COMMENTS TO AMR SEMINAR #79

CASE NO. 1 – CONTRIBUTED BY ABBAS AGAIMY:

Reza Alahghebandan: Great case – my first impression was a "dedifferentiated" AC, but apparently the term is not recommended by WHO.

Phil Allen: The local symptoms of the massive, recurrent ameloblastoma must have been pretty severe to have precipitated radical maxillary facial surgery before moving to treat the lung adenocarcinoma. I expect that the lung tumor will be the more likely to kill the patient, unless he has other life-threatening co-morbidities.

Ira Bleiweiss: Agree. Or "Carcinoma ex-ameloblastoma"?

Kum Cooper: Thank you, Abbas, for this instructive and educational case. I last saw an ameloblastic carcinoma in Africa over 25 years ago.

Goran Elmberger: Great case! AMECA - secondary type. Ameloblastoma component classical with follicular, plexiform and acanthomatous components. Ameloblastic carcinoma component undifferentiated histology with broad interanastomosing trabeculae with central necrosis of comedo type. Small undifferentiated basaloid cells with high mitotic index. Subtle hints to ameloblastic nature in form of vague nuclear palisading and focal dentinoid/osteoid formation. Not easy to make diagnosis if you do not have history or ameloblastoma component. De novo cases with this morphology would be challenging. IHC with Glypican-3, BRAF and CT4 might provide help. History, radiological findings, CPC and broad differential diagnostic thinking necessary!

Franco Fedeli: Ameloblastic carcinoma. Interesting - very rare case. What about chromogranin?

Brandon Larsen: This seems to be a convincing case of ameloblastic carcinoma, but I must admit that without having a prior history of ameloblastoma, I would've had to perform molecular testing on this case. With that clinical history, additional testing wasn't necessary, but it would be interesting to see what molecular testing would show in each component. It sure looks like a basaloid squamous cell carcinoma in most areas! Thanks for sharing.

Masaharu Fukunaga: Thank you very much for the interesting and beautiful case with detailed discussion, I have experienced a few cases of ameloblastic carcinoma. Thank you, Abbas.

Anais Malpica: Ameloblastic carcinoma in ameloblastoma. I find interesting that the expression of p53 and p16 is the same in both components.

Thomas Mentzel: Dear Abbas, many thanks for this morphologically spectacular case!

Fred Petersson: Great case. Not very prominent subnuclear vacuolization/reverse polarity in the ameloblastomatous component on my section. In my experience gnathic and sinonasal malignancies often stay localized for quite some. As you say, a singular "met" should enjoy the benefit of the doubt as being a secondary primary until proven otherwise.

Preetha Ramalingam: Nice example showing transition from ameloblastoma to ameloblastic carcinoma.

Tiziana Salviato: A fascinating case, I am puzzled by the epithelium-attached part, similar to adenoid cystic carcinoma. Could the adenoid-like part be a morphologically different aspect of ameloblastic carcinoma?

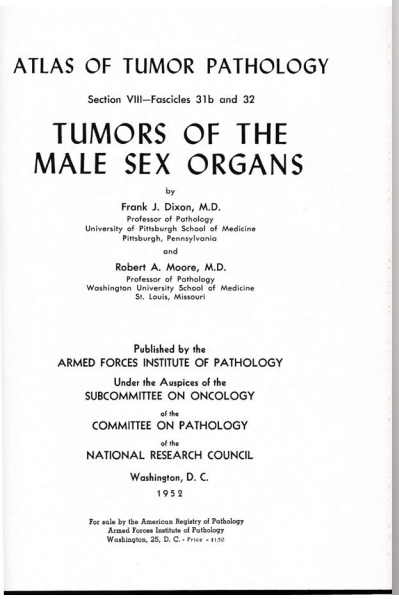
David Suster: Ameloblastic carcinoma, nice example with the background ameloblastoma that can still be identified.

Saul Suster: Very nice case. We have seen a similar case which metastasized repeatedly to lung; the initial metastasis was impossible to diagnose until the history of ameloblastoma became available.

CASE NO.2: CONTRIBUTED BY FATIMA CARNEIRO:

Reza Alahghebandan: Nice case. I wonder if beta-catenin positivity in this tumor is a "potential" predictive marker of benignity, similar to the one in Sertoli cell tumors.

Phil Allen: When I started in pathology in 1962, testicular tumors were pretty well restricted to seminoma, teratoma, embryonal carcinoma and choriocarcinoma. I include below a scanned image of the 1952 AFIP first series fascicle, "Tumors of the Male Sex Organs" (Fig 1). The testis, epididymis, prostate, urethra, seminal vesicles, penis and scrotum were all included in this 178-page publication. Tumors of the testis were covered in 72 pages (fig 2). The latest fifth series fascicle (Fig 3) published in 2022 is restricted to the testis and adjacent tissues but has still expanded to 698 pages. The older I get, the longer and harder everything has become.


ATLAS OF TUMOR PATHOLOGY

Section VIII—Fascicles 31b and 32

TUMORS OF THE MALE SEX ORGANS

by

Frank J. Dixon, M.D.
Professor of Pathology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

and

Robert A. Moore, M.D.
Professor of Pathology
Washington University School of Medicine
St. Louis, Missouri

Published by the
ARMED FORCES INSTITUTE OF PATHOLOGY
Under the Auspices of the
SUBCOMMITTEE ON ONCOLOGY
of the
COMMITTEE ON PATHOLOGY
of the
NATIONAL RESEARCH COUNCIL
Washington, D. C.
1952

For sale by the American Registry of Pathology
Armed Forces Institute of Pathology
Washington, 25, D. C. - Price - $1.50

Fig. 1

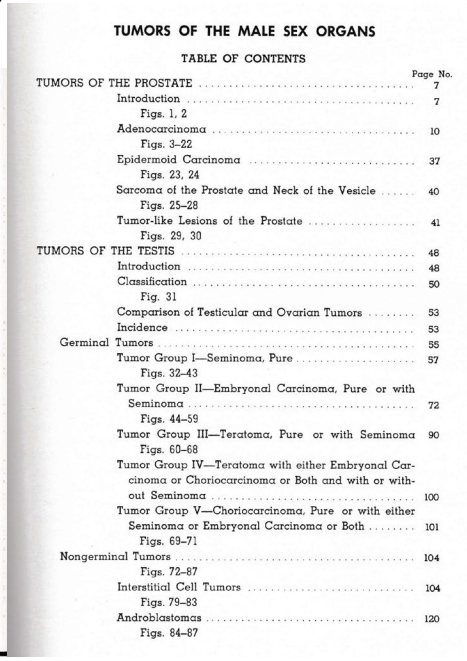
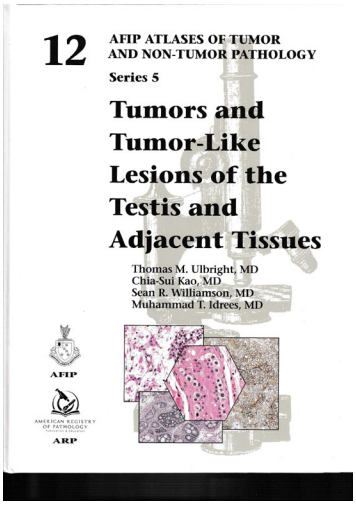

TUMORS OF THE MALE SEX ORGANS

TABLE OF CONTENTS

Fig. 2


12

AFIP ATLASES OF TUMOR AND NON-TUMOR PATHOLOGY

Series 5

Tumors and Tumor-Like Lesions of the Testis and Adjacent Tissues

Thomas M. Ulbright, MD
Chia-Sui Kao, MD
Sean R. Williamson, MD
Muhammad T. Idrees, MD

AFIP

ARP

Fig. 3

Ira Bleiweiss: Very, very signet ring cell-ish. As a breast pathologist, I was especially struck ad misled until seeing the gender and source of the lesion.

Kum Cooper: A fascinating case Fatima. I have only seen this in the ovary before but was aware of the testicular variety especially when Michal brought to our attention.

Goran Elmberger: Great and rare case! Signet ring stromal tumor (PSRSTT)! Question for Michal: why dropping out the "cell" part of name usually included in other entities characterized by signet ring cells? Shorter perhaps better.

Franco Fedeli: I think that this type of tumor is related to pancreatic solid pseudopapillary neoplasm in the testis, presented for the first time in 2012 in International AMR in Stockholm.

Brandon Larsen: I was not aware of the existence of this tumor type before seeing your case, Fátima, and I'm certain that I would mistakenly call this metastatic signet-ring cell carcinoma every day of the week. The cytology is quite atypical, and it would be very easy to overlook the absence of mitotic figures. On a frozen section slide, it would be even more challenging!

Masaharu Fukunaga: Thank you very much for the challenging case and concise discussion. My initial diagnosis was sex-cord tumor, Sertoli cell tumor. On second look, I agree with your diagnosis.

Anais Malpica: Although the mitotic activity is inconspicuous, this tumor shows more cytologic atypia than the one seen in a typical signet ring cell stromal tumor of the ovary and the one described for similar tumors in the testis.

Thomas Mentzel: Great case and it's interesting that this kind of signet-ring carcinoma is supposed to have an excellent prognosis in contrast to other types of signet-ring carcinoma.

Fred Petersson: Cytologically quite atypical compared to the few cases of this entity that I have seen. My impression was malignant - ?metastatic ca, primary adeno ca, dedifferentiated/epithelioid LS and funny mesothelioma. Convincing IHC – that of solid-pseudopapillary pancreatic tumor (!). I wonder if this could be a potentially malignant variant. Curious to see a wide panel of molecular genetic tests – and compare with a cytologically bland example of this entity.

Preetha Ramalingam: This case is challenging. The degree of atypia is unusual for signet ring stromal tumor. I also considered microcystic stromal tumor with signet ring cells which would have similar immunophenotype and I have seen one case in the testis.

Tiziana Salviato: I've never seen a similar case! I'm just awed. Looking only at the HE without reading the clinical data, the first thought was a metastasis from gastric carcinoma, but of course, it could not be, given the age.

David Suster:

Saul Suster: An educational experience for me! I don't get to see much GYN pathology.

CASE NO.3: CONTRIBUTED BY MASAHARU FUKUNAGA:

Reza Alahghebandan: Thank you for the case.

Phil Allen: Thanks for this case, Masa. Presumably the endosalpingiosis was bilateral and caused both ectopic pregnancies.

Ira Bleiweiss: I agree that this is benign. No endometriosis, I assume?

Kum Cooper: Masa this is such an unusual case all around: from clinical to the morphological findings. Thank you for sharing.

Goran Elmberger: Beautiful and florid case! Interestingly, most previously published cases seem to be described outside the tuba uterine. Wonder if this has something to do with repeated extrauterine ectopic pregnancies. Claimed to have high correlation with gynecological malignancies in fertile women necessitating close surveillance.

Franco Fedeli: Atypical endosalpingiosis. In this case papillae were not seen. I thought a typical endosalpingiosis.

Brandon Larsen: I agree that the architecture of this proliferation is certainly consistent with a form of endosalpingiosis, but I would need to share this with my GYN colleagues to feel confident about the diagnosis. Thanks for sharing.

Masaharu Fukunaga: This is my case. I think this may be salpingitis isthmica nodosa, not atypical endosalpingiosis. I welcome your opinions.

Anais Malpica: I would say that this case represents an example of exuberant and atypical endosalpingiosis as it shows both a florid proliferation of glandular elements lined by tubal type epithelium (ie, exuberant part) and focal papillary formations and epithelial tufting without cell detachment within the proliferating glandular elements (ie, the atypical part). Whenever I make this diagnosis, I recommend follow up. Of note, there is no consensus on the diagnosis of atypical endosalpingiosis to the point that cases reported as such include cases that correspond to either an incipient serous borderline tumor or an incipient low grade serous carcinoma (please see images of Talia KL, Fiorentino L, Scurry J, McCluggage WG. A Clinicopathologic Study and Descriptive Analysis of "Atypical Endosalpingiosis". Int J Gynecol Pathol. 2020 May;39(3):254-260. doi: 10.1097/PGP.0000000000000600. PMID: 31033796).

Thomas Mentzel: Another member of the group of intermediate grade neoplasms!

Fred Petersson: Never seen this degree of florid/atypical endosalpingiosis before. Architecturally very worrisome, cytologically not frightening. Thanks.

Preetha Ramalingam: Nice case of atypical endosalpingiosis. The intraglandular papillae are only focally present and there is variable atypia.

Tiziana Salviato: At first sight, I would have thought of an implant from a serous borderline tumor.

David Suster: Would consider signet ring stromal tumor vs microcystic stromal tumor versus metastatic disease in this case, could possibly test for CTNNB1.

Saul Suster: Scary process! Some of the glands appear to be infiltrating muscle; not a finding I would expect in a benign process. The absence of cytologic atypia, however, is somewhat reassuring.

CASE NO.4: CONTRIBUTED BY JESSE MACKINNEY:

Reza Alahghebandan: Incredible case... I would also agree with a malignant progression in background of an atypical metanephric neoplasm.

Phil Allen: I haven't seen or read about these features before. I agree that malignant progression of a metanephric tumor associated with a second hit SMARCB-1 mutation is the most likely explanation.

Ira Bleiweiss: I had no clue but looks bad.

Kum Cooper: Never seen this combination before! Thank you for sharing, Jesse.

Goran Elmberger: Very interesting and unique case! Secondary (?) SMARCB1-deficient renal medullary carcinoma with great rhabdoid cell morphology. If this represent high-grade transformation, we need to keep our eyes open for this mechanism in other organ systems (all?) where SMARCB1 deficient tumors have been or will be described. Deep molecular sequencing of the separate tumor components might give some clue to interrelationship between the two tumor components, but it is established that these tumors generally have few genetical changes so that may not be an easy task. Many experimental and clinical studies are ongoing to find molecular targeting therapy for this aggressive tumor.

Franco Fedeli: I have never seen a case with dual differentiation: SMARB-1 deficient carcinoma and metanephric neoplasm.

Brandon Larsen: Interesting case, Jesse. I've never seen a tumor quite like this, but it looks like a Wilm's tumor gone bad to me, with a SMARCB1-deficient dedifferentiated rhabdoid component. I wonder if the patient's somewhat older age could explain predominance of metanephric morphology in the background, if this is indeed a Wilm's tumor gone bad. Regardless, I agree that this likely represents malignant progression of a single neoplasm, rather than a collision tumor.

Masaharu Fukunaga: A very interesting case. Thank you, Jesse. I think that it is dedifferentiated metanephric tumor with SMARCB1-deficent tumor component.

Anais Malpica: Atypical metanephric adenoma associated with a SMARCB1 deficient carcinoma. There is a single case report with suboptimal images that may be the only case of something similar reported thus far. Zhang Z, Chen J, Zhou J, Liu Y, Feng Z, Tang L, Jin Y. Clinicopathological study and diagnosis of rhabdoid tumor of kidney combined with metanephric adenoma. Chin Med J (Engl). 2014;127(24):4290-1. PMID: 25533836. Also, the slide received shows areas of cytologic atypia in the metanephric adenoma component, but no conspicuous mitotic activity as seen in the picture of the handout.

Thomas Mentzel: Many thanks and I think as well that the third explanation of a multiple hit neoplasm (progression of atypical metanephric tumour) seems the most likely.

Michael Michal: My first impression was Wilms tumor with rhabdoid/SWI-SNF associated differentiation/dedifferentiation. So, I definitely favor your third option too, we know this phenomenon well from a bunch of other tumors. Cool case!

Fred Petersson: Wonderful case of metanephric neoplasm with dedifferentiated/HGT! Pronounced rhabdoid morphology.

Preetha Ramalingam: This was a challenging case. I came across a study of rhabdoid tumor of the kidney associated with metanephric adenoma (PMID: 25533836). This case would be best classified as atypical metanephric adenoma or metanephric adenoma-epithelial Wilms tumor overlap neoplasm.

Tiziana Salviato: This is an amazing case; my first thought was an adult Wilm's tumor with a sarcomatoid-rhabdoid component.

David Suster: Very unusual, looks like some kind of de-differentiating tumor, like Wilms tumor with an undifferentiated rhabdoid component that looks like a SMARCA4-undifferentiated tumor.

CASE NO.5: CONTRIBUTED BY MICHAL MICHAL:

Reza Alahghebandan: Very nice example of such tumor!

Phil Allen: Granulosa cell tumor with hepatic differentiation, left ovary. I would probably have missed the hepatic differentiation.

Ira Bleiweiss: Agree but the hepatic differentiation was very focal on my slide.

Kum Cooper: I recall reading about this many years ago…but never saw a case. Thank you, Michal as always sharing fascinating cases.

Goran Elmberger: Adult granulosa cell tumor with focal hepatic cell differentiation. Interesting rare case. A rare case of heterologous differentiation?

Franco Fedeli: Hepatic cell differentiation in granulosa cell tumor. Is lipofuscin the pigment present inside of the cells?

Brandon Larsen: Was FOXL2 mutation testing performed? I'd be interested to see the molecular genetic abnormalities in this tumor. It does indeed look like a variant of adult granulosa cell tumor but the hepatoid cells are an unusual finding. Thanks for sharing.

Masaharu Fukunaga: Thank you very much for the interesting case, Michal. The cells you indicated hepatic differentiation seem to be stromal luteinized cells with round nuclei, prominent nucleoli and abundant eosinophilic cells.

Anais Malpica: The presence of hepatoid differentiation can also be seen in Sertoil-Leydig cell tumors as part of heterologous differentiation.

Thomas Mentzel: How can we interpret this aberrant differentiation in an otherwise typical granulosa cell tumour?

Fred Petersson: Never seen before. Amazing case of MM-type ☺

Preetha Ramalingam: Nice case and the IHC distinguishes from Leydig cells.

Tiziana Salviato: Good to know! I was unaware that there could be hepatocyte differentiation in the granulosa cell tumor.

CASE NO.6: CONTRIBUTED BY MICHAL MICHAL:

Reza Alahghebandan: Very nice example of such lesion!

Phil Allen: Adenomyomatous hyperplasia of prostatic analogue glands, vulva, female aged 58. There is even some squamous metaplasia from estrogen exposure.

Ira Bleiweiss: Very weird. Looking at the slide blindly, I thought it was prostate, so I guess it's a good name.

Kum Cooper: I recall you shared with us an entire book on this subject a few years back. I believe the author was of Czech origin!

Goran Elmberger: Adenomyomatous hyperplasia of prostatic analogue glands in the vulva. Highly interesting phenomenon occurring in lower female genital tract. In cervix – vagina some speculation on metaplasia secondarily to androgen treatment. No signs of gender dysphoria here?

Franco Fedeli: Is the clear cell modification due to estrogen production in woman?

Brandon Larsen: Beautiful case of a rare entity.

Masaharu Fukunaga: Another interesting case. I reported a case of a penis-like cervical polyp with prostatic analogue glands.

Anais Malpica: Adenomyomatous hyperplasia of prostatic analogue glands (Skene's glands) in the vulva. Of note, the section of the Bartholin's duct in the vicinity can be mistaken for a portion of ureter.

Thomas Mentzel: Amazing case, but given that "females can very rarely develop cancer in a pair of organs called the Skene's glands, which originate from the same tissues in an embryo that give rise to the prostate gland" nothing is impossible…

Fred Petersson: I they were thought some embryonal rests. PSA IHC = knock out (of me). I guess origin is Skene's glands?

Preetha Ramalingam: Nice example of this entity.

Tiziana Salviato: I was not aware that there could be this entity in the vulva, although I knew that there are embryonic remnants of prostate tissue in the female genital tract.

Saul Suster: Thank you, Michal for sharing this very rare case. Parenthetically, I learned a couple of years ago from a book given to me by our friend Hugo Dominguez that Skene was not only a great anatomist but also the man who created the science of geology. A true renaissance man!

CASE NO.7: CONTRIBUTED BY MICHAEL MICHAL:

Reza Alahghebandan: It is a very interesting case and again it seems to me that we are going to keep finding more SWI/SNF family deficient tumors in various organs and settings.

Phil Allen: Poorly differentiated clear cell tumor with chordoma-like loss of SMARCB1 on chromosome 21, synovium of left knee. I think I saw two similar synovial tumors of the knee about 30 years ago during the immunohistochemical stone age. I never knew what they were. One recurred and may have metastasized, but my memory of the cases is now very hazy. I have always doubted that extra-axial chordoid tumors are related to, or the same as, genuine midline chordomas and I have noticed how "specific" immunohistochemical stains usually became less specific with the passage of time. I expect that the same fate awaits the interpretation of CNV plotting.

Ira Bleiweiss: Not sure what this is but I'm still not sure why it's chordoma. I'll just stick to breast.

Kum Cooper: Not just an extra-axial chordoma but a poorly differentiated variety…another fascinating case!!! The late Dr Rosai would have called this "the man from Istanbul"! (oops just noticed that you labelled it exactly that!). Thank you, Michael.

Goran Elmberger: Wow! That's something. Congratulations for the diagnosis! Primary poorly differentiated extra-axial extra-skeletal chordoma (parachordoma). Exceedingly rare according to recent reviews, but probably under-recognized. Juxta articular position and most often around knee has been published in early series (Tirabosco R et al 2008). Even in retrospect, it is hard to see any morphological tips. Perhaps a few areas with clear cells including some cytoplasmic vacuolization and perhaps some signet ring cell like changes. No physaliphorous cells. No extracellular myxoid stroma. No differentiated component. Still IHC profile very consistent with chordoma and a very interesting match with the methylation profiling. In addition, SMARCB1 deficiency fits well with poorly differentiated variant. Perhaps more commonly occurring than we know…

Franco Fedeli: Very rare case. Thank you for the interesting discussion. Without molecular study the diagnosis is impossible.

Brandon Larsen: I'm not sure I would've ever arrived at a correct diagnosis in this case, as there are no chordoid features and the anatomic site is so unusual for chordoma. It's hard to argue with your workup, though! What a strange case.

Masaharu Fukunaga: It is a great case with detailed comments. Histology seems be far from conventional chordoma. Thank you, Michael.

Anais Malpica: Extremely difficult case as the lack of typical areas of chordoma and the prominent inflammatory component are confounding factors. For me the take home message is to include this entity in the differential diagnosis and obtain brachyury when dealing with a solid proliferation of cells with clear cytoplasm. An example of errand initial diagnosis was reported in the article below
O'Connor P, Cheung YY, Green DC, Lefferts JA, Jo VY, Kerr DA. Extra-Axial Poorly Differentiated Chordoma Initially Misdiagnosed as Epithelioid Sarcoma. Int J Surg Pathol. 2024 Nov 13:10668969241286086. doi: 10.1177/10668969241286086. Epub ahead of print. PMID: 39533889.
The inflammatory component has been mentioned in the article below:
Rekhi B, Michal M, Ergen FB, Roy P, Puls F, Haugland HK, Soylemezoglu F, Kosemehmetoglu K. Poorly differentiated chordoma showing loss of SMARCB1/INI1: Clinicopathological and radiological spectrum of nine cases, including uncommon features of a relatively under-recognized entity. Ann Diagn Pathol. 2021 Dec;55:151809. doi: 10.1016/j.anndiagpath.2021.151809. Epub 2021 Aug 27. PMID: 34482218.

Thomas Mentzel: Wow, what a case! Congratulations, and this case shows the need for advanced technology in selected cases!

Fred Petersson: Very difficult diagnosis. Masterly walk-through and diagnostic work-up. I was thinking Gli-altered sarcoma, inflammatory epithelioid myofibroblastic tumor/sarcoma, but I knew I was wrong.

Preetha Ramalingam: The diagnosis would be impossible to make without molecular profiling. The lack of typical areas of chordoma in the given slide and the brisk inflammatory cells are confounders. From a morphologic standpoint there are features of myoepithelial carcinoma which would also be SMARCB1 negative. The brachyury positivity is the most important marker for this differential.

Tiziana Salviato: Outstanding case! Emphasizes the increasing importance of molecular biology for diagnostic purposes.

David Suster: Poorly differentiated malignant neoplasm - would need a broad workup!

Saul Suster: Great case, Michael – thank you for sharing it. It is clear that we are moving into a whole new era in which genetics will play the dominant role for diagnosis. Hopefully we will move quickly to standardize methodology and the various testing platforms to make the results from the "little black box" more credible and reliable.

CASE NO.8: CONTRIBUTED BY MARKKU MIETTINEN:

Reza Alahghebandan: Amazing case of dedifferentiated chordoma!

Phil Allen: How did the block from which the seminar slides were cut manage to survive for successful retrieval over 35 years after the surgery? It's almost impossible here in Adelaide to retrieve blocks more than 20 years old.

Ira Bleiweiss: Dedifferentiated for sure.

Kum Cooper: Thank you, Markku. Great dove-tail to Michael's case!

Goran Elmberger: Great teaching case! Dedifferentiated chordoma. History and previous histology needed. Nothing here in morphology or IHC to make you diagnose a chordoma. I guess methylation analyses could have helped. I remind myself of a couple of dedifferentiated melanomas I encountered where only molecular analyses could help prove diagnosis.

Franco Fedeli: Without clinical history I suspected a synovial sarcoma.

Brandon Larsen: Unlike Michael Michel's case 7, the diagnosis is a bit easier as long as the clinical history is available, but it would be very easy to misclassify this as MPNST without the clinical history, particularly with loss of H3K27me3. I wasn't aware of this recently reported pitfall. Thanks for pointing this out.

Masaharu Fukunaga: It is a very interesting tumor. It looks like spindle cell rhabdomyosarcoma.

Anais Malpica: Dedifferentiated chordoma with a predominant spindle cell component. The latter seen as the sole component in the recurrence. The loss of H3K27me3 is a confounding factor.

Thomas Mentzel: In the slide I had the fibrosarcomatous, dedifferentiated component was seen only ☹

Michael Michal: Without knowing the clinical history, I think I would have been absolutely happy to call it MPNST. :) To my understanding, brachyury would not help me anyway as it is lost in the dedifferentiated chordoma part. This again shows that the MPNST morphology hides a heterogeneous group of tumors.

Fred Petersson: Translocated spindle cell sarcoma to my eyes. Dedifferentiated chordoma - challenging dx indeed – in the far back of my mind. The site and history is helpful. Thanks!

Preetha Ramalingam: This was a good learning case about dedifferentiated chordoma. In the provided slide however, only the spindle component is present and as such would need to be worked up for other sarcomas. The clinical history is the most important tool to facilitate the diagnosis in this case.

Tiziana Salviato: A fascinating case that underlines the importance of knowledge of clinical data.

David Suster: Looks like MPNST from low power, would need an appropriate clinical history and workup to subclassify.

Saul Suster: This looks like a treated synovial sarcoma by H&E. Impossible to diagnose without the history and the IHC.

CASE NO.9: CONTRIBUTED BY CESAR MORAN:

Reza Alahghebandan: Nice case!

Phil Allen: A neighbor of mine, a former plumber, died of peritoneal mesothelioma only three months ago. It will take another decade at least before belated Australian asbestos restrictions reduce our incidence of mesothelioma.

Ira Bleiweiss: Agree; nice.

Kum Cooper: Thank you, Cesar. Good to see you back again!

Goran Elmberger: Great case! IHC and molecular findings supportive. CDKN2A/9p21/p16 very useful in verifying sarcomatoid mesothelioma. I just got BAP1, MTAP and EZH2 IHC up here in Linköping claiming a sensitivity of 98% and a specificity of 100% in diagnosis of mesothelioma. Very useful also in cytology and in situ proliferations. I miss my old EM… PS my experience from reading FISH 9p21 myself is that a homozygous deletion is present in 100% of tumor cells in mesotheliomas.

Franco Fedeli: Sarcomatoid mesothelioma with lymphoid infiltration reminiscent of lymphohistiocytic mesothelioma.

Brandon Larsen: Agree! A rather lovely case of sarcomatoid mesothelioma, which happens to show transitional morphology in many areas (a pattern now lumped into the sarcomatoid category by the WHO given its similar behavior to conventional sarcomatoid mesotheliomas).

Masaharu Fukunaga: This is a relatively straightforward case.

Anais Malpica: Biphasic mesothelioma with a predominant sarcomatous component.

Thomas Mentzel: Great case of a poorly differentiated mesothelioma with focal rhaboid features.

Fred Petersson: High-grade sarcomatoid malignant tumor – mesothelioma. IHC nails it.

Preetha Ramalingam: Nice case of biphasic mesothelioma, predominantly sarcomatoid.

Tiziana Salviato: Interesting case: Strangely, BAP1 is retained.

David Suster: Sarcomatoid carcinoma of the lung vs sarcomatoid mesothelioma vs other undifferentiated malignancy. Interesting case, mostly composed of an undifferentiated tumor with focal rhabdoid morphology (some areas look like A SMARCA4-deficient undifferentiated thoracic "tumor" although most are now thought to be carcinomas). The differential on H&E for me would include mesothelioma, metastasis of undifferentiated melanoma, and undifferentiated pleomorphic sarcoma.

CASE NO.10: CONTRIBUTED BY DELIA PEREZ-MONTIEL:

Reza Alahghebandan: Nice case!

Phil Allen: I fear I would have called this a seminoma.

Ira Bleiweiss: Wow! I never would have thought of metastatic prostate here without the history.

Kum Cooper: Great case Delia. Blind it looks like lymphoma!!!

Goran Elmberger: Great case! Testicular metastasis from an undifferentiated prostatic carcinoma. First metastases are uncommon in testis and second undifferentiated prostate carcinomas are rare. Double challenge. After seeing a case like this I try to make myself always remember not to forget the possibility of a metastasis when I see a biopsy or resection specimen with a poorly differentiated tumor. Frankly but perhaps a bit unpractical any poorly differentiated tumor should be viewed as a CUP until proven otherwise. As always getting history and review of previous tumor sections are mandatory. Today many of us are luckily digitized so this makes the burden easier. In Linköping, the first Swedish lab to get fully digitized, we now keep over 11 years all cases fully digitized at 40 X. A treasure chamber!

Franco Fedeli: Undifferentiated prostatic carcinoma. Very difficult diagnosis without clinical history.

Brandon Larsen: Without a prior knowledge of a history of prostate cancer, this would be difficult to recognize! Thanks for sharing.

Masaharu Fukunaga: Initially I consider a seminoma or hematogenic malignancy. Thank you, Delia, for the detailed discussion. We do not use "undifferentiated" or "anaplastic" carcinoma in Japan.

Anais Malpica: Undifferentiated carcinoma. Essentially, the diagnosis is confirmed with a positive staining for NKX3.1. It would be interesting to explore the expression of SMARC4 and SMARB1 in this tumor as it shows rosettes similar to those described by Abbas in his paper of sinonasal SMARC4 deficient carcinomas.

Thomas Mentzel: For me (and without seeing the primary) the lesion looks like an undifferentiated, small cell (neuroendocrine?) neoplasm…

Michael Michal: My brainstem idea was spermatocytic tumor given the pretty large variability of tumor cell size. Hope IHC would stop me from calling it that 😊

Fred Petersson: Pitfall! I got the initial impression of a seminomatous tumor. Just solid sheets of malignant cells. Looking back at the slide, the quite prominent nucleoli should perhaps have raised the possibility of prostate carcinoma. Great case!

Preetha Ramalingam: The diagnosis is facilitated by the NKX3.1 staining. Given the presence of follicle like spaces and undifferentiated morphology may consider doing SMARCA4 and possibly SMARCB1. A few abortive rosettes are present which has been described in SMARCA4 deficient sinonasal carcinoma (PMID: 31934917).

Tiziana Salviato: Interesting case: Knowing the medical history is also underlined here.
As Delia rightly points out, the terms 'undifferentiated' and 'anaplastic' should be clarified.

Saul Suster: Thank you, Delia for this great case. Without the history I would have missed it!

CASE NO.11: CONTRIBUTED BY VANIA NOSE:

Reza Alahghebandan: Nice case!

Phil Allen: Thyroid carcinomas in the elderly seem to be more aggressive than those in the young. I once had a histologically bland but macroscopically angio-invasive Hurthle cell carcinoma in an elderly

male which I initially under-diagnosed on frozen section. The surgeon could see the extensive angio-invasion, but it was not present in the frozen section.

Ira Bleiweiss: Agree.

Kum Cooper: Thank you, Vania for sharing your interesting endocrine case.

Goran Elmberger: Important update! DHGTC. Follicular growth pattern predominant. Clear nuclear atypia indicative of papillary carcinoma. Geographic necrosis. Ki67?

Franco Fedeli: In this case tall cells are the type of the cells of the differentiated thyroid carcinoma. Is tall cells present in all cases.

Brandon Larsen: This case makes me glad that I have good head and neck colleagues down the hall. On a busy day, I might've signed this out as conventional PTC arising in a background of lymphocytic thyroiditis and moved to the next case. Obviously, I need to share more cases with them!

Masaharu Fukunaga: Differentiated high-grade thyroid carcinoma is very new to me. Vania, thank you very much for sharing and the clear-cut definition of this type of carcinoma. Chronic thyroiditis is observed in the background.

Anais Malpica: I do not see an elevated mitotic index, and I find the necrosis characterization challenging. Did the patient have a previous needle biopsy? I will need to keep up with the new nomenclature for thyroid carcinoma.

Thomas Mentzel: It seems like a very difficult classification….

Fred Petersson: Necrosis quite subtle on my section. Educational case. Thanks.

Preetha Ramalingam: This case was challenging. From low power the tumor has features of follicular variant of papillary thyroid carcinoma. In the provided section I did not see >5 mitoses/10hpfs. The necrosis was challenging to interpret as it has a more hyalin quality with admixed viable nuclei and associated with hemosiderin and foamy histiocytes and not overtly coagulative type. This may have been better represented in other sections.

Tiziana Salviato: Exciting case; the classification is becoming increasingly complicated when we talk about follicular-derived DHGTC.

David Suster: Thyroid carcinoma, mostly follicular patterned; with focal areas that have squamoid-morule-like formations or some focal squamous differentiation; background shows some necrosis but I can't tell if this is infarct type from a previous procedure or the tumor itself.

Saul Suster: Very interesting change in the WHO regarding thyroid cancer terminology. Is there any demonstrated significance regarding prognosis, treatment, or behavior between all these new categories? It seems like the differentiated high-grade carcinoma may be the equivalent of what used to be called widely invasive follicular carcinoma.

CASE NO.12: CONTRIBUTED BY RAUL PERRET:

Reza Alahghebandan: Very humbling and nice case!

Phil Allen: Probable intra-abdominal solitary fibrous tumor with *EWSR1::WT1* fusion. Forty years ago, I think this would have been called a hemangiopericytoma. About thirty years ago, it would probably have changed its name to solitary fibrous tumor. It could still be called that without too much fear of being regarded as reactionary or counter-revolutionary. Naturally, I think that morphology should always Trump immunohistochemistry and molecular interpretations. I still regard the clinical and morphological features as being bound together by the everlasting bonds of a kind of pathological matrimony.

Ira Bleiweiss: To me this looked very much like a granulosa cell tumor.

Kum Cooper: Thank you for sharing this fascinating case. I first read about this entity in the GYN tract (3 cases from the Mayo Clinic), but did not believe it. I guess now that additional cases (GI etc) have been recognized it is on its way towards its own place in the ever increasing formidable ST classification. I agree with you that in modern times a combination of morphology and molecular works best. As to whether LG or HG as in conventional DSRCT….well only time will tell with additional follow up and behavior of these tumors.

Goran Elmberger: Challenging case! Peculiar histology. Strands of epithelial like trabeculae. In certain areas I see plenty of typical mitoses. Ki67? Follow-up? Good discussion. I have no experience with ths. Constellation of findings might indicate variant DSRCT as you suggested. Still IHC odd where sarcoma EWSR1-NFATC2 and CIC rearranged sarcomas show similar phenotype. Maybe something unique not well described? I agree with your recommendation to keep such cases under surveillance. One-day the solution and publication might be due.

Franco Fedeli: A difficult case to classify only with HE. I thought of an epithelioid myofibroblastic tumor.

Brandon Larsen: I must admit that I have no idea what this tumor is! It's quite distinctive, but it's hard to call this DSRCT for all the reasons you mentioned. It certainly highlights the difficulty we face when molecular findings don't correspond with the clinical presentation or morphologic findings. In such cases, I personally choose to fall back on the clinical presentation and traditional morphology, and I agree with your diagnosis of unclassifiable round/spindle cell tumor.

Masaharu Fukunaga: Welcome, Raul. Thank you for the very rare and challenging case and the discussion. *EWSR1:WT1* tumor. It histologically seems to be in the category of hemangiopericytomatous tumors.

Anais Malpica: *EWSR1::WT1* fusion tumor. An example of a recently described tumor with a histological appearance that can be mistaken for other tumors. Certainly, there are small foci reminiscent of adult type granulosa cell tumor. This neoplasm underscores the importance of molecular testing to provide a definitive diagnosis. So far, cases have behaved as low grade tumors.

Thomas Mentzel: Many thanks for this case and the interesting discussion (at the H&E slide I was thinking of a solitary fibrous tumour….).

Michael Michal: First, I was entertaining the possibility of PATZ1 sarcoma due to the mixture of round/spindle cells and the location. The immunophenotype also partially overlaps…anyway, was surprised to learn that *EWSR1::WT1* (non-DSRCT) may express sex-cord stromal markers! Would be interesting to test this IHC on more cases.

Fred Petersson: Translocation-associated sarcoma not within the (nowadays fairly wide) spectrum of DSRCT. Erudite presentation and impressive work-up.

Preetha Ramalingam: There is histologic resemblance to angiomatoid fibrous histiocytoma and some but not all features of classical DSRCT are present. I found in some areas up to 15 mitoses/10hpfs as well

as variable atypia. The evolving group of non-DSRCT *EWSR1::WT1* tumors need further study with respect to their behavior. (Schoolmeester PMID:34099870 and Warkme PMID:38158126). The diagnosis is facilitated by the molecular testing.

Tiziana Salviato: Very interesting case. I remember a similar case we had in the past that was diagnosed as an intra-abdominal desmoplastic small round cell tumor. Certainly, nowadays molecular biology is of great support for diagnosis, but the old H&E and the clinical context, in my opinion, cannot be neglected. I agree, however, that this type of neoplasm should be grouped together and further studied.

David Suster: To me this looks like an unclassified spindle cell tumor that needs a big work up; would have considered on H&E nerve sheath tumors, dedifferentiated liposarcomas, or some kind of low grade sarcoma with myogenic differentiation.

Saul Suster: Thank you, Raul for sharing with us this amazing case, and welcome to the Club! The morphology of this tumor is quite distinctive and unlike anything I've seen before. It has a distinctive biphasic appearance, and the spindle areas are somewhat reminiscent of reticular perineurioma. I agree this has no resemblance with DSRCT and is probably unrelated to it. The immunophenotypic expression of such a wide array of markers is confusing and rather unhelpful. The molecular alteration is obviously helpful, at least to set it aside as a distinctive clonal process but does not clarify its nature and instead introduces more difficulties for explaining the process. I doubt I'll ever see one of these again. If I do, I'll send it to you!

CASE NO.13: CONTRIBUTED BY KYLE PERRY:

Reza Alahghebandan: Great case!

Phil Allen: Doubtful epithelioid hemangioma with *GATA6::FOX01* fusion. This does not look much like the epithelioid hemangiomas (angiolymphoid hyperplasia with eosinophilia) that I have previously recognized. Have we excluded Kaposi's sarcoma?

Ira Bleiweiss: I leave it to the soft tissue gurus, but why is this not angiosarcoma.

Kum Cooper: The morphology bears much resemblance to the series of epithelioid and spindle cell hemangioma (Fletcher et al , AJSP, 2023). I saw a similar case in the chest wall soon after that paper. I wonder if I should have sequenced it!!

Goran Elmberger: Interesting case! EH. Unusual *GATA6-FOXO1* fusion. Solid epithelioid cell proliferation with blister cells and extravasated erythrocytes. Dissecting infiltration in skeletal muscle fibers. Great confirmatory value of detecting translocations in DDX.

Franco Fedeli: Epithelioid hemangioma. I did not know this type of fusion. I thought a cutaneous epithelioid angiomatous nodule.

Brandon Larsen: Agree… nice case of epithelioid hemangioma. The confirmed GATA6:FOX01 fusion is the icing on the cake. Thanks for sharing.

Masaharu Fukunaga: Epithelioid hemangioma with *GATA6:FOXO1 fusion.* Thank you, Kyle. It looks like pyogenic granuloma with epithelioid morphology. This shows lobular pattern and non-infiltrate margins.

Anais Malpica: This case shows at least 15 mitoses per 10 HPFs, which is unusually high considering the cases of epithelioid hemangioma with *GATA6::FOX01* fusion described thus far. Atypia like the one seen in this case has been described though.

Thomas Mentzel: Great case of an epithelioid haemangioma showing an unusual fusion as reported by Christina Antonescu!

Michael Michal: I suspected vascular tumor but based on the epithelioid morphology, lack of obvious vasoformation (I see there is some now!) and due to the high number of stromal neutrophils I was heading more in the direction of pseudomyogenic hemangioendothelioma. Thanks for sharing this case!

Fred Petersson: I was concerned with a low-grade vascular neoplasm. Very rare case of cutaneous epithelioid hemangioendothelioma; low-grade atypia + impression of infiltrative architecture and not few mitotic figures. Too wild for a cutaneous angiomatous nodule. A funny KS and Gli-altered neoplasm also initial possibilities for me. The number of cases published so far are limited. It will be interesting to see with time more cases and long FU, if this tumor has any propensity for malignant behavior. Thanks for sharing this educational case.

Preetha Ramalingam: This was a challenging case. While the morphology and the reported fusion appear to be compatible with epithelioid hemangioma, I found up to 9 mitoses/10hpfs including 4 in one field. I wonder if this is better characterized as atypical epithelioid hemangioma.

Tiziana Salviato: Fascinating case of a tumor in a very unusual location. The hemangioendothelioma hypothesis was ruled out due to CAMPTA -1 negativity.

David Suster: Vascular neoplasm; thinking of epithelioid hemangioma versus Kaposi sarcoma versus possible Kaposiform hemangioendothelioma. Some rare mitotic activity is identified but I'm not quite at angiosarcoma yet.

Saul Suster: I agree with the diagnosis of epithelioid hemangioendothelioma and, considering that this lesion was 0.4 cm in greatest diameter, would be willing to bet the farm that it is benign. Epithelioid hemangiomas and hemangioendotheliomas can show great variability in morphology, so the histologic features do not phase me out. I think the novel translocation is certainly interesting, but I doubt that it justifies considering this a different "entity". I suspect that, as with immunohistochemical markers, we are going to slowly discover that tumors are capable of great molecular promiscuity resulting from unstable neoplastic cell populations and that not every new fusion we encounter is necessarily a message from the mountain that will illuminate our minds to greater understanding. But in the meanwhile, for the young ones, keep pushing those translocations and testing for more bizarre fusion partners – it's a great path to career-building at this stage of the game!

CASE NO.14: CONTRIBUTED BY TIZIANA SALVIATO:

Reza Alahghebandan: My humble opinion is that I would favor a sarcomatoid/undifferentiated carcinoma in this setting and such tumors can lose keratin expression as undifferentiated malignant tumors often do, when they progress to become less differentiated.

Phil Allen: Recurrent sarcomatoid carcinoma of oral cavity with negative epithelial markers. Despite the negative markers, some of the tumor cells in the H and E stain look as though they are trying to be epithelial.

Ira Bleiweiss: Despite the negative keratins, this still feels like a sarcomatous squamous cell carcinoma.

Kum Cooper: Thank you Tiziana, based on the history I would have called this a recurrent sarcomatoid carcinoma. I guess sarcomas are extremely rare in the head and neck mucosal sites and even in the absence of epithelial markers (along with history), this best fits with sarcomatoid carcinoma.

Goran Elmberger: Hard case! Not easy come to a definitive dx based on given information. Based on short interval after radiation, I guess some dedifferentiated variant of previous squamous cell carcinoma or undifferentiated independent tumor would med more probable. In the old days, we did EM on cases like this in search of differentiation clues. I guess comparative molecular analysis and methylation profiling might come up with some ideas. Genetically based fingerprints tend to stay even after morphological and immunohistochemical dedifferentiation.

Franco Fedeli: Morphologically very similar to the postoperative nodule of the bladder but I agree that this lesion is a sarcomatoid carcinoma of the larynx.

Brandon Larsen: I would favor a radiation-induced sarcoma here. If I read your case description correctly, it sounds like radiation was delivered in 2020, which was 4 years ago. That's enough time for radiation-induced sarcoma to develop. Without good squamous marker expression and no prior sarcomatoid component, I suspect this is a new tumor but I'd be interested to hear other opinions.

Masaharu Fukunaga: This is interesting and challenging. I prefer sarcomatoid carcinoma. Thank you, Tiziana for taking care of the International AMR meeting in Venice. We had a lot of fun.

Anais Malpica: High grade sarcomatoid neoplasm, favor sarcomatoid carcinoma. I would have tried also MOC31.

Thomas Mentzel: Given the location and the history I do agree with the interpretation of a recurrent keratin negative pleomorphic (sarcomatous) carcinoma.

Michael Michal: I definitely vote for recurrent sarcomatoid carcinoma given the clinical history.

Fred Petersson: High-grade epithelioid and spindle cell malignancy in a patient with previously treated SCC. We often encounter similar cases in practice. Sarcomatoid SCC (with loss of all epithelial IHC markers) vs. treatment/radiation-associated sarcoma vs. de novo high-grade pleomorphic sarcoma NOS. I guess molecular signature and comparison with previous tumor material would be very helpful/the only way to clarify this. Challenging case.

Preetha Ramalingam: The differential remains open. Given the relatively short recurrence in the I would favor sarcomatoid carcinoma. Could consider MOC31 or Claudin 4.

David Suster: Sarcomatoid neoplasm, would need a workup with a lot of cytokeratins and various other lineage specific markers.

Saul Suster: I think Tiziana that the clinical setting heavily supports this being recurrent squamous cell carcinoma. Immunohistochemical stains are not infallible, and we not infrequently encounter cases in which they cause more confusion and consternation than help.

CASE NO.15: CONTRIBUTED BY DAVID SUSTER:

Reza Alahghebandan: Nice case!

Phil Allen: Malignant phyllodes tumor with heterologous stromal overgrowth. The long 12-year history of slow growth with recent rapid acceleration suggests that the sarcomatous component arose from the stroma of a "benign" or low grade phyllodes tumor.

Ira Bleiweiss: Agree entirely. Very nice malignant phyllodes with very rare rhabdomyosarcomatous and not so rare osteosarcomatous differentiation. Also, nice subepithelial stromal condensation in the spindle cell areas.

Kum Cooper: Thanks David. Were often consulted by our breast colleagues as to whether these are phyllodes or pure sarcoma.

Goran Elmberger: Interesting case! Malignant PT with unusual heterologous differentiation. I suppose IHC helps in picking up RMS component.

Franco Fedeli: Malignant phyllodes tumor. Great case. In the slide I do not see the osteosarcoma area.

Brandon Larsen: Nice case of malignant phyllodes tumor, David, complete with heterologous elements. Thanks for sharing. The benign phyllodes-like elements in the background are very subtle in my recut slide, but this would certainly be at the top of my differential diagnosis, even if I couldn't find a benign phyllodes tumor in the background. Seems to be a regular reason for my breast colleagues to ask my opinion on their cases, whenever they see spindle cells. Thanks for sharing.

Masaharu Fukunaga: A beautiful case of malignant phyllodes tumor with osteosarcoma and rhabdomyosarcoma components. It is an educational case, thank you David.

Anais Malpica: Great example of malignant phyllodes tumor with heterologous differentiation (rhabdomyosarcoma only in my recut).

Thomas Mentzel: Many thanks for sharing this great case!

Fred Petersson: Good case! A good principle is that until proven otherwise sarcomas in the breast should be considered malignant phyllodes tumors. We have had a few cases over the years and sampling (resections) is critical. Very nice polyphenotypic mesenchymal/sarcomatous differentiation.

Preetha Ramalingam: From the provided section, the tumor is composed of a high grade sarcoma with rhabdoid morphology. I would have worked it up with SMARC4 as well as RMS markers and per provided summary the latter was confirmed. I did not appreciate the phyllodes or osteosarcoma components very well in this slide.

Tiziana Salviato: Interesting case, underlining the evolution of an undiagnosed phyllodes tumor.

CASE NO.16: CONTRIBUTED BY SAUL SUSTER:

Reza Alahghebandan:

Phil Allen: Anaplastic clear cell thyroid carcinoma. This is a nice contrast to case 11 of this seminar. Regardless of the nomenclature, the prognosis is likely to be dismal.

Ira Bleiweiss: Thyroid carcinoma only by location, location, location.

Kum Cooper: Saul I agreed with your diagnosis of anaplastic carcinoma with the differential of metastatic RCC.

Goran Elmberger: Tough case. PAX8 + and remnants of a conventional follicular tumor (?) in favor of ATC but molecular findings not really what one would expect of a thyroid carcinoma. Other tumor/sarcoma?

Franco Fedeli: I saw the case without clinical history, and I thought of an hepatocellular carcinoma. Nothing in the liver?

Brandon Larsen: I've never seen a tumor quite like this before, but I agree with your interpretation that this is an anaplastic thyroid carcinoma. Whether or not it started life as a clear cell follicular thyroid carcinoma and then dedifferentiated into an anaplastic thyroid carcinoma is less clear and could be debated, but this distinction likely doesn't matter clinically. I suppose this should reassure us as pathologists that our terminology isn't so critical here. The molecular findings are curious, but I don't know what to make of them. In the end, this is the kind of case where our oncologists would likely be more interested in the NGS results than in my diagnosis, if any therapeutic targets could be found. The prognosis is undoubtedly abysmal.

Masaharu Fukunaga: Another challenging case, my first impression was clear cell renal cell carcinoma, metastatic, however, nuclear atypia is remarkable. I agree with your diagnosis of anaplastic thyroid carcinoma.

Anais Malpica: Super difficult case, malignant epithelioid neoplasm with cytoplasmic clearing; certainly, a metastatic renal cell carcinoma needed to be ruled out. This being said the landscape of tumors with clear cells and EWSR1 rearrangement in the head and neck region keeps expanding: clear cell myoepithelial carcinoma, clear cell odontogenic carcinoma, hyalinizing clear cell carcinoma, etc.

Thomas Mentzel: The given diagnosis seems to be the most logical.

Fred Petersson: In my book – and clinical practice, focal positivity for cytokeratins AE1/AE3, CK18 and scattered nuclear positivity for PAX8 in this clinical context is strongly supportive of anaplastic thyroid carcinoma. Not uncommonly all CKs are negative and focal weak PAX8 immunoreactivity is all one gets. On another note, (nearly) all thyroid lesions, both benign and malignant can display clear cell features.

Preetha Ramalingam: This case has a wide differential including tumors with EWSR1 fusion in the head and neck region. Morphologically, PEComa would be in the differential however, the IHC would argue against this diagnosis. As the tumor is EWSR1 positive I wonder if knowing the fusion partner may shed some light?

Tiziana Salviato: A further example of dedifferentiation of thyroid carcinoma evolving to anaplasia. Another lesson to be learned from this case: one must insist on looking for evidence and not be satisfied with a single section and, above all, the need to know the clinical history.
Unfortunately, I have no memory of a case like this.

Saul Suster: My case. Extensive clinical and imaging studies has failed to identify any tumor elsewhere so far.