen: Elastofibroma dorsi (originally reported by Finnish pathologists Jarvi and Saxen [1921-2021]; the latter was my professor and got me into pathology). Tumor is usually described as subscapular, but as such it can be close to the parietal pleura.

Michael Michal: Very unusual location for elastofibroma. I have seen a few subcutaneous cases at various places on the chest wall outside the typical interscapular area but had no idea it can occur on the pleura!

Fred Petersson: Looks like elastofibromatous / fibroelastotic change to me. Focal non-specific? Exclude idiopathic pleuroparenchymal fibroelastosis ?

Delia Perez-Montiel: It looks like a dorsal elastofibroma.

Saul Suster: My case. The lesion was present in the parietal pleura *inside* the chest cavity and did not involve the outside chest wall or subcutis. It was applied against the intercostal muscles and not in proximity with the scapula. There was no lesion observed in any other location, subscapular or otherwise.

Paul Wakely: Elastofibroma involving pleura.