

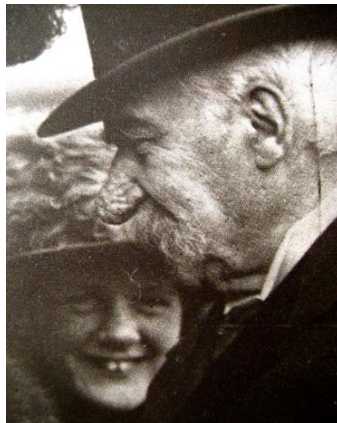
COMMENTS FOR AMR SEMINAR #75

CASE NO. 1 – CONTRIBUTED BY: Phil Allen, M.D.

Abbas Agaimy – Giant rhinophyma! Good illustration of a terrible clinical presentation, though only subtle histological findings, thanks for sharing Dr. Allen.

Phil Allen – Giant rhinophyma. My case.

Gerald Berry – Extraordinary example of giant rhinophyma! The gross image is more dramatic than the microscopic findings. I was intrigued by your reference to JP Morgan, so I Googled it and found this picture:



Ira Bleiweiss – OMG What a horribly disfiguring lesion yet so histologically innocuous.

Alberto Cavazza – Very interesting clinical presentation. I have never seen before this degree of facial deformity in rhinophyma.

Kum Cooper – Thank you Phil. I have not seen the histomorphology of this lesion before.

Göran Elmberger – Impressive case. Agree - macroscopy more diagnostic than histology.

Franco Fedeli – It is more impressive the macroscopic aspect than the histological findings.



An Old man and his grandson by Domenico Ghirlandaio an Italian painter of XV century.

Masaharu Fukunaga – Thank you very much for the interesting case, giant rhinophyma, Phil. It is clinically and pathologically very impressive. The histogenesis must be interesting.

Thomas Krausz – I also never had opportunity to see a case of rhinophyma. Thank you very much for submitting it. The gross pathology is dramatic. Examining the slide without previously reading the discussion and looking at the gross picture, I could not arrive to a specific diagnosis even though I observed the extensive telangiectasis, edema, chronic inflammation, sebaceous hyperplasia, dilated hair follicles, some of which contain demodex. The association with rosacea is important. Excellent discussion.

Brandon Larsen – I've never seen a case of giant rhinophyma before. Thanks for sharing. The clinical photos are quite dramatic, and your comments were very educational. I never knew that about JP Morgan, either, which is a fine piece of historical trivia!

Delia Perez-Montiel – I have not seen a case like this before. Thanks for sharing it.

Fredrik Petersson – Thanks! Never seen a "real" case before. Clinically grotesque - with non-specific histopathological changes. On my section, the sebaceous hyperplasia is somewhat limited, but there is a marked excess of stroma. Apparently, there is a fibrous variant of rhinophyma with stroma and mucin, but few or no pilosebaceous units. In most standard dermatopathology textbooks, the sebaceous component is emphasized and commented on, even though the illustrations clearly reveal an increased stromal component as well.

Brian Rubin – The gross picture is amazing. I've never heard of this before, so I was glad to learn about it. Seems like a good opportunity to look at gene mutations to try and uncover some interesting pathogenesis.

Niels Rupp – A very interesting case, showing the discrepancy of histology and clinical view. I have seen one case with a clinical suspect of giant rhinophyma, which turned out to be an angiosarcoma on histology.

Paul Wakely, Jr. – One of the most extreme examples of facial disfigurement I've encountered. One wonders how the patient allowed this lesion to progress to such a stage without medical intervention.

Saul Suster – Pretty impressive gross photograph – gross!

CASE NO. 2 – CONTRIBUTED BY: Kum Cooper, M.D.

Abbas Agaimy – Pretty example of lung hydatid, very rare (we almost never see) compared to liver lesions, thanks Kum.

Phil Allen – Hydatid cyst, lung, from a Botswanan male. Back in the 1950's, the Australian sheep town of Hamilton, Victoria, was sometimes proclaimed as the hydatid capital of the World, largely because of the 1928 monograph by the Victorian surgeon, Harold R Drew, who like his British barber ancestors preferred to be called "Mister" rather than "Doctor." As a young medical student in the fifties, I remember attending an excellent lecture by the aged but still eloquent Mr Drew on echinococcus granulosus of bone, which he said grew like echinococcus alveolaris and did not form cysts until it reached the soft tissues. As I have never seen echinococcus granulosus in bone, I cannot vouch for his accuracy, but I know that echinococcus alveolaris does not form macroscopically apparent cysts but insinuates laminated membrane diffusely through the liver, simulating the gross appearances of a diffuse neoplasm. Fortunately, alveolaris is pretty well confined to the Northern Hemisphere. After eighty years of dog deworming and prevention of liver eating by farm dogs, we can now surrender the hydatid crown to Botswana.

Gerald Berry – I agree with the diagnosis of hydatid cyst. Most of the cases we see (fortunately infrequently) have been liver cysts.

Ira Bleiweiss – Yecch and eew. Those are my favorite diagnostic terms for worms, but a beautiful example if one likes those sorts of things. Thanks Kum.

Alberto Cavazza – Very nice case.

Göran Elmberger – Nice case; I found all capsule components and one lucky protoscolice with hooklets in my slide. Is it possible to differentiate between E. granulosus and another species like E. multilocularis on histological grounds?

Franco Fedeli – Hydatid cyst of the lung. It is not an uncommon lesion in Sardinia, an Italian Island.

Masaharu Fukunaga – Thank you very much for the interesting case and detail discussion of hydatid cyst of the lung, Kum. It can be observed in the northern part of Japan, Hokkaido.

Ondra Hes – We see from time to time hydatid cyst; frequency is slightly increased. As I am working as volunteer for Wild Animals Rescue Station in Plzen, I know frequency of echinococcosis in wild animals (we screen some selected groups of animals). Incidence is increasing during the last 5 years (Central European trend). We have 100% of foxes infested, as well as martens and surprisingly high incidence in beavers and coypus (nutria). I think we can expect higher numbers of cases even in humans....

Thomas Krausz – Very nice example. I haven't seen it in the lung before.

Brandon Larsen – I agree. A very nice case of Echinococcus. It's been quite a few years since my colleagues and I have encountered one of these in our consultation practice.

Thomas Mentzel – Many thanks, and haven't seen this for ages.

Delia Perez-Montiel – Nice example of Hydatid cyst.

Fredrik Petersson – Nice laminated cyst wall with germinal epithelium/cells, but no protoscolices on my section.

Brian Rubin – Yuk- parasites! My slide didn't have hooklets, but the pathology seems characteristic in other respects.

Niels Rupp – A very nice case in an uncommon localization. Some while ago, I saw a case of an echinococcus in the kidney, mimicking cystic clear cell carcinoma due to the xanthomatous reaction and only very few parasitic elements.

Paul Wakely, Jr. – Nice example to add to my limited parasite collection Kum.

Saul Suster – I hadn't seen an example of this since I arrived in the US from Israel, except for one case in bone that we had at Mount Sinai Hospital in Miami when I was a resident.

CASE NO. 3 – CONTRIBUTED BY: Luca Di Tommaso, M.D., FIAC

Abbas Agaimy – Atypical type A thymoma originating in background of a micronodular thymoma. Beautiful case and discussion, I think I have seen a similar case last year.

Phil Allen – Possible atypical type A thymoma ex micronodular thymoma. Saul hasn't seen this before, but the WHO committee would doubtless be able to fit it in somewhere. I try and avoid becoming trapped in the thymic nomenclatural labyrinth. I believe our emeritus club member, Juan Rosai, keeps the prognosis simple by checking for macroscopically apparent invasion.

Gerald Berry – I think the necrosis and abundant angioinvasion would push me over to thymic carcinoma. As noted, an aggressive clinical behavior is a strong possibility.

Ira Bleiweiss – Agree. Thymoma, cystic.

Alberto Cavazza – I agree, a very unusual case: another example of the combined histology that can be found in thymoma.

Kum Cooper – Interesting case indeed. I called it thymic carcinoma arising in a micronodular thymoma.

Göran Elmberger – Very interesting case. Typical component of micronodular thymoma with lymphoid stroma in some areas also gradually changing to thymoma with rosette-like structures, both uncommon variants of type A thymoma. Progression to high grade thymoma/thymic carcinoma abrupt and distinct with necrosis and lymphovascular invasion. Would be interesting to see some molecular studies of the two components to see if this represents HG transformation (“dedifferentiation”) or collision tumor. To me the most probable event is transformation. Any follow-up info available? Lastly, I must admit that I am a bit confused by time honored nomenclature regarding thymic epithelial tumors. In most other organs we call epithelial tumors being invasive, showing metastases and ultimately killing patients right out carcinomas. I know there are other examples avoiding the nomenclature of carcinomas for tumors with clear potential for malignant behavior such as NET’s but really this is exception to the general rule. In thyroid pathology it’s all about invasiveness through capsule and LVI. In salivary gland pathology the trend has been to rename many low-grade tumors as carcinomas (mucoepidermoid carcinoma).

Franco Fedeli – Atypical thymoma in a micronodular thymoma. Another evidence of the unifying classification of thymoma.

Masaharu Fukunaga – Atypical type A thymoma. A very nice case. Thank you very much.

Thomas Krausz – I agree that this is at least an atypical thymoma arising from a micronodular thymoma. The nodules of larger, epithelioid tumor cells with necrosis and mitoses in the background of micronodular thymoma are worrisome for a more aggressive thymic neoplasm and make me think about a process of “dedifferentiation”.

Brandon Larsen – This is a beautiful case and I’ve never seen this particular combination before. I admit that I still struggle with the “atypical type A thymoma” concept and how to distinguish this from an unusual type B3 or even thymic carcinoma, but this is a pretty convincing example. Regardless of its classification, I would worry about the potential for aggressive behavior in this particular case.

Thomas Mentzel – The slide shows nicely the two tumor components; however, the atypical cells look for me rather round or epithelioid. It’s amazing that the neoplasm is not called a carcinoma despite frank angioinvasion and extensive tumor necrosis.

Fredrik Petersson – Invasive thymic epithelial tumor with large areas of necrosis. Limited micronodular component. The mitotic activity is not impressive on my section, but there is good number of apoptotic bodies. I have a gut-feeling that the Ki-67 proliferation index is quite significant. Nuclear atypia is there, but to my eyes not severe. Looking forward to the discussion.

Brian Rubin – I was glad I got to thymoma on this case.

Niels Rupp – A worrisome case, difficult to categorize. Would be interested in the clinical follow-up.

Paul Wakely, Jr. – Lovely example of invasive atypical thymoma.

Saul Suster – This is obviously a very controversial case and one on which the jury is still out. I have seen 3 other cases like this in my personal consults over the years. Cesar Moran published a paper on thymic carcinomas arising in micronodular thymomas and he might have a different interpretation on this case. Despite the may “scary” features, I doubt this tumor will behave like a frank carcinoma. The areas that look like vascular invasion could not be confirmed as such on CD31 staining. Thymomas tend to do the same as thyroid tumors in which entrapment of tumor islands within the capsule with retraction artifact will closely simulate vascular invasion, or tumor deposits will lie adjacent to small vessels in the capsule creating the impression of vascular invasion, but when vascular markers are applied the tumor deposits are outside the vessels. I expect the clinical follow-up will help take me out of my misery.

CASE NO. 4 - CONTRIBUTED BY: Barbara Gazic, M.D., PhD

Abbas Agaimy – Rare example of NTRK uterine sarcoma, a rather molecular-based diagnosis. It is a trend to try to subclassify all non-smooth muscle non-stromal sarcoma uterine malignancies via molecular subtyping. Indeed, some like this case have therapeutic relevance. Was pan-TRK IHC done on this case?

Phil Allen – NTRK fusion sarcoma, uterine cervix. Will the molecular testing prove to be more specific than the S100 stain with the passage of time?

Ira Bleiweiss – Wow. I would not have thought of this diagnosis. I also would not have thought of melanoma here.

Gerald Berry – Yet another new entity for me as I no longer sign out Gyn cases!

Alberto Cavazza – Very interesting case, with a succinct and useful descriptions of NTRK fusion uterine sarcoma.

Kum Cooper – Wow what a fantastic case!!! Thank you for sharing. Never thought I would get to see a slide of this new described entity!

Göran Elmberger – Great case illustrating new group of molecularly defined tumors where diagnosis is important as a predictive marker. How often should we run an NGS panel? Would IHC NTRK antibodies work as screening tool?

Franco Fedeli – NTRK fusion positive uterine sarcoma. A new entity to include in differential diagnosis with other non-epithelial tumors.

Masaharu Fukunaga – Histologically undifferentiated spindle cell sarcoma. Small rhabdoid cell are observed in a limited area. S100 and CD34 positivity is clue to screening. Thank you very much.

Thomas Krausz – Highly educational case (agree with diagnosis), with a broad differential diagnosis. It shows the importance of molecular study for the correct diagnosis. Thank you very much for submitting.

Brandon Larsen – Fascinating case, and thanks for sharing. I encountered my first NTRK-rearranged sarcoma last week in an older adult (at least the first case I recognized), and now your case is my second. It's a great reminder of the helpfulness of recognizing the unusual combination of strong S100 and CD34 staining in a monotonous spindle cell sarcoma, to prompt testing for NTRK rearrangements or performing TRK immunohistochemistry. It sounds like you confirmed the fusion with NGS, but it would've been interesting to see TRK IHC, too, as cases with a NTRK3 fusion apparently have nuclear TRK staining (as opposed to cytoplasmic staining with NTRK1 or NTRK2 fusions). I wonder if your case would've shown the same IHC pattern.

Thomas Mentzel – Many thanks for sharing this example of a new entity, defined by characteristic genetic changes and an interesting immunophenotype. Was Sox10 negative?

Michal Michal – We have recently a case of uterine stroma tumors with STRN-NTRK3 rearrangement (American Journal of Surgical Pathology, 2019; 43:1152-1154).

Delia Perez-Montiel – Very interesting example of the unusual tumor. The only case that I have receive have besides the fusiform cells small cluster of epithelioid cells, like sex cord tumor, and small clusters of clear cells, did you see that in other areas of the tumor?

Fredrik Petersson – Great and educational case! It is my understanding that this group of mesenchymal tumors with frequent co-expression of S-100 protein and CD34 is something that is being carved out. A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes. Genes Chromosomes Cancer. 2018 Dec;57(12):611-621. The histopathologic appearance ranges from bland to sarcomatous. This case clearly belongs to the latter.

Brian Rubin – Cool case. I'm always looking to get more experience with *NTRK* fusion sarcomas. CD34 and S-100 positivity is a consistent theme and should raise suspicion in these very rare neoplasms.

Niels Rupp – Great case of this emerging entity. We recently had a similar case, leading to extensive discussions how to treat these kinds of tumors, in particular in young patients with desire to have children. We really need to know more about the biological behavior. At least there are powerful systemic treatment options available, and I was stunned seeing a child with NTRK3-rearranged infantile fibrosarcoma after inhibitory therapy. It was not possible to even guess that there has been a tumor.

CASE NO. 5 – Ondřej Hes, M.D.

Abbas Agaimy – Classical example of a “HOT” and not “LOT” tumor. I think the term high-grade is a little bit misleading and these lesions should not be graded as they almost all have an indolent biology. I agree recognition is needed due to TSC/mTOR alterations and distinction from other renal “Pinkomas” is relevant. Thanks, Ondra for fine contribution and discussion.

Phil Allen – Incidentally found 2.3 cm, oncocytoma, kidney. I think this tumor is benign. I have difficulty in understanding how He and associates could call their tumors high grade when they say: “Ten patients with available follow up information were alive and without disease progression, after a mean follow-up of 28 months (1 to 112 months).”

Gerald Berry – Nice example of a lesion with a very catchy name!

Ira Bleiweiss – Agree. Oncocytic for sure. Did the authors really have to call this tumor HOT? With that kind of acronym were they unabashedly just trying to call attention to it? The classification of renal tumors has really undergone rapid alphanumeric expansion.

Alberto Cavazza – An entity I ignored, thanks for sharing. My only perplexity refers to the name: I fear the clinicians may incorrectly assume that the clinical behaviour is high grade, whereas if I understood correctly it is a low grade tumor and the term high grade refers just to cytology.

Kum Cooper – Thank you Ondřej for sharing this case. I had read the MSK paper (who did not use HOT in the title) but missed your Virchows paper.

Göran ElMBERGER – Interesting new emerging entity? Larger series with follow-up data needed to see if it is more aggressive than oncocytoma (3% metastatic rate described in few published series! Perhaps cases of HOT?).

Franco Fedeli – My first diagnosis was an oncocytoma with some feature of chromophobe carcinoma. I was unaware of this new entity.

Masaharu Fukunaga – This is my second time to see HOT. What does ‘high grade’ mean in this tumor? Thank you very much for the interesting case and detail discussion, Dr. Hes.

Thomas Krausz – This variant of renal cell tumor is new to me; I hope I will recognize it next time. When I looked at the slides, before reading the discussion, I was considering some strange variant of chromophobe renal cell carcinoma. The cytoplasmic vacuolation is striking. I am wondering about the nature of these vacuoles, are they degenerative or contain some specific substance?

Brandon Larsen – Thanks for sharing. I was not aware of this entity before.

Thomas Mentzel – Another interesting and new entity in the growing family of primary renal tumors.

Fredrik Petersson – Fascinating morphology. I have never encountered this before – at least I cannot recall it. Why label them “high-grade” when they are benign?

Brian Rubin – I had not heard about HOT before but it’s a great name.

Niels Rupp – Very interesting case, showing nicely the differential diagnosis of the difficult field of renal oncocytic tumors.

Paul Wakely, Jr. – Ondřej, I am not so HOT on calling these tumors high-grade if none of them pursue an aggressive course. Did you do EM on any of these cases – if so, what’s in that voluminous cytoplasm, mitochondria, vesicles, etc?

Saul Suster – Thanks for sharing this with us Ondra; yet another new kidney entity!

CASE NO. 6 CONTRIBUTED BY: Jesse McKenney, M.D.

Abbas Agaimy – Rare example of metastatic NSCLC presenting as renal mass, papillary lesions are at special risk to be misinterpreted as renal primary, another argument to use PAX8 more frequently, thanks Jesse, beautiful case.

Phil Allen – Metastatic pulmonary adenocarcinoma in the right kidney. I fear that I would have called this a primary renal carcinoma. Next time, (if there is one), I should get it right.

Gerald Berry – Interesting to hear that the collecting duct carcinoma appears to be vanishingly rare! Nice example of the need to keep an open mind for the possibility of a metastatic lesion!

Ira Bleiweiss – Wow. Very interesting pattern.

Alberto Cavazza – An interesting case with a useful comment on collecting duct carcinoma. A lung carcinoma clinically presenting as a metastasis is not so rare in small cell carcinoma, less frequent in other histotypes. In particular, I have seen some cases presenting as an intestinal mass.

Kum Cooper – The “entrapped” glomeruli within the tumor is a good feature of metastases. Thank you for sharing this interesting case.

Göran Elmberger – Good discussion and reminder of never forgetting possibility of metastases. I guess one should always be skeptical about this being a primary and look for precursors and/or challenge presumed status of primary tumors. It pays off not too seldom.

Franco Fedeli – You have to think about kidney metastasis when the morphology does not fit very well with classical renal tumor.

Masaharu Fukunaga – A wonderful and interesting case. Thank you, Jesse, for the concise and informative discussion. It seems really like a kidney cancer.

Ondra Hes – I have very similar experience; collecting duct RCC is very rare and lot of “collecting duct RCC” cases are something else. I always try to exclude everything around this diagnosis. I´ve been in one (will not mention the author) urologic meeting in Paris, very prominent urologist showed series a of 20+ collecting duct RCCs, 12 out of 20+ diagnosed based on core biopsy. I´ve asked him, how they can be sure. Answer was: “I believe my pathologist”; no comment...I think this is the reason for conflicting data about collecting duct RCC in literature.....

Thomas Krausz – Yes, morphologically “high grade” carcinoma with broad differential. Great catch.

Brandon Larsen – Interesting case. I certainly wondered about something akin to “collecting duct carcinoma” or urothelial carcinoma with glandular differentiation and didn’t realize I was looking at metastatic lung cancer until I read your comments.

Thomas Mentzel – Is there any histological clue that let you think of a metastatic disease?

Delia Perez-Montiel – Great case for differential diagnosis, also, metastasis to kidney is a rare phenomenon. The micropapillary component, as in other organs, is associated with grater dissemination and atypical metastasis.

Fredrik Petersson – Thanks for this great case – which again shows us “never to let our guard down” – and that the protocol for “metastatic work-up” at the clinical department in question should perhaps be revised. A tubulocribriform pattern is most prevalent on my section. Collecting duct carcinoma, a species near extinction??

Brian Rubin – Interesting that two of our members presented cases of metastatic lung carcinoma presenting in unusual ways. These cases remind us all that metastatic carcinoma of unknown primary is from lung approximately 80-90% of the time and that we need to think about metastatic lung in cases where the histology is “off” for a primary neoplasm.

Niels Rupp – Extraordinary case. Looking at the nuclei, (at least focally) there are very prominent nucleoli with suggested halos, really tempting me to favor a FH-deficient carcinoma. This case very nicely shows that one always has to be aware of this rare metastatic situation and should use immunohistochemistry in indistinct case.

Saul Suster – Thanks for sharing this very rare case. I have been collecting unusual metastases for many years and don't have many in the kidney – it appears the kidney is more or less a "sanctuary" organ and one that is not prone to accommodate the development of metastases. Nice case.

CASE NO 7. – CONTRIBUTED BY: Markku Miettinen, M.D.

Abbas Agaimy – GIST with significant imatinib response. Was it exon 11 mutant? Thanks Markku.

Phil Allen - GIST with histological imatinib response. Thanks for this most instructive case Markku. The Australian Government will only subsidise imatinib therapy once there is a proven histological diagnosis and we hardly ever see small preoperative core biopsies of tumors near the bowel.

Gerald Berry – Since neo-adjuvant therapy seems to be the rule rather than the exception these days for a wide range of tumors, it is nice to see examples of dramatic alterations induced by the drugs.

Ira Bleiweiss – Another example of how weird post treatment pathology can be and how we always have to be alert to new patterns.

Alberto Cavazza – Thanks, an interesting case with a useful and concise comment.

Kum Cooper – Nice classic example Markku. Thank you. These features are important to recognize especially in metastatic sites e.g. ovary that present with masses following treatment.

Göran Elmberger – GIST was not in my differential. Important knowledge.

Franco Fedeli – Imatinib treatment changes completely the morphology of this tumor. It is useful to know the regression of the tumors to avoid wrong diagnosis.

Masaharu Fukunaga – I have never seen any GISTs with a histological imatinib response. Thank you, Markku.

Thomas Krausz – Very useful educational and diagnostic points, thank you very much.

Brandon Larsen – Great example of treated GIST! I agree.

Thomas Mentzel – Many thanks, and it's very helpful to see these extensive treatments associated with morphological changes in a given neoplasm.

Delia Perez-Montiel – Thank you for the example.

Fredrik Petersson – Spectacular response! Was it seen throughout the tumor?

Brian Rubin – Very typical case of treated GIST, something we don't see that often. I'm always impressed that there are pockets of GIST cells left after treatment, hence the requirement for lifelong therapy with KIT/PDGFRα inhibitors.

Niels Rupp – Interesting morphology.

Paul Wakely, Jr. – Nice example of imatinib treated GIST. I wonder if the original dx of GIST was made by EUS-guided FNA.

CASE NO 8. – CONTRIBUTED BY: Fredrik Petersson, M.D.

Abbas Agaimy – Rare example of cellular (variant) head and neck PMT, very difficult diagnosis as it is almost always matrix-poor in the head and neck area, giant cells are the best clue, thanks Fred.

Phil Allen - Phosphaturic mesenchymal tumor (6.5 cm), right nasal cavity, right maxillary sinus and both ethmoids. I seem to recall that we have seen at least one of these before in the Club, but I still failed to recognize this one. The fat is distinctive and could well be part of the tumor. Congratulations on making the diagnosis, Fredrik.

Gerald Berry – Agree. Nice example.

Ira Bleiweiss – Thanks Fredrik. I had no idea what this was.

Alberto Cavazza – I agree, nice case and interesting discussion.

Kum Cooper – Thanks Fred. This is the 4th case I'm seeing this year. After Markku's case, we had two cases (sinonasal and acetabulum; both resected).

Göran Elmberger – Good case. When as in my slide the characteristic calcified stroma is not represented the diagnosis is difficult if the case is clinically "silent" as in present case. High index of suspicion in hot spots like SN tract!

Franco Fedeli – Phosphaturic mesenchymal tumor. A complete discussion about this rare tumor associated with paraneoplastic syndrome.

Masaharu Fukunaga – Phosphaturic mesenchymal tumor. It is very difficult to make a diagnosis on H&E. My initial impression was extraskeletal mesenchymal chondrosarcoma. Thank you for sharing this nice case with detailed discussion.

Thomas Krausz – Agree with diagnosis. The diagnosis of phosphaturic mesenchymal is often problematic, but when most of the histologic features are present it can be suspected. Of course, IHC, FISH and the clinical history confirm the diagnosis. Usually there is no separate bone biopsy to show osteomalacia, but in the submitted case, I believe, the maxillary bone exhibits features of osteomalacia with abundant osteoid.

Brandon Larsen – I agree. A lovely example of PMT, showing all of the characteristic features. I just saw a case of PMT in consultation last week in the sinonasal cavity that looked identical. Luckily, the clinical history included osteomalacia, which nobody had noticed before, which always makes the diagnosis easier. Thanks for sharing.

Thomas Mentzel – What a wonderful example of PMT showing nicely the typical bluish material.

Delia Perez-Montiel – Great discussion.

Brian Rubin – Cool case – no doubt about the diagnosis. Thanks for the thorough discussion.

Niels Rupp – Thank you very much for contributing this case. Certainly, a rare differential in the head and neck, but important to add. In particular when not having the giant cells or matrix included in the biopsy, a sarcoma such as synovial sarcoma or a glomangiopericytoma would come to my mind.

Paul Wakely, Jr. – Many thanks Fredrik for this unusual neoplasm in this unusual location, and for the wonderful discussion and the exhaustive references. I was thinking perhaps this was going to be a biphenotypic sinonasal sarcoma before I read your report.

Saul Suster – Very difficult case to diagnose in the absence of a pertinent history or areas displaying the characteristic "grungy" calcification.

CASE NO. 9 – CONTRIBUTED BY: Santiago Ramon y Cajal, M.D.

Abbas Agaimy – Undifferentiated retinoblastoma, never seen before, thanks for sharing.

Phil Allen - Retinoblastoma in enucleated eye. This is the first one I have seen, probably because I have never worked in either an eye or a children's hospital. Thanks for the contribution.

Ira Bleiweiss – Agree. Thanks, I've never seen one.

Alberto Cavazza – A tumor I have never seen (or recognized) in my routine, thanks for sharing.

Kum Cooper – Nice case. Last I saw this was in Africa!

Göran Elmberger – Thanks! As you say rare tumor never seen before. In Sweden eye pathology is centralized to eye hospital so we don't see much anymore. Knudson made important contributions to understanding TSG – "Mendel och cancer genetics"! Swedish or Danish ancestry?

Franco Fedeli – Retinoblastoma. A rare tumor with a classic morphology. Thank you for showing us this case.

Masaharu Fukunaga – Undifferentiated retinoblastoma, very beautiful case. Its clinical presentation is very interesting. Thank you very much, Santiago.

Thomas Krausz – Agree with diagnosis, very nice case. I have seen only one case in the last 10 years which was primarily treated by surgery.

Brandon Larsen – I haven't seen a case of retinoblastoma in a long time, and appreciate you sharing this. It's a great example.

Thomas Mentzel – Many thanks for sharing this excellent slide with a very rare neoplasm.

Fredrik Petersson – Malignant small round blue cell tumor with vague rosettes. Certainly, consistent with retinoblastoma. Any IHC done?

Brian Rubin – Beautiful example of something I never had an opportunity to see.

Niels Rupp – Thanks a lot, this is my first "real" slide from a retinoblastoma.

Paul Wakely, Jr. – Classic example of retinoblastoma; beautiful Flexner-Wintersteiner rosettes. Don't see these cases anymore since there is a separate children's hospital in my city. Thank you, Santiago.

Saul Suster – Nice case. I hadn't seen retinoblastoma since my years as a resident in Israel, but here at the Medical College of Wisconsin we have a very large eye service and the luxury of having a dedicated ophthalmic pathologist. We must have hundreds of ocular melanomas and dozens of retinoblastomas sitting in our files, if someone is interested!

CASE NO. 10 – CONTRIBUTED BY: Murray Resnick, M.D.

Abbas Agaimy – Rare example of "tumor-near/to-tumor-metastasis", NSCLC metastasis in surgical GI specimens is rare, and to present within colorectal carcinoma resection specimen is exceptional, thanks Murray for excellent pitfall case.

Phil Allen – Pulmonary adenocarcinoma metastatic to the serosa overlying a primary colonic carcinoma in an eighty-year-old female with previous renal cell carcinoma. As the astute reporting pathologist noted, the serosal metastasis has a different appearance from the colonic adenocarcinoma, even in the H and E, but I failed to notice the difference until I read the history. The patient seems to suffer from one of the multiple carcinoma's genetic abnormalities.

Gerald Berry – A nice example of a collision tumor.

Ira Bleiweiss – Agree. Definitely a collision of two tumors.

Alberto Cavazza – Very nice case (see my comment on case 6). A primary-metastatic collision tumor is something we encounter from time to time.

Kum Cooper – Thank you Murray. Great case! Both the sporadic MSI-H and the metastases.

Göran Elmberger – Observant!

Franco Fedeli – The possibility of metastatic lung cancer in colon cancer cannot be excluded on the bases of morphology and phenotype.

Masaharu Fukunaga – Interesting case. Thank you for sharing it.

Thomas Krausz – Excellent case of high educational value.

Brandon Larsen – What a strange case. I probably would've blown this off as simply a different component of the same GI tumor and not worked it up further. I'm not sure I would've stained it at all, without knowing first that the patient had a prior history of lung cancer!

Thomas Mentzel – What a coincidence! To be honest I would never think on this possibility, well done!

Delia Perez-Montiel – Great acuity to suspect that it is another neoplasm.

Fredrik Petersson – Great case! Two histologically distinct adenocarcinomas. Simple efficient IHC. Very nice Crohn-like nodular lymphoid aggregates associated with the MSI-H colonic mucinous tumor on my section.

Brian Rubin – The "other" case of metastatic lung carcinoma presenting in an unusual way.

Niels Rupp – Interesting case of a rare tumor collision.

Paul Wakely, Jr. – Nice diagnostic pick-up by pathologist who first saw this case. I probably would have overlooked it and just called it more of the same.

Saul Suster – The focus of metastatic lung cancer is definitely different but easy to miss. Without the history, it would be very hard to act on it.

CASE NO. 11 – CONTRIBUTED BY: Kenneth Schoolmeester, M.D.

Abbas Agaimy – Molar-associated exaggerated placental/implantation site. Alarming histology, not aware of this lesion before, thanks for teaching me.

Phil Allen – Molar associated exaggerated placental implantation site. It is not clear to me how this differs from a placental site trophoblastic tumor. Follow up information would be of interest.

Ira Bleiweiss – Agree. A really scary amount of atypia.

Alberto Cavazza – A useful point on molar gestation and trophoblastic atypia, thanks.

Kum Cooper – Thank for educating me on this phenomenon which I was not aware/nor seen before. Could these cells be the precursors to choriocarcinoma (in this setting of complete mole)?

Göran Elmberger – Impressive atypia. Good to remember.

Franco Fedeli – Molar-associated exaggerated placental/implantation site. It is an interesting association. Could they be related to each other?

Masaharu Fukunaga – Agree. It should be differentiated from placental site trophoblastic tumor. (PSTT). PSTT forms a mass. On the contrary this lesion does not forma mass.

Thomas Krausz – I agree that the nuclear atypia is greater than one could see at conventional implantation site. Without the history of previous complete hydatidiform mole the interpretation would be more difficult. Absence of mitosis is also reassuring.

Brandon Larsen – I wasn't aware of this phenomenon before. Very nice case. Thanks for sharing, Kenny.

Thomas Mentzel – Many thanks, but this case is far from my usual business...

Michal Michal – I would be concerned already about gestational choriocarcinoma in this case.

Delia Perez-Montiel – I agree, molar-associated exaggerated placental/implantation site.

Fredrik Petersson – Educational case. Thanks!

Brian Rubin – Thanks for this case – I rarely get to see cases like this. I am always impressed with the pleomorphism of trophoblasts.

Niels Rupp – Scary morphology. Interesting, that given another context, this cytology would probably fulfill any cytological criteria of malignancy.

CASE NO. 12 – CONTRIBUTED BY: Ady Yosepovich, M.D.

Abbas Agaimy – Unusual case combining malignant phyllodes/lipophyllodes with ADH and DCIS, the lipo component was subtle in my slide and easy to overlook. Parallel to this I had a case of phyllodes in a teenage girl with ADH/DCIS as well, was there any association with hereditary background? Thanks, Ady for this fine contribution.

Phil Allen – “Malignant” (2.8 cm diameter) phyllodes tumor, left breast in a cancer family patient. The histological appearance in the myxoid component differs from that seen in a myxoid liposarcoma and is more like the myxoid change seen in some lipoma-like liposarcomas. While this small tumor fulfills the criteria for a malignant phyllodes tumor, the chances of it recurring or metastasizing after a wide local excision are small.

Gerald Berry – An aggressive appearing malignant phyllodes tumor.

Ira Bleiweiss – Agree. A case well-known to me.

Alberto Cavazza – An interesting combination of findings.

Kum Cooper – Thanks Ady. Ira did share this case.

Göran Elmberger – Interesting and challenging case with dual atypias in epithelial and stromal component. Seems to be a good morphological fit with suggested diagnosis, but since it is a rare diagnosis, I wonder if translocation markers for mLPS (t(12;16)(q13;p11) involving DDIT3 (CHOP) and FUS genes (90-95%) or infrequent variant t(12;22)(q13;q12) involving DDIT3 and EWSR1) could be found.

Franco Fedeli – Myxoid liposarcoma in malignant phyllodes tumor. It would be fascinating to study the possibility of translocation t(12;16)(q13;p11).

Masaharu Fukunaga – Malignant phyllodes tumor with liposarcoma and ductal carcinoma in situ. This slide is very beautiful with variable features.

Thomas Krausz – Very nice case of malignant phyllodes tumor with foci of ductal carcinoma in situ. I am not entirely convinced about the “myxoid liposarcomatous” differentiation. I feel that the vacuolated cells in the richly vascular stroma are not real lipoblasts (pseudolipoblasts). Many of the vacuoles contain some myxoid stromal mucin either flocculent or with margination at the periphery of vacuoles (in contrast to genuine lipoblasts where the vacuoles are usually optically entirely clear and indent the nucleus). In the submitted case rare nuclei are indented but the majority are not. I also feel that the rich vascularity does not strictly qualify for the “chickenwire” pattern of real myxoid liposarcoma. I have seen heterologous liposarcomatous differentiation in some malignant phyllodes tumors, but their classification in the line of soft tissue lipogenic tumors is difficult, even though some resemble well-differentiated or pleomorphic type of liposarcoma. I had an opportunity to see a metastatic myxoid liposarcoma in the breast. The primary was in the thigh.

Brandon Larsen – Maybe my slide isn't representative of the whole lesion, but I was having trouble convincing myself that there is truly a myxoid liposarcomatous element here. I wonder if this is simply "myxoid liposarcoma-like" morphology in the stromal component, analogous to the type of change that was recently reported in dedifferentiated liposarcomas having "myxoid liposarcoma-like" areas where the tumor had acquired *DDIT3* amplification (see Mantilla JG et al, Mod Pathol. 2019;32:585-92). It would be interesting to know the genetic abnormalities present in your case.

Thomas Mentzel – A nice case of a rare variant of malignant phyllodes tumor, many thanks!

Fredrik Petersson – Fascinating case! The atypical – in-situ component displays a prominent pagetoid pattern + distinct focal expansion of some ducts by malignant cells. Just curious if any IHC (e-cadherin) was done? Concomitant LCIS. The stromal component shows mitotically active atypical spindle cells, lipoblasts and in some areas, chains/files of epithelioid cells with? intracytoplasmic lumina; almost in an epithelioid hemangioendothelioma-like fashion. Any IHC done? Molecular?? I cannot help to wonder about the molecular pathogenesis of the myxoid liposarcomatous components in malignant PTs.

Brian Rubin – I agree with diagnosis of malignant phyllodes tumor, but my slide didn't have the liposarcoma-like elements. The picture in your case description is compelling. I'm not sure how often liposarcoma-like elements are associated with malignant phyllodes tumor, but I have seen it before.

Niels Rupp – Intriguing, that these kinds of tumors can grow like a certain entity but probably do have a distinct genomic background.

Paul Wakely, Jr. – I wonder if this tumor would demonstrate the *DDIT3* rearrangement similar to primary soft tissue myxoid liposarcoma.

CASE NO. 13 – CONTRIBUTED BY: Cyril Fisher, M.D.

Abbas Agaimy – Thanks Cyril. I agree the differential diagnosis is very challenging, a background lesion (metaplastic carcinoma or phyllodes) needs be excluded and all three entities indeed have no specific markers. So, sampling remains the best marker to work it up.

Phil Allen – Triple negative metaplastic carcinoma with pleomorphic liposarcomatous differentiation, right breast. I am a little sceptical of a diagnosis of primary pleomorphic liposarcoma in this case, Cyril. I think there is some lobular carcinoma in situ in slide A. Metaplastic carcinoma also has the diagnostic virtue of being a relatively common tumor when compared with primary liposarcoma of the breast.

Ira Bleiweiss – I agree, Cyril, but kind of reluctantly. As you say there is no good pattern of phyllodes tumor. I assume you did not find a hyalinized fibroadenoma at the periphery (as I have observed in nearly every malignant phyllodes I have seen). Liposarcoma is the most common heterologous element to occur in malignant phyllodes and is not terribly unusual (in my practice at least). I think this is a good example of the danger in going too far out on a diagnostic limb with a core biopsy. A p63 stain on the core biopsy would have been useful as it is generally at least focally positive and usually extensively positive in a metaplastic carcinoma. Most metaplastic carcinomas do not respond to neoadjuvant chemotherapy, unlike other more typical triple negative breast carcinomas, so the lack of response does not really help in the differential diagnosis. Primary sarcoma of the breast is a diagnosis I only make after exhaustive exclusion (of metaplastic carcinoma with lots of keratins and p63) and malignant phyllodes with lots of sampling.

Alberto Cavazza – Great case and comments. For a non-expert like me, the lipoblasts are the only clue at least to consider this possibility. Probably the combined expression of CK and S100 is another clue, in this histological context.

Kum Cooper – Thanks Cyril.

Göran Elmberger – Challenging case after chemotherapy. In slide A I get the feeling of a well demarcated possibly preexisting tumor with some stromal atypia and suggestive chicken wire vascularity. Preexisting phyllodes tumor after treatment?

Franco Fedeli – Epithelioid variant of pleomorphic liposarcoma. My first impression was a sarcomatoid carcinoma and the positivity for Ck and S100 was in account of this diagnosis.

Masaharu Fukunaga – A challenging case. It is very hard to make a diagnosis only with H&E section. Chronic fibrocystic like changes are observed in non-tumorous areas.

Thomas Krausz – Beautiful example of epithelioid variant of pleomorphic liposarcoma in the breast. Cyril, thank you very much for the excellent discussion.

Brandon Larsen – Tough case. I wonder what the morphology would've looked like if the tumor was never treated prior to resection. Morphologically, I agree that this looks like pleomorphic liposarcoma, but I probably would've interpreted this as being most in keeping with metaplastic carcinoma, with pleomorphic liposarcomatous overgrowth and perhaps treatment-related disappearance of any recognizable conventional IDC or DCIS component. To me, a lot of the background looks like an old tumor bed with treatment response, even if there was no clinical evidence of response to therapy.

Thomas Mentzel – Excellent case, and fortunately, scattered pleomorphic lipoblasts are seen in section B otherwise...

Fredrik Petersson – Pleomorphic lipoblasts seen on both my slides A and B. The IHC findings – possibly interpreted as a "remnant expression profile" of a carcinoma? Thank you for an unusual and interesting case.

Brian Rubin – Beautiful case Cyril and great discussion.

Niels Rupp – A very nice case, dealing with the difficult differential diagnosis of metaplastic breast cancer. A comprehensive genomic profile would be quite interesting in this case.

CASE NO. 14 – CONTRIBUTED BY: Kyle Perry, M.D.

Abbas Agaimy – Very rare example of dedifferentiated chondrosarcoma, likely arising from an enchondroma. Thanks for beautiful illustration and superb discussion Kyle.

Phil Allen – Slide 1: Almost completely necrotic liposclerosed tissue, bone and cartilage fragments and a small focus of viable, histologically benign fibrous tissue, open biopsy, upper end of right femur. Slide 2: Necrotic liposclerosed tissue and bone, some islands of viable new bone, vascular granulation tissue, and fragments of atypical cartilage, resection of upper end of right femur. I cannot make a diagnosis of a high-grade sarcoma on these two sections, but the extensive necrosis is unexplained and a cause for concern. I am not competent to interpret the radiology and I personally would wait for a decade or so to allow substantiation of the diagnostic specificity of the IDH2 mutation in this situation. It would be unusual for a high-grade bone sarcoma to metastasize to the left ileum and left femoral shaft without also having pulmonary metastases. In difficult cases like this, I like to check the history for the duration of symptoms and for the possibility of any relevant omissions. As I am a hopeless radiologist, I also like to sit down with the radiologist to see if there is a definite radiological diagnosis of an aggressive high-grade sarcoma. If the radiologist is confident of a high-grade sarcoma, I would check that the tumor has been completely sampled. If this is a dedifferentiated chondrosarcoma, there should be some viable high-grade sarcoma somewhere amongst all the necrotic tissue. Perhaps the tumor is a grade 2 chondrosarcoma which has somehow caused avascular necrosis.

Alberto Cavazza – Simply an impossible case for me.

Kum Cooper – Thanks Kyle for sharing this case. Yes, it is always disconcerting with the low-grade dedifferentiated cases. In fact, our oncologists ask us routinely what the grade of the dedifferentiated areas are. This dilemma also extends to post-radiation sarcomas as which I always assumed by definition to be high grade until I reviewed a case previously seen by Chris Fletcher. I spoke to him and his reply was that if they are not high grade, he uses intermediate grade. Not sure what the oncologists do about that though!

Göran Elmberger – Great case. Utility of IDH as marker. IHC available.

Franco Fedeli – Dedifferentiated chondrosarcoma. In my slide I have been able to see this tumor perhaps due to the fixation of the material after decalcification.

Masaharu Fukunaga – A very educational case. Thank you for your guideline to make a final diagnosis.

Thomas Krausz – This is a diagnostically very difficult case, but I agree with the interpretation.

Brandon Larsen – Interesting case, certainly more challenging than most cases of dedifferentiated chondrosarcoma. Thank goodness we have IDH1/2 mutation testing now. Like you, I strongly suspect that the necrosis represents a high-grade component.

Thomas Mentzel – Many thanks for this interesting case! Probably it's the same as in dedifferentiated liposarcoma that the morphology (and the "grading") of the dedifferentiated component is not prognostic.

Fredrik Petersson – Educational and nice presentation. The case shows the value of molecular genetics and the sine qua non of radiological – pathological correlation. Unfortunately, only ghost spindle tumor cells on my 1st slide. Clearly malignant, infiltrative spindle cells on the 2nd. Thanks.

Brian Rubin – Agree with dedifferentiated chondrosarcoma with an unusually low-grade dedifferentiated component. I saw a similar case a long time ago and also sent it to Andrew for his thoughts.