COMMENTS TO AMR SEMINAR #49

CASE NO. 1 – CONTRIBUTED BY DR. ALLEN

Phil Allen: Female adnexal tumour of probable Wolffian origin (FATWO), mesentery and retroperitoneum. My case.

David Ben-Dor: To me this is a biphasic neoplasm which if situated in an extremity would make me think of synovial sarcoma. But since Phil Allen has much greater expertise in the field of soft tissue tumors, I'm sure he ruled it out for good reasons (and didn't think of it being worthy of mentioning). To my (albeit limited understanding) FATWO is to a certain extent a diagnosis of exclusion, whose identification is to a certain extent circumstantial (location in the broad ligament) and also relies on it not looking like anything else easily recognizable, which can make it into a grab bag of whatever doesn't look like anything in particular. There is a focus of myxoid lesion with cells arranged in cords- would this fit in with the proposed diagnosis? Whatever the situation, wouldn't the patient have been better off had the lesion been removed 10 years ago when it might have been more manageable? Can a FATWO grow to such a great size and create such complications? Is the implication that this lesion might have been present 40 years ago and came back to haunt the patient? I thought that with the reigning fastidious British mentality the Australians would be better at saving old slides.

Ofer Ben-Itzhak: FATWO of mesentery and retroperitoneum was a surprise for me. While the first slide resembles mullerian adenosarcoma, the second resembles stromal sarcoma with sex-cord like structures, but to some extent also FATWO.

Gerald Berry: In addition to the diagnosis of FATWO I also considered adenosarcoma in my differential diagnosis. Overall I like FATWO.

Michele Bisceglia: Female adnexal tumor of probable Wolffian origin, mesentery and retroperitoneum.
Without reading the clinical history I looked at the 1.2 slide first and thought it was a FATWO. Then I looked at the slide 1.1 and got uncertain, but I think that there are some reports and illustrations in the literature showing so striking adenopapillary architecture as seen in your slide 1.1. Immuno should help in order to ascertain the real nature of this lesion.

Thomas Colby: Some of this looks like adenosarcoma to me so I would wonder about sex cord stromal/FATWHO-like elements in the stromal component of an adenosarcoma.

Kum Cooper: Whilst slide 1.2 has some resemblance to FATWO; slide 1.1 looks
distinctly biphasic Mullerian to me. Could this be a recurrent Mullerian
Adenosarcoma (related to the previous hysterectomy?)

Goran Elmberger: I feel very unsure on this case. Solid part (1.2) looks like possible sertoli Leydig tumor but cystic part (1.1) looks a bit Mullerian to me with ciliated cell, cytogenic/ovarian-like stroma and absence of any muscular coat.

Hugo Dominguez-Malagon: I see a spindle shaped sarcomatous component and glandular areas. I would call this case malignant mixed tumor (carcinosarcoma) of probable Mullerian origin.

Giovanni Falconieri: I almost ignore the subject. Regretfully I cannot comment.

Christopher Fletcher: Assuming that both slides come from the most recent specimen, then I would have difficulty recognising this as FATWO. Instead, to me, the appearances are suggestive of a mixed Müllerian lesion and I would be concerned about the possibility of recurrent adenosarcoma, perhaps related to some unstated pathology in the prior hysterectomy performed when this woman was relatively young. Either way, in the absence of data concerning the original hysterectomy and unilateral oophorectomy, then it would be difficult to come to a definitive diagnosis regarding this lesion. I would be very interested to hear what the GYN experts in the group have to say about this case.

Andrew Folpe: I agree that the more solid piece is good for FATWO. The involvement of the fallopian tube is very strange- I was thinking about all sorts of other things just looking at that section. I shared this with two GYN pathologists here at Mayo, both of whom agreed with FATWO. Thanks for sharing this very interesting case.

Jeronimo Forteza-Vila: Atypical stroma and nuclear morphology are not usual in a FATWO tumor. I would think in a "endometrial stroma sarcoma over an endometriosis".

Janez Lamovec: I have no personal experience with this tumor. Comparing illustrations from articles and books, the tumor is quite similar to FATWO in slide 1.2 but appears as an epithelial-stromal type tumor in slide 1.1. Waiting for the opinion of experts

Thomas Mentzel: Actually, I have no experience with FATWO, but H&E histology shows a biphasic neoplasm. Did immunohistochemical stainings confirm this diagnosis?

Michal Michal: It is very interesting lesion, however, I would not call it as FATWHO. In the slide 1.1, I see an endometriosis and in the slide 1.2, I see a Mullerian tumor having a low-grade sarcomatous and an epithelial component.

Juan Rosai: I don't like very much the diagnosis of FATWHO for this tumor, and neither do my able associates. We would rather interpret this neoplasm as a Mullerian adenosarcoma possibly arisen in endometriosis (there are nice collection of histiocytes beneath the epithelium), and characterized by so called stromal overgrowth, with the emergence of a high grade sarcoma. Interestingly, the latter contains some gland-like elements which still look stromal as far as their cytology goes.

Elvio Silva: Histologically it looks like a FATWO but since the location is unusual I would like to see at least a calretinin and CD10 positive. We have seen FATWO in unusual locations in the abdomen as a recurrence of a primary lesion from the soft tissue around the Fallopian Tube.

Josh Sickel: Agree with diagnosis of FATWO arising from ovary on slide #2.

Dominic Spagnolo: I do not think this is a FATWHO. It looks more like a mixed mullerian tumor, adenosarcoma on slide 1.1, and the more solid portion in slide 1.2 looks like a stromal sarcoma showing sex-cord like differentiation. Were IPOX's done? Is the original ovarian pathology known?

James Strauchen: What an interesting case! Slide 1b looks like FATWHO with a "sieve-like" pattern, but slide 1a looks much more endometrioid resembling a MMMT. Is there immuno? The FATWHO are supposedly positive for calretinin.

CASE NO. 2 – CONTRIBUTED BY DR. BACCHI

Phil Allen: Infiltrating intestinal perineurioma, ileum. This tumour is more vascular and whorled than any of the illustrations in Chris' paper (Am J Surg Pathol 2005; 29: 859-865).

David Ben-Dor: Hats off for the interesting diagnosis. I wonder to what extent the florid vascular proliferation seen in the slide is intrinsic to the lesion and if it can't be simply reactive granulation tissue secondary to the intussusception (given the marked ulceration and hemorrhages). Looking through Chris Fletcher's article the presence of vessels isn't stressed (at least per my reading). How do you think of this diagnosis if all you get are a few colonoscopic biopsy fragments containing a few spindle cells?- I guess you don't.

Ofer Ben-Itzhak: Beautiful case of ileal perineurioma supported by appropriate immunoprofile (Glut 1 and Claudin 1 also stain these tumors).

Gerald Berry: Agree with perineurioma. I must admit that I haven't seen it in this location but the histology and Immunophenotype fits.

Michele Bisceglia: Intestinal perineurioma. Thank you. This is the first case I see in the gastrointestinal site. Parenthetically last year had the opportunity to make a review for the Italian journal Pathologica on both intraneural and soft tissue or extraneural perineuriomas (ST/ENP) (Bisceglia M, et al. Pathologica 2005; 97:92-114), just before Chris Fletcher's paper on the intestinal perineuriomas appeared. Here is the paragraph of that review regarding all the locations which were on record up to that time "*Soft tissue perineurioma or extraneural perineurioma usually occurs in the skin (22,24,32,33,48) as well as in superficial and deep somatic soft tissue (9,13,18,22, 50). However, intraoral (case 2 of a series of 6 in ref. [35], 43), paranasal intrasinusal (18), intraosseous (3,41), retroperitoneal soft tissue (44), and visceral locations have also been observed. Visceral locations of STPN/EPN have been mainly renal both in childhood (17,26), occasioning the clinically difficult differential diagnosis of Wilms' tumor (17), and also adulthood (12,39). A unique intraventricular case in the central nervous system is on record, having histological, immunophenotypical and ultrastructural similarities to the soft tissue analogues (27)*". The numbers refer to references quoted in that review.

Thomas Colby: Intestinal perineurioma seems reasonable (and Chris Fletcher has spoken!). This lesion appears to have more vessels than those illustrated in the AJSP article.

Kum Cooper: Lovely case Carlos. The other differential diagnosis is of course the recently described fibroblastic polyps (J Clin Gastroenter 2005, 39(9):778-78). Thanks. It is amazing how areas of the tumor resemble the different variants of meningioma?

Hugo Dominguez-Malagon: Completely agree with the diagnosis of perineurioma, it has a meningotheliomatous appearance.

Goran Elmberger: Extraordinary case. Seems to fit well with Chris Fletchers paper. As you point out the main differential would be c-kit negative GIST. Did you have the opportunity to check other relevant markers as Claudin, caldesmon and PDGFR mutation?

Giovanni Falconieri: Beautiful case, Carlos. Having no direct background on this I cannot render a diagnostic opinion. Just a great and instructive contribution, as always!

Cyril Fisher: Perineurioma of ileum, terrific case, thanks, Carlos

Christopher Fletcher: This lesion is unusual in being notably infiltrative and only some areas show really typical features of perineurioma, whereas others have a non-distinctive appearance. However, we did find striking EMA positivity at the time Carlos sent the case in consultation and, combined with the multifocally whorled growth pattern and, in places, delicate cytoplasmic processes, then this would certainly seem to fit best with an intestinal perineurioma.

Andrew Folpe: Agree with perineurioma. Thanks, Carlos.

Jeronimo Forteza-Vila: The presence of myxoid areas and the positivity for EMA are definitive for the diagnosis. Differential diagnosis must include GIST and "inflammatory myofibroblastic tumor"

Janez Lamovec: A rare location of a very rare tumor. Architecturally, it does not appear quite those cases described in the article you mention – at least in regard to marked vascularity with cellular whorls.

Thomas Mentzel: Many thanks for sharing this unusual case of intestinal perineurioma, and as said, interestingly, numerous vessels are seen, and tumour cells tend to form perivascular whorls (as in other forms of perineurioma). In addition to elongated spindled cells plump tumour cells with slightly enlarged nuclei are seen as well.

Juan Rosai: I must confess that my H&E diagnosis before I read the immunohistochemical profile was that of inflammatory fibroid tumor. It is in the right location, is characteristically associated with intususception, and is composed of a benign-looking stromal component which is highly vascularised and accompanied by scattered eosinophiles. However, the CD34 negativity and strong positivity for EMA are obviously not very supportive of this interpretation and give some credence to the alternative of a perineurioma. If this is the correct diagnosis, one wonder hw many lesions that were called inflammatory fibroid tumors in the past would be renamed perineuroma at present.

Josh Sickel: Carlos, thanks for submitting this spectacular case. I suspect many of these have been diagnosed in the past as GIST with "unusual features".

Dominic Spagnolo: Agree with perineurioma, intestinal. Thank you for this rare case.

James Strauchen: A good case for the teaching file! Thank you.

CASE NO. 3 – CONTRIBUTED BY DR. BEN-ITZHAK

Phil Allen: Core needle biopsy of hydatid disease, presumably E. granulosus, left ilium, sacral wing and posterior vertebral body with extension into pelvic soft tissues.
What a magnificent case! There was a time (1930-1950) when Hamilton, Victoria, a sheep farming town in South-eastern Australia was recognised as the hydatid capital of the world, and the local surgeon, whose name I can't remember, was proclaimed Hydatid King, at least in the British Empire. In the fifties, I attended a lecture in Adelaide on hydatid disease of bone by this impressive surgeon. The one point I can still remember was his assertion that in bone, E. granulosis grew like E. multilocularis, reverting to the usual cystic growth pattern where it extended outside the bone into soft tissues. I have not read the article by George et al (reference 5) but I wonder if PCR distinguishes E. granulosis from E. multilocularis. E. granulosis is now rare in Australia and strict animal quarantine laws have resulted in E. multilocularis being seen only in human immigrants.

David Ben-Dor: Congratulations on the astute diagnosis (made without having proper clinical information- I'm not sure I have picked up the laminated fragments surrounded by the giant cells or understood what their significance) and welcome to the club. As I write this Northern Israel is being pounded by missiles- I hope that by the time these comments get distributed things will have quieted down and return to normal.

Gerald Berry: Agree. My slide had only minimal numbers of organisms.

Ofer Ben-Itzhak: My case. I admit that the histology of hydatid cyst in the slide is very subtle due to overwhelming degenerative and reactive changes. The patient was a farmer from a Druze village in the Gallilee, where sheep raising is common. I do not know the reasons for the decline in this disease incidence (and especially the surgical resections) here, probably a combination of improved sanitation and more effective drugs.

Michele Bisceglia: Hydatid cyst (echinococcosis) of bone. Hi, dr. ben-Itzahak, welcome to the club! Rare case, difficult to diagnose, since the paucity of the fragmented laminated membrane. We have in our files here one case of (lumbar vertebral) bone location and another case of soft tissue location in the thigh (quadriceps muscle).

Thomas Colby: Hydatid cyst is not unreasonable. I had very little of the distinctive membranes, but I think I would have been lucky to even think of it anyway.

Kum Cooper: Welcome to the club Ofer! This case brings memories of Africa to me. I submitted a case to this seminar (AMR 23) from Africa of a patient who had ruptured cysts of the liver with abdominal recurrence literally being a belly full of cysts! The submission included a kodachrome of the cysts! A potential hazard to sticking a needle into these cysts is fatal anaphylactic shock.

Hugo Dominguez-Malagon: Initially I did not see the hooklets, In Mexico apparently the disease is not endemic (or not diagnosed) nice case, thank you

Goran Elmberger: Difficult and interesting. Not common in Stockholm but occurs. I could retrospectively imagine characteristic parts of laminated membrane material of cyst capsule but did not find any hooklets in my slide.

Giovanni Falconieri: Our experience with echinococcosis sounds somehow similar to yours, with not uncommon cases observed in rural areas of Sardinia and southern Italy, due to sheep farming. Yet I must admit that this is the first example of bone location of a hydatid cyst. The way it was diagnosed also sounds pretty unusual. Thanks for this exotic case and welcome to the Club, Ofer. I wish you and your people may get soon some relief from the anguishing and sorrowful time recently experienced.

Cyril Fisher: Wow – hydatid of bone in a core biopsy. Never seen this before.

Christopher Fletcher: What a remarkable case! I have not previously seen a hydatid cyst in bone – many thanks.

Andrew Folpe: Not in a million years would I have figured that one out (especially since my slide doesn't have hooklets).

Jeronimo Forteza-Vila: I agree with you; it is a difficult diagnosis.

Janez Lamovec: We don't see this lesions anymore. Decades ago, we saw them occasionally, often at autopsy.

Thomas Mentzel: Thanks for sharing this unusual case in bone.

Juan Rosai: Great case of hydatid cyst of bone. I have not seen one of these in skeletal system for a very long time (actually since my Argentinian years).

Josh Sickel: Amazing case, subtle histologic features! I've seen only one case of Echinoccocus at our hospital, diagnosed by FNA of a cystic lung lesion.

Dominic Spagnolo: A great case of echinococcosis involving bone. Thank you.

James Strauchen: We rarely see hydatid cysts other than in the liver. I missed the hydatid cyst wall entirely (there were only a couple of small fragments on my slide). What is the pale mucoid material that elicits the foreign bpdy reaction?

CASE NO. 4 – CONTRIBUTED BY DR. BLEIWEISS

Phil Allen: I don't know anything about kidney tumours but I note in the latest kidney fascicle that the authors, Murphy, Grignon and Perlman, say that a diagnosis of congenital mesoblastic atheroma should be questioned when applied to individuals over two years of age. The seminar case exhibits many of the features described in metanephric stromal tumours in that series 4 fascicle.

David Ben-Dor: I guess that despite the ominous histological appearance and mitotic activity the tissue is capable of responding to whatever normal mechanisms there are which control growth of tissue in children.

Gerald Berry: Agree. Beautiful case.

Michele Bisceglia: Cellular type of congenital mesoblastic nephroma (CMN). Agree that this is a congenital mesoblastic nephroma, but I think this is an example of mixed type – classic and cellular type. Classic type, which has been analogized to infantile fibromatosis was never found associated with a chromosomal translocation, while cellular type which has been analogized to congenital fibrosarcoma has mostly the same chromosomal translocation t(12;15)(p13;q25)

as the latter (Argani P and Ladanyi M. Recent advances in pediatric reanlneoplasia. Adv Anat Pathol 2003;10:243-260). CMN of mixed type was also found associated with the above translocation. About CMn, please let me say here the following notes which I recently learnt. The cellular type also is often cystic. CMN is a renal tumor of the first 3 years of life. The oldest patient so far on record is a 29 months old infant. Beckwith warns against diagnosis of a CMN after the age of 3 years. CMN is alpha SMA positive and CD34 negative. Those cases of CMN diagnosed as such after that age are most likely metanephric stromal tumor (MST) (Argani P and Beckwith JB. AJSP 2000; 24:917-926). MST is CD34 positive and alpha-SMA negative. Notice: in our AMR seminars only one case of pediatric CMN was previously presented (Bisceglia M, AMR Seminar 14, case 2). Another case (also Bisceglia M, AMR Seminar 13, case 14) of so-called "adult" mesoblastic nephroma (plus multicystic nephroma), which actually has to be currently interpreted as mixed epithelial stromal tumor of the kidney (see: Bacchi C. AMR Seminar 34, case 1; Michal M, et al. Mixed epithelial and stromal tumors of the kidney. A report of 22 cases. Virchows Arch. 2004;445:359-67).

Thomas Colby: Agree with diagnosis.

Kum Cooper: Thanks Ira; and this tumor also shares the same cytogenetic abnormality as congenital fibrosarcoma t(12;15).

Hugo Dominguez-Malagon: Mesoblastic neprhroma, beautiful case, thank you.

Goran Elmberger: Congenital mesoblastic nephroma mixed pattern?

Giovanni Falconieri: I agree. Shall look forward to Michele & Michal opinions! Beautiful case, Ira, thank you.

Cyril Fisher: Congenital mesoblastic nephroma, great case. Genetic data would be interesting.

Christopher Fletcher: Great example of cellular mesoblastic nephroma!

Andrew Folpe: Very nice example of a cellular congenital mesoblastic nephroma (infantile fibrosarcoma of the kidney). Were the genetics done?

Jeronimo Forteza-Vila: I agree with you diagnosis; an unusual entity.

Thomas Mentzel: Many thanks for this nice case of a rare entity that is closely related to infantile fibrosarcoma, confirmed by identical cytogenetic findings.

Juan Rosai: I would go along on with the diagnosis of a cellular type of congenital mesoplastic nephroma, although it is hard for me to see how a tumor that looks so awful in areas can behave in a benign fashion. What I mean is that some areas look truly sarcomatous. I guess that is why clinico-pathologic correlation is so vital to our specialty.

Josh Sickel: I've only seen this rare lesion in a teaching set. It's hard to believe that something this atypical will not behave aggressively.

Dominic Spagnolo: Beautiful example of mixed mesoblastic nephroma with cellular and classic patterns. There are tubules showing embryonal metaplasia, and in my section there is also a nodule of cartilage. Have only ever seen a couple of these. Thanks.

James Strauchen: Nice one!

CASE NO. 5 – CONTRIBUTED BY DR. COOPER

Phil Allen: Repeatedly recurrent (x2) phosphaturic mesenchymal tumour with no associated phosphaturia, dermis and subcutis, left lower leg. That's what it looks like to me too. On the basis of Andrew's excellent paper, there must be only a small risk of metastases occurring in this case.

David Ben-Dor: The question is whether one is supposed to recognize this tumor based on the histological findings in the absence of the usually associated metabolic abnormalities (to figure this out I guess I would have to delve into the 30 page reference).

Ofer Ben-Itzhak: Great example of this very rare tumor, I have seen two such tumors, both of which were associated with phosphaturia and osteomalacia (one of which was published in Sem. Arthritis Rheum, 25:35, 1995).

Gerald Berry: I think this is the second example in the AMR seminar collection. Nice case.

Michele Bisceglia: Phosphaturic mesenchymal tumor, without phosphaturia. Kum, it would be extremely interesting to test immunohistochemically this case (as well as those other cases without phosphaturia) with antibody against FGF-23,

which is specifically immunoreactive in phosphaturic mesenchymal tumors. This testing I think was never performed in such a subset of this entity.

Thomas Colby: Agree with diagnosis; this case is sufficiently atypical that its recurring behavior is not surprising.

Hugo Dominguez-Malagon: Very illustrative case of a posphaturic mesenchimal tumor, never seen one before. Thank you Kum.

Goran Elmberger: Dear Kum did the patient show any evidence of oncogenic osteomalacia? If this was not present and if serum and urine calcium/phosphate levels were ok it might be difficult to diagnose case as PMT. I agree the morphological picture is partly in accordance of what is described for this entity by Folpe et al but with my limited experience of soft tissue pathology I could also consider lumping the lesion into the category of giant cell tumor of soft tissues? The PMT was also grouped under the heading of hemangiopericytomas with unusual features in Enzinger 4'th ed and I am not sure the vascular pattern is convincing for this "entity". Is it the stromal characteristics that makes the histological picture patognomonic?

Giovanni Falconieri: Thanks Kum for submitting another extraordinary case. I have seen it in slide seminars only and must admit that it is very challenging.

Cyril Fisher: Phosphaturic mesenchymal tumor, many thanks, Kum. It's good to have a nice example.

Christopher Fletcher: The range of different patterns present in this lesion seems to me quite characteristic of phosphaturic mesenchymal tumour. We have certainly seen morphologically convincing examples unassociated with any biochemical abnormality, which begs the question as to how best to define lesions of this type. The repeated recurrence in this patient (over a ten year period, combined with the focally notable cellularity and mild nuclear atypia) raises the possibility that this particular example may ultimately be more aggressive.

Andrew Folpe: Very good example of a PMTMCT. I think we illustrated 3 examples of histologically classic PMTMCT without known phosphaturia in our paper, and I have seen 2 or 3 since then. The recognition that this really is a specific entity doesn't seem to have spread widely- I just read a radiology case report on oncogenic osteomalacia, where the patient reportedly had a "degenerating hematoma, with myxoid zones and chondroid metaplasia..." Finally, on my section, this tumor starts to get quite cellular, with mitoses and increased nuclear atypia- I am concerned that this is progressing to a fully malignant lesion. Let us know what happens with this case, Kum.

Jeronimo Forteza-Vila: I had never seen any similar case; thank you for let me know it.

Janez Lamovec: This is a real diagnostic challenge, particularly in cases without oncogenic osteomalacia and no wonder that some of such cases were diagnosed as osteosarcoma. We had never seen this lesion in our daily practice, only some seminar cases.

Michal Michal: Today I saw one typical of mesenchymal phosphaturic mesenchymal tumor without apparent phosphaturia in my referral cases.

Thomas Mentzel: That's strange – histologically, the neoplasm shows classical features of phosphaturic mesenchymal tumour, but no associated phophaturia has been reported. Are there any other abnormalities in the serum? Did neoplastic cells stain positively for FGF-23?

Juan Rosai: I thought that this tumor was a sarcoma with metaplastic bone formation and osteoclast like giant cells, and that it had the components that have been described in so called phosphaturic mesenchymal tumor. It sounds funny, though, to make this diagnosis in a tumor that is not associated with phosphaturia.

Josh Sickel: A great slide for the teaching collection. I still haven't encountered this lesion in practice.

Dominic Spagnolo: Thanks Kum for this nice (a)phophaturic mesenchymal tumor. We recently saw a case in-house. Should we not be calling these something else, seeing as a significant minority as you say do not show phophaturia?

James Strauchen: The nonphosphaturic variant of phosphaturic tumor! The "grungy" matrix is nicely demonstrated.

CASE NO. 6 – CONTRIBUTED BY DR. DIETZE

Phil Allen: Ameloblastoma left maxilla. I would not have thought that there is enough atypia to qualify this as an ameloblastic carcinoma. However, the distinction between the two is somewhat artificial because even histologically bland ameloblastomas can metastasize.

David Ben-Dor: The reverse polarization exhibited by a large number of cells at the periphery of the tumor islands is certainly in favor of the suggested diagnosis. Examining the slide before reading the history, I assumed that this is a

tumor arising in skin and thought of trichilemmal carcinoma as a possibility. Curiously there are foci in which the tumor seemingly merges with the epidermis, but it is known that sometimes tumor metastatic to or invasive into benign tissue can seemingly adapt to its surroundings and mimic its originating there.

Gerald Berry: I think that ameloblastic carcinoma is a good diagnosis for this lesion. I was not aware that immunohistochemistry was being used to classify these odontogenic neoplasms.

Michele Bisceglia: Ameloblastic carcinoma. Agree on the diagnosis given. Thank you for this rare case.

Thomas Colby: Squamous carcinoma with clear cell features; my experience with ameloblastic carcinoma is nil but that designation seems reasonable.

Kum Cooper: Without the IHC this looked like clear cell odontogenic carcinoma.
Much thanks.

Hugo Dominguez-Malagon: I agree with the diagnosis of ameloblastic carcinoma, however I must say that the differential diagnosis with clear cell squamous cell carcinoma and other clear cell tumors is difficult to establish.

Goran Elmberger: I was tempted towards the diagnosis of clear cell odontogenic carcinoma given the prominent clear cell features, the marked focal granularity of central cells, the prominent hyalinized and calcified basal membrane like stroma and areas resembling CEOT and odontogenic ghost cell ca. I interpret tendency for inductive mineralization that would be in contradiction of an ameloblastoma or ameloblastic carcinoma. In the AFIP fascicle there is a statement that areas of typical ameloblastoma could be found within CCOC that might explain IHC results. Definitively variant of odontogenic carcinoma.

Giovanni Falconieri: Difficult case. I agree that the lesion has a basaloid pattern reminiscent of that seen in ameloblastic lesions and the striking nuclear palizading and atypia is consistent with ameloblastic carcinoma. It would be interesting to have follow up information, when available. Thanks for this interesting and challenging case.

Cyril Fisher: like a good diagnosis – I've no experience of this.

Christopher Fletcher: I agree that this lesion looks ameloblastic in type but can we really be sure that this is malignant? I have no expertise in this area and will welcome the comments of others.

Andrew Folpe: Agree with ameloblastic carcinoma- thanks for the nice example.

Jeronimo Forteza-Vila: I agree with your diagnosis.

Janez Lamovec: I am not able to differentiate a so-called clear cell odontogenic carcinoma from clear cell variant of ameloblastic carcinoma.

Thomas Mentzel: Histologically, an infiltrating and obvious malignant clear cell neoplasm is seen. Given the reported immunohistochemical findings and the tumour cell cytology, I was thinking (despite the solid growth of the neoplasm, that is lacking typical stromal changes) on myoepithelial carcinoma (malignant myoepithelioma).

Juan Rosai: Good case of malignant clear cell tumor of odontogenic origin, consistent with so called ameloblastic clear cell carcinoma.

Josh Sickel: Beautiful example of a rare tumor!

Dominic Spagnolo: I would agree with your interpretation of ameloblastic carcinoma, but not based on any personal experience of this. Thanks for the case.

James Strauchen: Ameloblastic carcinoma. Nice case!

CASE NO. 7 – CONTRIBUTED BY DR. Eusebi

Phil Allen: Rosai-Dorfman disease, left temporal lobe and meninges with no recurrent disease at 10 years. I have never previously seen CNS Rosai-Dorfman and have only seen about two soft tissue cases. Fortunately there are at least two World experts on this disorder in the club, and I look forward to their comments

David Ben-Dor: The lesional histiocytes show varying degrees of pleomorphism and strange nuclear features approaching those of Reed-Sternberg cells; I didn't know that this can be seen in this lesion. I also found an atypical mitosis. But I've never seen a case in real life. But Dr Rosai in his textbook does mention metastatic melanoma as a possible differential diagnosis and also points out that "RDD like changes" can be sometimes seen in Hodgkin's disease. I know that exposure of brain tissue to materials it isn't used to, such as blood (in hemorrhages and hemorrhagic

infarctions) and pus leads to fibrosis (bland ischemic infarcts are supposed to heal via gliosis only), so it would seem that the brain doesn't like this process. This could be an excuse to visit the fancy restaurant to inquire as to the lady's condition- would being a member of the AMR get one a discount?

Ofer Ben-Itzhak: Great case. In the last years I have seen increasing cases of cutaneous Rosai-Dorfman disease, but I have not seen intracranial example (or missed it).

Gerald Berry: Agree. I didn't get a chance to show Dr. Dorfman the case or elicit his thoughts on the prognosis.

Michele Bisceglia: Rosai-Dorfman disease of the meninges. Agree. Up to less than 3 years ago, while making a review of Erdheim-Chester disease in the meninges and brain (Bisceglia, et al. Adv Anat Pathol. 2003;10:160-71), I was involved in looking also for Rosai-Dorfman disease in the same area (as differential diagnosis), and found the following articles which might be of interest here: 1. Osenbach RK. J Neurosurg 1966; 85:692-696; 2. Foucar E, Rosai J, Dorfman RF, et al. Neurology 1982;32:365-371; Song SK, et al. AJSP1989;13:406-412.

Thomas Colby: Given the immunohistochemistry and the follow-up I would have to go along with Rosai-Dorfman disease but I was bothered by the cytologic atypia. To me the fibrous is part of this lesion regardless of its site.

Kum Cooper: Thank you Vincenzo. I saw many more cases of RDD (5 or 6 a year) in Africa including the meninges (than I do here in Vermont; 2 cases in 7 years!)

Hugo Dominguez-Malagon: Rosai Dorfman, I have never seen an intracranial case, thank you.

Goran Elmberger: Interesting and rare case. Emperipolesis is a great tip of. What is the speciality of their cuisine?

Giovanni Falconieri: I have not seen cases of RDD outside slide seminars. Gorgeous case, Vincenzo. Thanks for this submission. Shall look forward to the "Master" comment.

Cyril Fisher: Authenticated case of Rosai-Dorfman disease involving the CNS!

Christopher Fletcher: Very convincing example of Rosai-Dorfman disease. I can personally recollect seeing only one example in CNS tissue in the past – as I remember, that one also was associated with some stromal fibrosis.

Andrew Folpe: I thought this looked a little bit funny for extranodal RD, but then again, I seldom see dural tumors. I shared this with Bernd Scheithauer, who thought that this was RD involving the dura. So there you have it from someone much more knowledgeable than me.

Jeronimo Forteza-Vila: I agree with the diagnosis if Dr. Rosai confirmed it.

Janez Lamovec: Extraordinary case. Thank you for your contribution.

Thomas Mentzel: Many thanks for this nice case.

Juan Rosai: Not the most typical case of the disease, but acceptable in view of the strong S100 protein positivity.

Josh Sickel: There is a surprising degree of nuclear atypia in the lesional cells.

Dominic Spagnolo: Beautiful example of Rosai-Dorfman disease involving dura and brain. We see a fair bit of surgical neuro-oncology here, but our neuropathologist tells me he is not aware of any case in our files. As for the fibrosis, given all the immune cells in the lesion, perhaps it is not surprising this has happened.

James Strauchen: Rosai-Dorfman! We have seen a number of intracranial presentations over the years, mostly dural, and one case with no apparent connection to the dura. Many of the "inflammatory pseudotumors" of the dura reported in the literature are actually Rosai-Dorfman.

CASE NO. 8 – CONTRIBUTED BY DR. FISHER

Phil Allen: Diffuse ganglioneuromatosis of the ileum in a patient with NF-1 and a malignant retroperitoneal peripheral nerve sheath tumour. Thanks for this excellent case and the discussion, Cyril.

David Ben-Dor: I pity the poor patient. The images of the S100 stained slides are very nice and demonstrative.

Gerald Berry: Beautiful example of neurofibromatosis of the bowel.

Michele Bisceglia: Diffuse ganglioneuromatosis in a NF-1 patient. Nice case, Cyril. Have one in my files. Other gastrointestinal manifestations in NF-1 on record, in addition to those already listed, are the following: gangliocytic duodenal paraganglioma, ampullary duodenal adenocarcinoma, and varied types of enteropancreatic neuroendocrine tumors.

Thomas Colby: Spectacular case.

Kum Cooper: Thanks Cyril. We see the localized type of ganglioneuroma presenting as polyps in the colon; but the diffuse type is a "treat".

Hugo Dominguez-Malagon: Nice case and discussion of difuse ganglioneuromatosis of the intestine.Thank you.

Goran Elmberger: Agree. Difficult to pick up on mucosal biopsy! Must be rare. Thanks.

Giovanni Falconieri: This is phenomenal. The repertoire of extraordinary cases is piling up fast in this seminar.

Christopher Fletcher: Beautiful example of ganglioneuromatosis involving the small bowel – I have personally only seen one or two cases previously and have never received one as an actual surgical specimen.

Andrew Folpe: Fantastic example of ganglioneuromatosis. As luck would have it, the very next week I saw a case of MPNST arising in intestinal ganglioneuromatosis- I will have to submit it for this club.

Jeronimo Forteza-Vila: Very interesting case.

Thomas Mentzel: A very interesting case of diffuse ganglioneuromatosis in a patient with neurofibromatosis type 1.

Juan Rosai: Great example of so called ganglioneuromatosis.

Josh Sickel: I've only read about this condition in textbooks. Have only encountered solitary polypoid ganglioneuromata in practice.

Dominic Spagnolo: Wow! Great case Cyril. The ganglion cells are also present within the plexiform neurofibromatous nerves outside the gut wall. How can one be sure the ganglion cells represent a hyperplastic process? I find it easier getting my head around a hybrid plexiform neurofibroma/ganglioneuromatosis.

James Strauchen: Remarkable case! I was unaware of this association.

CASE NO. 9 – CONTRIBUTED BY DR. FLETCHER

Phil Allen: Oncocytic glomus tumour. I trust that your technicians have not been too heavy-handed with the eosin, Chris!

David Ben-Dor: There are areas which show the usual features of non-oncocytic glomus tumor. I admit that many of the cells show increased eosinophilia, but I always thought that true oncocytic change implies significant cell enlargement (required to accommodate the numerous mitochondria) and cytoplasmic granularity (which is hard to make out). Could the eosinophilia be a degenerative process related to the long duration of the lesion? It isn't stated whether EM or immunohistochemical stains for MART were performed.

Gerald Berry: I have not seen such n oncocytic pattern in this group of tumors. It is remarkable.

Michele Bisceglia: Oncocytic glomus tumor. On a recent review of the literature, while preparing a paper on Oncocytoma of Soft Tissue for the journal Pathologica (Bisceglia M, et al. 2005;97:343-360), had the opportunity to make a review of this issue, and obviously looked also for the other non-epithelial tumors with oncocytic changes. Here it is a paragraph from that review: "*Few examples of tumors of non-epithelial origin with oncocytic changes (e.g., adult rhabdomyoma [3], epithelioid leiomyosarcoma [4], glomus tumor [5], paraganglioma [6], extramedullary plasmacytoma [7]) are also on record. In these latter cases however the light microscopical, electronmicroscopical and immunohistochemical features of the cell lineage of differentiation were still retained and identified. Only two cases of genuine oncocytomas of soft tissues have been reported so far in the world literature (8-10)*". The numbers refer to the refs quoted in that paper.

Thomas Colby: Glomous tumor; the cells are a little pink but I am not sure I would go as far as oncocytic. And don't we need to prove there are large numbers of mitochondria to use that term?

Kum Cooper: Thanks Chris. I recognized the glomoid nature but not the oncocytic differentiation!

Hugo Dominguez-Malagon: Glomus tumor, it certainly looks oncocytic, thank you.

Goran Elmberger: Difficult case. Looking blindly at slide I entertained dx of carcinoid but I had a hard time recognizing tissue of origin. Might be a tip of for mesenchymal nature.

Giovanni Falconieri: Nice case, Chris. Learning will never end looking at this club glasses!

Cyril Fisher: Glomus tumor with oncocytic change, most unusual. Fortunately there are small areas with more typical histology.

Andrew Folpe: Oncocytic glomus tumor- nice case.

Jeronimo Forteza-Vila: I had never seen any similar case.

Janez Lamovec: Without reading a history this appears almost as a parathyroid adenoma! Thank you for this exceptional case.

Thomas Mentzel: Many thanks for this unusual glomus tumour mimicking an epithelial neoplasm.

Juan Rosai: Beautiful example of a very solid form of glomus tumor. I don't know whether I would have recognized it as onocytic.

Josh Sickel: Agree with diagnosis of glomus tumor. I wasn't aware of the oncocytic variant.

Dominic Spagnolo: I have to say, I thought this was a solid glomus tumor, and it did not strike me as being particularly oncocytic. Was there confirmation of it being mitochondria-rich?

James Strauchen: Looks like a glomous tumor by pattern. I was unaware of the oncocytic variant.

CASE NO. 10 – CONTRIBUTED BY DR. FORTEZA-VILA

Phil Allen: Sarcomatoid carcinoma of the adrenal gland. I agree with the diagnosis. I prefer that term to adrenal carcinosarcoma.

David Ben-Dor: An interesting diagnosis. It's also interesting that given the expected malignant behavior of adrenal carcinomas and sarcomatoid carcinomas (and this lesion combines both!) the patient went for three years without metastases. I apologize but I don't know what ENE is supposed to mean. I was also taught by Chris Fletcher a few years ago that EMA can be positive in leiomyosarcomas.

Ofer Ben-Itzhak: Malignant tumor of adrenal, maybe sarcomatoid adrenocortical carcinoma (would be interested to know results of Inhibin, Calretinin, Melan A, CD99). The histology and the positive muscle markers raise the possibility of epithelioid PEComa (HMB45 stain?). I also considered a peculiar variant of follicular dendritic cell tumor, but the muscle markers are unusual for this possibility.

Gerald Berry: I couldn't appreciate an epithelioid component in my slide. It looks a very undifferentiated malignant neoplasm to me.

Michele Bisceglia: Sarcomatoid carcinoma of the adrenal gland. Am not sure that this is a well documented case of carcinoma. Cytokeratin stains are not mentioned (how were CK 8/18?). Look forward to others' opinions. Would exclude epithelioid leiomyosarcoma first, testing even for other muscle specific markers (e.g. calponin, h-caldesmon). In my opinion, leiomyosarcoma of the adrenal, which has been described, might be a possibility here.

Thomas Colby: Agree with diagnosis.

Kum Cooper: I was going down the complete opposite route of phaeo/pecoma/FDC!!!

Hugo Dominguez-Malagon: Sarcomatoid carcinoma of the adrenal, there is a striking inflammatory component in the sarcomatous area.

Goran Elmberger: Very interesting case. Lesion has a "clonal" appearance but no definitive adenoma identified in my slide. In AFIP fascicle and WHO the terminology still seems to be carcinosarcoma but I would as yourself prefer the terminology of sarcomatoid carcinoma since I do not really believe collision tumors to be that common. Ofcourse the mesodermal origin of adrenal cortex does mix up the logics somewhat.

Giovanni Falconieri: In my section I see two different things. One is a clearly malignant tumor made up of epithelioid, sometimes multinucleated or spindle cells: I agree that this may represent an example of sarcomatoid carcinoma of the

adrenal gland. You did not mention keratin stain so I presume it was negative, which is not surprising in adrenal carcinoma. Then, in continuity/collision with such sarcomatoid lesion, there is a a pleomorphic tissue featuring large, mono- or multinucleated atypical cells with clear nuclei sitting within a lymphocyte-rich background that looks. In that area the tumor has a "lymphoepithelioma" like face. Thanks for contributing this nice and difficult case.

Cyril Fisher: Sarcomatoid carcinoma, amazing case.

Christopher Fletcher: Seems convincing, although it is surprising that the adjacent adrenal gland is pretty much intact. I apologise but I am unfamiliar with ENE – what is that? It would be interesting to know whether this tumour showed any staining for Melan-A or inhibin.

Andrew Folpe: I would favor a leiomyosarcoma, probably arising from the adrenal vein, over a sarcomatoid carcinoma. The morphology is not bad for LMS, and the immunohistochemical results would seem to point rather strongly in that direction (SMA, PMA, desmin positive).

Jeronimo Forteza-Vila: Before immunohistochemistry results, the differential diagnosis must include malignant melanoma and rhabdomyosarcoma.

Janez Lamovec: One of the neoplastic nodules is so densely infiltrated with lymphoid cells that almost simulates lymphoma. We once had a case that was to some extent similar to other nodules with spindle cell in this case but it presented as one single large nodule

Thomas Mentzel: Thanks for sharing this rare neoplasm.

Juan Rosai: I would not go beyond the diagnosis of anaplastic malignant tumor with inflammatory MFH-like features.

Josh Sickel: This has a PEComa-like appearance in some areas. The inflammatory component is also intriguing. Thanks for this extraordinary case!
Dominic Spagnolo: Could this be a follicular dendritic cell tumor?

James Strauchen: Thanks for this unusual case. I was unaware of a specific sarcomatoid variant of adrenal cortical carcinoma. The inflammatory component is striking resembling so-called inflammatory MFH.

CASE NO. 11 – CONTRIBUTED BY DR. GOWN

Phil Allen: Epithelioid schwannoma, breast. I think this has also been called neuroblastoma-like schwannoma (Am J Dermatopathol 25: 32-34, 2003).

David Ben-Dor: Interesting- I wonder if I would have considered this as a strange (possibly malignant) melanocytic lesion with the S100 positivity confusing the issue. This is a good reminder that not everything that is small and round and S100 positive is necessarily melanocytic.

Ofer Ben-Itzhak: Excellent, educating case.

Gerald Berry: Agree. Nice example of an epithelioid schwannoma.

Michele Bisceglia: Epithelioid schwannoma. Nice case. The first assessment of this entity I think was made by Swedish authors (Kindblom LG, Meis-Kindblom JM, Havel G, Busch C. Benign epithelioid schwannoma. Am J Surg Pathol 1998;22:762-70).
Thomas Colby: Agree with diagnosis.
Kum Cooper: Lovely example Allen. I saw a case a few months ago in the dermis/skin of the extremity.

Hugo Dominguez-Malagon: Epithelioid Schwannoma, I find difficulty in the differential diagnosis with a myoepithelial tumor that may be S100+ and collagen IV+. Electron microscopy would be interesting in this case.
Goran Elmberger: Very nice case. I had a similar lesion on my microscope some weeks ago from inguinal area 34 year old woman. The S100 and CT4 was very convincing but our soft tissue pathologist was so worried by the mitotic activity in that case he recommended signing out case as low-grade epitheloid MPNST. I had my doubts but followed his recommendations. Now I note at least 5 mitotic figures in my slide of your case?

Giovanni Falconieri: I don't know the subject so I must accept this interpretation. At a glance, tumor cells have a nevoid appearance. There is a nice though not constant delicate fibrous rim at the periphery. The mitotic index is low, yet concerning for a lesion expected to pursue a benign course. Thanks for contributing this rare case.

Cyril Fisher: Benign epithelioid schwannoma, very nice example.

Christopher Fletcher: Convincing example of epithelioid schwannoma. These lesions seem to show a distinctively microlobulated growth pattern and, as Allen says, also quite often seem to show degenerative nuclear atypia. For some reason, we seem to have seen more examples of this type of tumour over the past couple of years – I wonder what we all used to call them in the old days?

Andrew Folpe: Entirely agree with epithelioid schwannoma.

Jeronimo Forteza-Vila: Very interesting case.

Janez Lamovec: This tumor somewhat resembles an epithelioid myoepithelioma but given its negativity for keratins an EMA the latter diagnosis is excluded.

Thomas Mentzel: Given that the presence of epithelioid malignant changes in cases of schwannoma represents a putative precursor lesion of epithelioid malignant peripheral nerve sheath tumour (Am J Surg Pathol 2001; 25: 13-25), I found the presented case very difficult to diagnose, because scattered mitoses and some degree of atypia are evident.

Juan Rosai: I guess we will have to accept the diagnosis on the basis of the immunohistochemistry, because I would have never guessed on the basis of the H&E.

Josh Sickel: I completely missed the diagnosis. My first impression was a myoepithelial tumor.

Dominic Spagnolo: Thanks for this uncommon benign epithelioid nerve sheath tumor. On my slide I was impressed by focal nuclear pleomorphism and macronucleoli. As you say, it conforms precisely to the cases described by Laskin et al.

James Strauchen: Nice case! I have never seen one before (or if I did I called it something else!).

CASE NO. 12 – CONTRIBUTED BY DR. DAMJANOV

Phil Allen: Acral inflammatory myxohyaline tumour (Montgomery), foot. The virus-like inclusions are not too obvious but I have at least one other case on file where they were less prominent than in this instance. I started to recognise this tumour in about 2000 and since then, I have diagnosed about eight cases, including one on the trunk. (I am excluding seminar cases). I see between 600 to 700 referred soft tissue cases per year. As soft tissue tumours go, this one must be comparatively common. For the previous 30 odd years, I think I called them myxoid malignant fibrous histiocytomas or inflammations although they are perfectly easy to recognise, once someone else tells you how do it. Those of us who wear hats should take them off to Elizabeth, the uncrowned Queen of the AMR club. I am so pleased that her application was eventually successful (Ann Diagn Pathol 3: 262, 1999).

David Ben-Dor: Mundane is in the eyes of the contributor. I see only occasional soft tissue tumors but we had one of these a few years ago. There is a lot of fibrosis and inflammation, and given the history of previous treatment, it would be tempting to write this off as "reactive changes". There are hyperchromatic cells but there is also a degree of crush artifact in the slide which masks this to a certain degree and which makes it difficult to appreciate the fine cytologic details. To be perfectly honest I don't know if I would have picked this up.

Ofer Ben-Itzhak: I have seen only 2 cases of this tumor (since its definition in 1998), one from another hospital, and the other was a small one with more proximal location (elbow), which was confirmed by Dr. Fletcher. What was the type of the multiple hemangiomas? Are they associated with the current tumor?

Michele Bisceglia: Acral myxoinflammatory fibroblastic sarcoma (inflammatory myxohyaline tumor). Agree. This tumor was also described by Michal M, et al (Michal M. Inflammatory myxoid tumor of the soft parts with bizarre giant cells.Pathol Res Pract. 1998;194:529-33) with a report of 5 cases, at the same time (same year) when those other major papers by Montgomery et al, and Meis-Kindblom et al appeared).

Kum Cooper: Ivan post-sclerotherapy MIFS is not mundane! I think these tumors are rare in a general pathology sign out service. I have only seen three examples; one of which was published with the series with Janez. This paper also has a case with a cytogenetic abnormality (Ann Diagn Pathol 2002; 6:272-280).

Hugo Dominguez-Malagon: My experience with acral myxoinflammatory fibroblastic sarcoma is rather limited, I have seen two cases in my hospital (both after 1988 of course).

Goran Elmberger: Thanks. Great case to see for a new member in the club! Can not comment on frequency since our soft tissue pathology is sub specialized.

Giovanni Falconieri: Thanks for this excellent contribution. I agree with the interpretation since this case is comparable with others previously seen in slide seminars including the AMR. Regarding your question: I believe this has to be very

rare, yet I think that a minor but sizable number of cases go unrecognized either because the diagnostic features are buried within an excess of fibrous or myxoid stroma, hence received other names, or simply because people do not think about it.

Cyril Fisher: I think we are recognizing this tumor more frequently, and those working in soft tissue tumor referral centers might see several cases a year but no more than one per referring institution so it is still uncommon in daily practice!

Christopher Fletcher: Beautiful example of acral myxoinflammatory fibroblastic sarcoma! I do not think that these lesions are especially rare but they are undoubtedly exaggerated in consultation material. Many of them never make it to the bigger sarcoma clinics, because most of these tumours only pose problems in terms of local control and metastasis seems to be extremely rare. We have seen convincing examples arising in the proximal limbs or even on the trunk – but, again, such relatively unusual cases may well be exaggerated in consultation material.

Andrew Folpe: Good example of myxoinflammatory fibroblastic sarcoma. These are not terribly rare at all, in my experience. I have seen upwards of 4-5 in a single week (in consult cases), on more than one occasion. I've also seen a recent trend for people to underdiagnose more conventional myxoid MFH/myxofibrosarcomas as MIFS.

Jeronimo Forteza-Vila: I have not experience about this entity.

Janez Lamovec: I believe that this tumors are rare but Chris may give you an estimate of how common they are. We saw some 5 to 6 cases in 10 years time, some in consultation. In regard to morphology, the quality of interstitial matrix varies a lot: it may be almost completely myxoid or sclerotic, with or without sclerotherapy. However, the diagnostic cells – Reed-Sternberg-like, lipoblasts-like or virucytes-like are always present.

Michal Michal: Acral myxohyaline fibroblastic sarcoma. I see 1-2 cases a year, however, practically always in consultation. I am always amazed with the range of morphologic features. Some lesions have hardly perceivable emperipolesis (as this case) and some lesions have emperipolesis dominating the picture. (Kinkor Z., Michal M.: Inflammatory myxohyaline tumor with massive emperipolesis. Pathology Research and Practice, 2002; 198; 639-642.)

Thomas Mentzel: Many thanks for this nice case. Although it is difficult to estimate the exact frequency of this distinct neoplasm, it seems to be more frequent as previously believed, and many cases have been probably (mis)diagnosed as myxofibrosarcoma.

Juan Rosai: It has the morphologic features of the entity (AMFS) but I don't understand what is the relation with the multiple hemangiomas or the history of sclerotherapy.

Josh Sickel: I have not encountered this rare tumor in 17 years of practice.

Dominic Spagnolo: This is not mundane, and it is one of the best examples of myxoinflammatory fibroblastic sarcomas I have seen- thank you. This is not a common lesion at all in my experience.

James Strauchen: Nice case! The so called "virocytes" or "Reed-Sternberg-like" cells are supposedly characteristic. The involvement of a hemangioma must be unique!

CASE NO. 13 – CONTRIBUTED BY DR. LAMOVEC

Phil Allen: Undiagnosed, histologically atypical, xantho-inflammatory lesion, probably malignant, subcutis right side of chest wall, Erdheim-Chester disease, leprosy and malacoplakia to be excluded. This is rather like an inflammatory malignant fibrous histiocytoma. After seeing cases like this, one can understand why Oberling thought that his retroperitoneum lesions were inflammatory rather than sarcomas.

David Ben-Dor: I think that the term "malignant fibrous histiocytoma" was invented for a case such as this. That designation has fallen into disrepute and doesn't mean much anymore- but as a purely descriptive device it's convenient (isn't that still part of what pathologists do?).

Ofer Ben-Itzhak: I have never seen this kind of tumor. It has areas of "xanthogranuloma" and areas xantho and inflammatory components, the deep location and atypical cells are not features of the latter cellular neurothekeoma may express histocyte markers and CD10 (J. Cutan. Pathol. 31:568, 2004), and stains for NK1C3 and PGP9.5 may be suggested. (Malignancy arising in neurothekoma?)
A variant of inflammatory myofibroblastic tumor?

Michele Bisceglia: Unclassified malignant epithelioid and spindle cell tumor with clear cell features and bizarre giant cells and prominent inflammatory and foam cell component). Janez, your question is if (other than giving a descriptive definition) this tumor may be otherwise classified. If it is mesenchymal and if it is malignant, and if it is xanthomatous, and if it expresses histiocytic markers, why not to call it "xanthosarcoma". This was a genuine reasoning that I made.

Then I went to the index of Enzinger's and Weiss' textbook and found that xanthosarcoma is almost synonymic with inflammatory MFH, but this might be another matter.

Thomas Colby: The suggested diagnosis sounds descriptively appropriate. I can't really add anything.

Kum Cooper: Sorry Janez, I do not have any valuable contribution to make.
However, you now have two cases; so a third will make a series...correct?

Hugo Dominguez-Malagon: Sorry Janez, I have no idea, just dumped this tumor into the wastebasket and called it inflammatory MFH

Goran Elmberger: No I have not seen anything like this. Striking variation of pleomorphism. In some areas very bland cellular features reminiscent of hibernoma – brown fat. Maybe hibernoma with malignant "dedifferentiation", but on the other hand I might just be mistaking some macrophages for brown fat cells. IHC should easily sort out these thoughts.

Giovanni Falconieri: A difficult case Janez. Obviously, I cannot come up with a better interpretation.

Christopher Fletcher: Thank you, Janez, for continuing to torture me with this impossible case! In the slides submitted for this seminar, the foamy histiocytes are notably predominant and the bizarre clear cell component is relatively less conspicuous.

Andrew Folpe: I'd just call this a "sarcoma with prominent chronic inflammatory cell infiltrate". Not everything has a name.

Jeronimo Forteza-Vila: I think it could be an xanthomatous malignant fibrous histiocytoma.

Thomas Mentzel: To be honest I haven`t seen a neoplasm like this before. The neoplasm reminds me to a malignant histiocytoid neoplasm with clear and foamy cell changes.

Michal Michal: Acral myxohyaline fibroblastic sarcoma in non-acral location. The lesion has all three cells typical of this entity set in inflammatory background; 1. cells with emperipolesis, 2. cells with myxoid matrix in the cytoplasm and 3. cell with giant nuclei with nucleoli with Sternberg-Reed like features.

Juan Rosai: It looks like a malignant histiocytic tumor. I know it sounds crazy, but I thought of a neoplastic counterpart of Rosai-Dorfman disease.

Josh Sickel: I suspect many would classify this as "MFH", albeit politically incorrect!

Dominic Spagnolo: Sorry I have nothing to add Janez, and I don't have a name for this odd pleomorphic xanthomatous tumor. I guess it has to be at least a borderline lesion but I am not convinced it is necessarily malignant.

James Strauchen: I think this is an atypical fibrous histicytoma. Although there is marked nuclear pleomorphism, there are virtually no mitoses.

CASE NO. 14 – CONTRIBUTED BY DR. MIETTINEN

Phil Allen: Gastric Schwannoma. You may find this hard to believe but I saw an almost identical case in consultation about four hours ago. I don't think I have seen any others since I left the AFIP in 1970.

David Ben-Dor: I usually think of schwannomas when I find the classical features familiar to all residents: palisading and the Antoni A and B areas. These features weren't apparent (at least not readily) on this slide.

Ofer Ben-Itzhak: Thanks for the very clear discussion.

Gerald Berry: Nice example and discussion of gastric schwannoma.

Michele Bisceglia: Gastric schwannoma. Have seen 2 of such cases in the last 3-4 months. Marku, if you go my comment on the case of David Ben Dor (case 1) in AMR Seminar 48 you see the following statement there. "*Quite recently we have seen here a case of true gastric "schwannoma" with massive peripheral pseudolymphomatous lymphocytic infiltration: but the infiltrate was mixed (B- and T-cell with some follicles and reactive germinal centers) and was peripherally located."* The peripheral lymphoid infiltrate was really massive in my case.

Kum Cooper: Thanks for this example Marku. We see about one case a year of gastric schwannoma; supporting the need to target the IHC towards the differential diagnosis.

Hugo Dominguez-Malagon: Gastric Schwannoma, nice case.

Goran Elmberger: Must be very unusual. This might be a tumor where it actually was easier to review slide blindly first.

Giovanni Falconieri: Nice case. Very unusual, especially in the kit era.

Cyril Fisher: Beautiful gastric schwannoma, thanks, Markku.

Christopher Fletcher: Perfect example of gastric schwannoma – this is another tumour type which appears (probably artifactually!) to have become more common in recent years, probably because of the attention focused on GIST. These lesions are typically unencapsulated and may have a somewhat infiltrative margin, comparable to that seen in schwannomas of the upper respiratory tract.

Andrew Folpe: Thanks for the nice recut of a digestive schwannoma, and for the nice write-up.

Jeronimo Forteza-Vila: Negativity for c-Kit and SMA rule out GIST, lesion that I think it is the first diagnostic possibility.

Thomas Mentzel: A nice case of a large gastric schwannoma with degenerative atypia.

Juan Rosai: Very nice case of gastric schwannoma, and a good demonstration of how different this tumor looks from GIST and smooth muscle tumors.

Josh Sickel: The few cases I've seen have all had prominent reactive lymphoid stroma. Nice reminder that not all gastric spindle cell tumors are GIST's.

Dominic Spagnolo: Very nice example of gastric Schwannoma. Rare in my experience.

James Strauchen: Gastric Schwannoma. Nice case. Is there any significance to the lymphoid infiltrate at the periphery? Unlike peripheral nerve Schwannomas it seems circumscribed but incompletely encapsulated.

CASE NO. 15 – CONTRIBUTED BY DR. MICHAL

Phil Allen: Undiagnosed, 3cm, histologically indeterminate, round cell tumour with occasional mitoses, no pleomorphorism and perivascular hyalinisation, subcutis, trunk, ?EMA positive solitary fibrous tumour. I confess to a weakness for solitary fibrous tumours and a moderate aversion to all perineurial tumours. This illogical prejudice is due entirely to the "family" name, "perineurioma".

David Ben-Dor: Whatever you say, Michal. Thanks again for the kind expression of encouragement and support (more deserved by Ofer than by me).

Michele Bisceglia: Round cell variant of low-grade perineurial sarcoma (?). Might be. EM would be critical, and I would try it again to get more convincing features of perineurial differentiation, if the ones you already have are not very convincing.

Kum Cooper: Michal, I was working towards a myoepithelioma; but clearly the IHC
does not fit?

Hugo Dominguez-Malagon: No idea, Ouside the tumor there are ductal structures, could it be a rare skin adnexal tumor?.

Goran Elmberger: Getting late! I have no comment except for the prominent nuclear grooving?

Giovanni Falconieri: Looks a low grade tumor. There is a nice encapsulation; cell atypia and mitotic activity are not terrific but enough not to call this benign. I don't know the entity that you mention, Michal: my attention was also caught by the excess of plasmacells within the tumor and around hyalinized vessels (I would order a Congo Red stain). Is a rich vasculature part of the perineurioma morphologic spectrum? Cell discohesion and glassy cytoplasm may also suggest melanoma. I assume S100 was negative.

Cyril Fisher: Morphology and immuno suggest perineurial cell tumor with focal epithelioid change and some atypical features.

Christopher Fletcher: Difficult case which I personally would find very hard to classify on H&E – the appearances would not fit well within the currently recognised spectrum of perineurial neoplasms but I suppose that this does not exclude that possibility.

Andrew Folpe: I'm not really sure what that is. Perineurial sounds good. I also considered a variant of a mammary-type myofibroblastoma. It looks benign to me- conservative re-excision and followup should be enough.

Jeronimo Forteza-Vila: The presence of atypical cells, although few, are consisting with malignant lesion.

Janez Lamovec: This appears as a glomangiomyoma to me but with this immuno results, I don't know.

Thomas Mentzel: I find the idea of a predominantly round cell perineurioma very interesting. Also in typical cases of extraneural perineurioma, scattered plum or round cells are usually seen. However, is the neoplasm clearly malignant ?

Juan Rosai: What about a myoepithelioma of sweat gland derivation?

Josh Sickel: Very distinctive tumor……I don't have a clue!!

Dominic Spagnolo: I have no idea what this is. I would not intuitively thought of perineurioma, and indeed the deeply cleft/grooved nuclei I have never seen in perineurioma- they look more like the nuclei of dendritic cells. Further, what are the pleomorphic granulated cells- immature myeloids? (EMH?)- they don't all look like mast cells which are also prominent. Your idea of perineurioma is clearly a consideration based on the IPs, but I can't be sure. Yet another Michal special.

James Strauchen: Epithelioid something ?Schwannoma? perineurioma

CASE NO. 16 – CONTRIBUTED BY DR. SILVA

Phil Allen: Clear cell endometrioid neoplasm, right adnexa. I agree that it is different from other clear cell tumours of the female genital tract and don't think I have seen one before. The death rate of around 40% in a median follow-up time of 27 months suggests that it is a fairly high grade carcinoma, despite the comparatively bland appearances of the nuclei.

David Ben-Dor: thanks for affording us this pre-publication "sneak preview" of this interesting new entity. Architecturally to my mind in many places this tumor shows the merging large labyrinthine like spaces with minimal stroma seen in the expansile type of primary mucinous carcinomas of the ovary instead of the well defined small to intermediate sized glands seen classically in endometrioid tumors. The stroma where seen is not the reactive desmoplastic type found in endometrioid carcinomas, and the nuclei are in places very bland and don't show the typical coarse chromatin pattern (though maybe this feature disappears in secretory carcinomas). On the slide I received the majority of nuclei are smack in the middle of the cell. Curiously I found one small focus composed of goblet like mucinous cells with bulbous protrusions into the lumen.

Gerald Berry: I look forward to the publication!

Michele Bisceglia: Endometrioid carcinoma of the ovary with massive clear cell changes. Beautiful case. Even the pathogenetic mechanism of this feature is analogous to the causes ascribed in the clear cell changes of some thyroid lesions (lipid, mucin, glycogen, hydropic change) we recently discussed in a review on unusual non-neoplastic lesions in the surgical pathology of the thyroid (Magro G, et al. Pathologica 2006;98:119-138).

Thomas Colby: Clear cell endometrioid neoplasm, nonsecretory type. Is this the one case in the series that was called a borderline tumor? If this is adenocarcinoma, what are the criteria to call it carcinoma?

Kum Cooper: Thank you Elvio for adding clarity to the clear cells that we occasionally encounter in the GYN endometrioid tumors. Thank for the abstract as well.

Hugo Dominguez-Malagon: Spectacular case of clear cell change in endometrioid carcinoma, thank you.

Goran Elmberger: Interesting and important ddx.

Giovanni Falconieri: Very intriguing case. At a glance I guess that many pathologists would call it secretory, low grade carcinoma. I believe that your paper on the matter shall fill a gap.

Christopher Fletcher: I have no experience with comparable lesions – thanks for the educational abstract.

Andrew Folpe: Thanks for sharing this "work in progress"- a very nice illustration that not everything in the GYN tract with clear cells is clear cell carcinoma.

Jeronimo Forteza-Vila: Thank you for this interesting case and your comments.

Janez Lamovec: What a case! Never seen, never heard of. Thank you very much.

Thomas Mentzel: Many thanks for sharing this distinct clear cell endometrioid neoplasm.

Juan Rosai: I would have called this tumor a clear cell adenocarcinoma of undetermined primary origin. It is hard for me to put in an endometrioid category on the basis of these slides.

Josh Sickel: Thanks for this very educational case.

Dominic Spagnolo: Are you calling these endometrioid carcinomas with clear cell change?

James Strauchen: An interesting phenomenon!

CASE NO. 17 – CONTRIBUTED BY DR. STRAUCHEN

Phil Allen: Adenoid glioblastoma with divergent epithelial-mesenchymal differentiation, left frontal lobe. I have never seen one like it before.

Ofer Ben-Itzhak: Malignant brain tumor composed fo small to medium-sized cells with areas of central necrosis – GBM like morphology, and areas of epithelial-like structures. I agree with the diagnosis of "adenoid" glioblastoma (and maybe gliosarcoma). However our neuropathologist raised a brow regarding the negative stainings for GFAP and S100.

Gerald Berry: Nice case. I did not immediately think of a glial neoplasm.

Michele Bisceglia: Adenoid glioblastoma. Nice case. Of course I assume that there were other areas of this tumor (not here presented) were the glial nature was assessed, otherwise from the immunostaining results, given here, one cannot say that this tumor is of astrocytic lineage.

Thomas Colby: Agree with diagnosis.

Kum Cooper: Thank you for the education. I probably would have called it a small cell GBM!

Hugo Dominguez-Malagon: Excellent case and discussion, thank you.

Goran Elmberger: Important knowledge. Having an interest in salivary gland pathology I must admit the pattern started turning the wheels in that direction.

Giovanni Falconieri: A magnificient case. I showed it to dr Pizzolitto, who is the chief of service and signs out all the neuropath stuff, and he told me that 2-3 cases like came to his attention this during the last 10 years. Thanks again for this contribution.

Cyril Fisher: Extraordinary appearance and difficult to call in the absence of both glial and epithelial markers.

Andrew Folpe: I have no idea. A variant of GBM sounds good.

Jeronimo Forteza-Vila: With HE sections my diagnosis was: PNET

Janez Lamovec: Neuropathologists may be familiar with this type of glioblastoma but I am not sure if this holds true for general surgical pathologists. I would first think of metastasis.

Thomas Mentzel: The neoplasm looks like a primitive neuroectodermal neoplasm. How do you explain the lack of GFAP expression?

Juan Rosai: Whatever you say.

Josh Sickel: We encountered a similar case a few years ago….very easy to confuse with a metastatic lesion.

Dominic Spagnolo: Spectacular example of adenoid GBM-thank you.

CASE NO. 18 – CONTRIBUTED BY DR. SUSTER

Phil Allen: Lipoblastic neurofibroma with signet ring lipoblast-like cells, right thigh. If I have seen one of these before, I must have missed it completely. Actually I missed these pseudolipoblasts as well on a quick glance, but they are very striking in some areas. Thanks for the contribution

David Ben-Dor: those lipoblasts are very interesting. The slide I received shows abundant thick collagen bundles- maybe this is from the case with neurofibroma, because I didn't see much which would make me think of schwannoma. There is also generalized chronic inflammation and a focus of severe inflammation with granulation tissue formation- I suppose these are incidental to the process illustrated.

Ofer Ben-Itzhak: Thanks Saul for this peculiar tumor which I have not seen before, and was not aware of.

Gerald Berry: Thanks for this very unusual appearing lesion.

Michele Bisceglia: Lipoblastic NST with signet-ring lipoblastic cells. Nice case. Have not seen one before (but was aware of your recent publication

Thomas Colby: Very unusual lesion.

Kum Cooper: Thank you Saul for this new entity corresponding to your recent series in AJSP. I certainly did not recognise it even though I had read your paper a while back.

Hugo Dominguez-Malagon: I do not remember seeing a case like this or misdiagnosed them. Thank you Saul.

Goran Elmberger: Thanks Saul. Very peculiar and interesting variant. Was the NF component typical with respect to IHC? Did it occur in the setting of NF syndrome? Thanks Paul for great case. I am pretty sure I would have made the same mistake. The fact WT-1 marks some of the celomic derived ovarian tumors makes it even more difficult. Retrospectively, I notice the peculiar Flexner-Wintersteiner rosette morphology. What are the thin thread-like luminar protrusions actually composed of?

Giovanni Falconieri: I don't know the entity. Morphologically I can just say that it does not look a nasty tumor.

Cyril Fisher: Thank you Saul for sharing this case. I have not seen examples of this.

Christopher Fletcher: Thanks, Saul – I do not recollect seeing any similar cases However, to me, this looks like a schwannoma with focally prominent superimposed chronic inflammation, including foamy histiocytes. In addition, there are quite numerous univacuolated lipoblast-like cells. I would personally have wondered if this is some type of degenerative phenomenon, particularly given the degree of associated inflammation.

Andrew Folpe: Neurofibroma with apparent lipoblasts. Enjoyed your recent AJSP paper, and was able to share the slide with Tony Plaza (who sends his regards).

Jeronimo Forteza-Vila: I had never seen any similar case.

Janez Lamovec: I have never seen such a tumor before.

Thomas Mentzel: Many thanks Saul for sharing this rare and interesting case.

Juan Rosai: I am glad to encounter an example of this entity, which I don't think I have seen or recognized before.

Josh Sickel: Very interesting and educational case! I've never seen this phenomenon before.

Dominic Spagnolo: Thanks for this rare case Saul- I have not encountered this lipomatous/lipoblastic change in a nerve sheath tumor before. Adipocytes in perineurioma have also been described, but as far as I know, no lipblast-like cells were seen in that report by Zamecnik.

James Strauchen: Schwannoma with lipoblasts (and also lymphocyte-like cells). I have never seen one of these before.

CASE NO. 19 – CONTRIBUTED BY DR. WAKELY

Phil Allen: Metastatic, entirely epithelial, adult Wilm's tumour, right ovary, 27 years after removal of the renal primary when the patient was then aged 26. Without the history I would have sworn its was a primary ovarian tumour.

David Ben-Dor: Personally I think that the assumption that a pathologist has to figure everything out on his own without receiving a complete history is something that only lawyers and juries are capable of considering reasonable. How could anyone figure this out without knowledge of the renal tumor excised previously (which itself was a rare and difficult diagnosis). I think considering this an "egregious faux pas" is unwarranted masochism. When will we pathologists stand up for our rights? This reminds me of that crazy case that Falconieri submitted, of the metastatic

ovarian endometrial stromal sarcoma to the lung- if I remember correctly that case also involved the primary being remote. The tumor certainly looks endometrioid to me and I'm sure that that's what I would have called it had I been on the front line.

Ofer Ben-Itzhak: Wonderful case! I would not have diagnosed this marvelous example of Rosai's "neighbour in Istanbul" phenomenon (Wilms' tumor in the ovary of a 53 year old woman!).

Gerald Berry: I did not place Wilm's near the top of my differential, perhaps because of the age!

Michele Bisceglia: Adult Wilm's tumor, monophasic epithelial type,metastatic to ovary. Paul, thank you very much for sharing this case with us, and congratulations on your utmost honesty. I would certainly have called it "well-differentiated endometrioid adenocarcinoma of ovary". Very instructive case!

Kum Cooper: Great case Paul. You are not alone in calling this endometrioid carcinoma?

Hugo Dominguez-Malagon: Agree with the diagnosis of metastatic adult Wilms tumor especially with the history of a renal tumor years before, however I find it difficult to differentiate from an ovarian epithelial tumor that also may express WT1.

Goran Elmberger: Another great case. Only think that made me slightly suspicious of infectious etiology was the intense neutrophilic infiltrate. Good to have seen!

Giovanni Falconieri: Well Paul, endometrioid carcinoma did ring very well to me, as well!

Cyril Fisher: Very difficult case when presenting in the ovary. It does resemble metanephric adenoma, with the differences you mention.

Andrew Folpe: Wow! There's no way you could have made this diagnosis without the history, although it makes perfect sense once you have it. A very instructive case.

Jeronimo Forteza-Vila: Thank you very much for this interesting case.

Christopher Fletcher: What a remarkable case – I do not think I would ever have recognised this as a Wilms tumour!

Thomas Mentzel: Whats for a case ! I would never think on this diagnosis to be honest, many thanks.

Juan Rosai: I confess I would have called this tumor an endometrioid carcinoma of the ovary myself. It remains a bizarre case, although the history provided and the immunohistochemical profile seem to leave no doubt about the contributor's interpretation.

Josh Sickel: I also thought this was an endometrioid adenocarcinoma. Adult Wilm's tumor involving the ovary?? Thanks for this amazing case!!

Elvio Silva: I did not know the diagnosis of this case but because of similar problems I have seen (and some of them my mistakes) I do not render a diagnosis of endometrioid unless some of the typical features of endometriod are present: significant variation in the histology from area to area, squamous cells, clear cells, adenofibroma, and spindle cell areas.

Dominic Spagnolo: This is really weird, Paul- adult, purely epithelial, metastatic after 27 years. Further, in some of the nodules (not all), many of the tubules are massively ciliated. Cilia can occur in Wilm's epithelium, but to this extent?? Could this be serous epithelial Wilm's in an adult. Was the original tumor also so ciliated?

James Strauchen: I haven't seen a monophasic epithelial Wilm's before! I could see where distinction from metanephric adenoma could be difficult. Thank you.

CASE NO. 20 – CONTRIBUTED BY DR. WAKELY

Phil Allen: Mycobacterial spindle cell pseudotumour, nose, in a patient with lymphoma and prostatic carcinoma. I'm pretty sure I would have missed this.

David Ben-Dor: This extremely astute diagnosis compensates for the "egregious faux pas" you committed in the last case. Could this patient have been immunosuppressed due to treatment for the known malignancies? Or did they arise on the basis of something else?- I would assume that AIDS isn't common in this age group (or maybe I'm naïve). As long as you brought up the possibility of immunosuppression related lesions, how about bacillary angiomatosis? I wouldn't have jumped on the possibility of metastatic prostate carcinoma or any other kind of carcinoma for that matter, but I'm

sure that I would called this a "granulation tissue polyp" without any further thought. Now I'll always be on the lookout for "boomerangs" and "bananas" when looking at inflammatory lesions.

Ofer Ben-Itzhak: Congratulations for the magnificent diagnosis! I would not have considered this possibility with no history of immunosuppression

Gerald Berry: Nice example of mycobacterial spindle cell pseudotumor. It will be a great teaching case. Thank you.

Michele Bisceglia: Mycobacterial spindle cell pseudotumor. Nice and instructive case as well. Thank you. The etiology is most frequently due to mycobacterium avium intracellulare. However I recall having seen a case which matched very well this entity in early 1980. It was from the palate in a sea-man which initially we thought it was an histiocytic tumor, which eventually (we did EM and found the diagnostic clue) was diagnosed leprosy. Even the case published in 1995 in Am J Dermatopathol (17:297-302 by Triscott JA, Nappi O, Ferrara G, Wick MR as "pseudoneoplastic" leprosy I think might be considered one of these cases (I had the opportunity to look at this latter case; as a matter of fact, while that case (1st biopsy) was being studied in Missouri, the patient who was Italian was hospitalized at our institution and we got other biopsies which revealed classic lepromatous (xanthomatous) leprosy. Parenthetically, Paul, you might be interested in immunostaining for S-100 protein. In the first case I mentioned of histoid / fibrohistiocytoma-like tumor case of leprosy of the palate, the fibroblast-like histiocytes were S-100 protein positive. I mentioned this finding in several places (meetings in Italy) and perhaps this finding was subsequently published by somebody in the literature. Antibody against S-100 likely cross reacts with the phospholipids of bacterial membrane, and since these cells (in leprosy) are full of bacteria ("globi") the histiocytes appear as S-100 protein positive in their cytoplasm. I do <u>not</u> think this case is leprosy, but the bacteria are similar and numerous, and you may got immunoreactivity for S-100 protein.

Kum Cooper: Another great case Paul! I saw several of these in Africa and they
can me a major diagnostic pitfall having seen cases mislabeled as
inflammatory myofibroblastic proliferation and even T-cell lymphoma. The atypia in your case appears to be confined to the blood vessels. The histiocytes have a foamy cytoplasm with uniform nuclei.

Hugo Dominguez-Malagon: Completely agree with the diagnosis of mycobacterial spindle cell pseudotumor, thank you Paul.

Goran Elmberger: I am not experienced with this tumor in the NF setting so I fully trust your opinion on malignant potential.

Giovanni Falconieri: Challenging case. Subtle features such as a blue hue in some cell cytoplasm might also point to MAI infection as this is often described. Yet I must admit that the overall impression at the beginning was that of a mucosal ulcer with exuberant granulation tissue beneath.

Cyril Fisher: Amazing case; and a reminder to think of doing a ZN in this type of case (I'm not sure I would have thought of it).

Christopher Fletcher: Great case – many thanks, I have not personally seen mycobacterial spindle cell pseudotumour in patients who were HIV-negative.

Andrew Folpe: Nice example of mycobacterial pseudotumor.

Jeronimo Forteza-Vila: Very interesting case.

Janez Lamovec: Without history and a pure epithelial morphology of the tumor in the ovary of the adult patient, no wonder that Wilms' tumor is a remote possibility to think about.

Thomas Mentzel: A nice case if this condition in an unusual location.

Juan Rosai: Very good case. In some areas it truly simulates a neoplastic process.

Josh Sickel: Brilliant diagnosis!!

Dominic Spagnolo: Very nice case, Paul- I was considering the same differentials including mycobacterial spingle cell tumor. Have never encountered it in this location.

James Strauchen: Missed it! Didn't think of it in this location.

CASE NO. 21 – CONTRIBUTED BY DR. WEISS

Phil Allen: Ganglioneuroma with "ancient" changes and necrosis in the neurofibromatous component, retroperitoneum attached to adrenal of a 65-year-old male with neurofibromatosis. I think it is benign too, and if Larry and I agree, there can be no possibility of error.

Andrew Folpe: Agree with ganglioneuroma.

Gerald Berry: I would agree with you Larry that it best fits in the benign camp.

Michele Bisceglia: Ganglioneuroma,with focal neurofibroam and atypical areas. I think it is benign, and would consider the atypical features as we do with (atypical) neurofibroma of soft tissue. About necrosis – it also might occur in some (cellular) schwannoma.

Kum Cooper: Larry I agree with the ganglioneuroma component. I was worried by the atypia!

Hugo Dominguez-Malagon: Ganglioneuroma, I also believe it is benign.

Giovanni Falconieri: I do not have the expertise and background needed to clear up the challenge of this intriguing case. However, because of the retroperitoneal location and necrosis I would feel hesitant to call this benign.

Cyril Fisher: Given the difficulty of predicting behavior in this type of tumor, I think I would go for uncertain malignant potential.

Christopher Fletcher: I agree that this lesion does not show convincing features of malignancy. Instead, it appears to be a ganglioneuroma showing focally striking nuclear atypia, the latter being evident adjacent to areas of what appears most likely to be infarction, with superimposed acute inflammation. Having said that, the appearances are certainly worrisome (especially in a patient with NF-1) and thorough sampling would always be necessary.

Jeronimo Forteza-Vila: Thank you very much, for this amazing case.

Janez Lamovec: I agree with you that this is more like an ancient type change and that this lesion is benign.

Thomas Mentzel: The evidence of strong and diffuse S-100 protein expression represents a good argument for the biologically benign behaviour of this large and centrally necrotic neoplasm.

Juan Rosai: I would go on with the diagnosis of ganglioneuroma and with the "gut-feeling" that the lesion is benign despite the marked atypia and the extensive inflammation.

Josh Sickel: The atypical features are disturbing, especially given the history of NF. I might have given this a UMP designation, just to be cautious.

Dominic Spagnolo: I agree there are no convincing features of malignancy in this nerve sheath tumor. The atypia looks "degenerate" akin to that seen in Schwannoma.

James Strauchen: I thought this looked like Schwannoma with "ancient" changes.

QUIZ CASE NO. 1 – CONTRIBUTED BY DR. WICK

Phil Allen: Poorly differentiated large cell malignant tumour, caecum, ? metastatic amelanotic malignant melanoma, ? poorly differentiated carcinoma, ?? malignant lymphoma, request immunohistochemistry and review of the clinical history.

Ofer Ben-Itzhak: Malignant epithelioid tumor of the cecum. I would do immunostains for the more common undifferentiated carcinoma and for the rare possibility of melanoma (metastatic?). However, due to the epithelioid cell reaction (pink cells focally surrounding tumor cells) I would also order stains for dysgerminoma (metastatic?), and since CD117 stains both this germ cell tumor and GIST, I would also order PLAP and OCT3/4.

Thomas Colby: Localized mesothelioma?; rule out metastatic breast cancer.

Kum Cooper: Welcome to the club Mark! Large cell neuroendocrine carcinoma.

Michele Bisceglia: Difficult to answer without immunos. Obvious malignant tumor; favour sarcoma.

Hugo Dominguez-Malagon: Poorly differentiated adenocarcinoma vs. neuroendocrine. If it was not in the colon I would also consider the possibility of a plasmacytoma.

Goran Elmberger: Proximally located, poorly differentiated adenocarcinoma (medullary carcinoma) with Crohn like granulomatous inflammation. HNPCC?

Giovanni Falconieri: Why not intraabdominal desmoplastic small cell tumor (but little desmoplasia, and cells not so small!). High-grade neuroendocrine carcinoma sounds also appealing. Tumor cells have a number of traveler fellows including small lymphos and eosinophils. By the way, welcome to the club, dr Wick!

Christopher Fletcher: This looks like a metastasis to me, more likely carcinoma than anything else but would need immunostains!

Jeronimo Forteza-Vila: I think it is a malignant tumor and I would think in a melanic or neuroendocrine nature.

Janez Lamovec: Medullary carcinoma of cecum?

Thomas Mentzel: Neuroendocrine carcinoma?

Juan Rosai: High-grade carcinoma with possible neuroendocrine differentiation, primary vs. metastatic.

Josh Sickel: Medullary carcinoma.

Dominic Spagnolo: Malignant undifferentiated "epithelioid" neoplasm, needing immunohistochemistry. Granulocytic sarcoma?, melanoma, undifferentiated carcinoma, epithelioid GIST, epithelioid vascular, etc. Favor granulocytic sarcoma.

James Strauchen: Microsatellite instability colon cancer.