COMMENTS TO AMR SEMINAR #60

CASE NO. 1 – CONTRIBUTED BY VOLKAN ADSAY:

Phil Allen: Massive gastric juvenile/hyperplastic polyposis (SMAD4 related) (foveolar-gland polyposis) with minute foci of adenocarcinoma invading the lamina propria. The invasion of lamina propria is not well shown in my slide. I can't see any parietal cells and there are numerous foamy macrophages in the lamina propria. I have never seen a case like this before. Thanks for the contribution. I look forward to seeing the publication of yet another gastric polyposis variant.

David Ben-Dor: I didn't know that juvenile polyps are found in the stomach but if I knew things like that I wouldn't need to be a member of the club. I found some dysplasia but if there is malignancy on this slide I overlooked it. I personally find the issue of dysplasia vs. reactive changes in the stomach to be very confusing.

Ira Bleiweiss: At first I didn't see convincing invasion in my slide. It took a lot of looking but there it was. Very subtle.

Michele Bisceglia: Massive gastric juvenile/hyperplastic polyposis (SMAD4 related) with minute foci of invasive carcinoma. We had here a very similar case in 1997 occurring in a 31-year old lady, who underwent total gastrectomy: also in our case the entire stomach was massively involved, and I (mis-)diagnosed it at that time as Menetrier's hyperplastic gastropathy (although I was aware that in Menetrier's disease the antrum is spared by the polypoid proliferations). Dysplastic adenomatous foci were also seen in our case. This lady had also clinical and laboratory symptoms consistent with that diagnosis. It was only in 2004 when 2 of her children were found affected with multiple juvenile (and/or) hyperplastic polyps of the colon that the juvenile polyposis syndrome was suspected, and the lady underwent repeat colonoscopy with several juvenile/hyperplastic polyps removed in a few years. Thus in our case and her family a final diagnosis of juvenile polyposis syndrome involving upper and lower gastrointestinal tract was made, and SMAD4 mutation was then molecularly discovered too. Gastroenterologists here have recently submitted a report on this case and her family for publication. Your case is most interesting due to the absence of polyposis in the colon (another case of juvenile polyposis restricted to the stomach was reported in Am J Med Genet 134A:326-329, 2005) and the association with (previous) us) development of colon cancer. Occasionally this syndromic juvenile polyposis can also be seen in association with cardiovascular (pulmonary arteriovenous malformation – source: previously quoted reference) or skeletal manifestations (hypertrophic osteoarthropathy - J Pediatr Gastroenterol Nutr 41:117-120,2005).

Tom Colby: Agree with diagnosis. I found the dysplasia and a few foci suspicious for invasion but I would probably want to study levels to convince myself on the invasive carcinoma. Was not aware of this syndrome.

Kum Cooper: They do look hyperplastic/hamartomatous. We have found that the PJS polyps in the stomach usually look more "hyperplastic" than hamartomatous (with the history helping us!). Anyway Menetrier disease was in my differential along with Cronkhite-Canada syndrome. My slide has areas of low grade dysplasia (but no cancer) reiterating the point that juvenile polyposis carries the risk for dysplasia/cancer. Thank you for this exciting case Volkan.

Otto Dietze: I have not seen this before, and was not aware of the SMAD 4 mutation.

Hugo Dominguez-Malagon: Impressive case, before I read the discussion I called it a hamartomatous polyp because in it has a component of long foveolar glands with cystic and undulating contours and abundant smooth muscle fibers in the stroma. I have not seen a case like this before.

Göran Elmberger: Wonderful case. New to me – never seen this. Beautiful example of genotype – phenotype correlation where I believe the detection of the SMAD4 gene mutation is essential for the diagnosis. From the histopathological perspective, I believe it would be quite problematic to put this polyp into one of the previously existing polyp categories. I see features of foveolar hyperplasia, juvenile polyp, hyperplastic polyp and also see lots of radiating smooth muscle more characteristic of a hamartomatous polyp of Peutz-Jegher type. Thus, I agree with you that this looks like a specific type of polyp in need of molecular identification and possibly a name of its own. Your suggestion of massive (gastric?) foveolar gland polyposis certainly captures the most prominent histopathological feature of this entity but I would suggest putting the SMAD4 mutation somewhere in the provisional name... The fact that this young woman already

suffered from a CRC must be more than a coincidental finding and this may prove important in outlining the risks and consequences of this genetical abnormality as well as in naming the syndrome. A recent paper by the Dutch group with van Hattem as first author elaborates further on the JPS genotype-phenotype correlation and suggests that the SMAD4 mutation associated polyp could be named the epithelial variant of juvenile polyp. Parenthetically, I note that we use the same gene marker in IHC but under another name DPC4 as one of the few potential markers for pancreatic ductal cancer in our CUO work. Possibly, in ductal pancreatic carcinoma this could represent a common disturbance within the same TGF-beta signalling transduction pathway on a non-germline basis?

Jonathan Epstein: Nice Example.

Vincenzo Eusebi: Agree with hyperplastic polyps, never seen a condition like the present one. In my section no invasive carcinoma present.

Giovanni Falconieri: Quite a case, Volkan. I have memory of a few cases of gastric polyposis but none to that extent.

Franco Fedeli: Massive gastric juvenile/hyperplastic polyposis (SMAD4 related) with minute foci of invasive carcinoma. Thank you very much. This case brought to light the histological problems related to the hamartomatous polyposis syndromes (juvenile polyposis syndrome and Peutz-Jeghers syndrome) of the upper and lower gastrointestinal tract. One would be interested also in the real diagnosis you made on endoscopic biopsies in this case. Without clinical information of suspected juvenile polyposis syndrome, based on a clinically known hereditary context or a known generalized juvenile polyposis of the colorectum affecting the patient in point, these findings as seen in endoscopic pathologic specimens from the stomach would be regularly diagnosed by the pathologist just as hyperplastic polyp or hamartomatous polyp. Histological features to distinguish gastric juvenile polyposis syndrome and other hamartomatous syndromes (Peutz-Jeghers syndrome) from hyperplastic polyps are unreliable, as attested by the recent paper mastered by E. Montgomery on this topic (Lam-Himlin et al. Morphologic characterization of syndromic gastric polyps. AJSP, Nov. 2010).

Cyril Fisher: New to me, very interesting account, many thanks.

Christopher Fletcher: For me, this is a wonderfully educational case, since I was not familiar with juvenile polyposis associated with germline SMAD4 mutation – certainly I have not previously seen any similar case. Many thanks.

Andrew Folpe: Fascinating case. My slide has some high-grade dysplasia, but no invasion.

Jerónimo Forteza Vila: We have no experience in the diagnosis of similar cases. It was hard for me to find the neoplastic areas.

Masaharu Fukunaga: Intramucosal, well differentiated tubular adenocarcinoma, gastric type, arising from a hyperplastic gastric polyp. Thank you very much the wonderful case and the detailed description, Volkan.

Janez Lamovec: I have never seen such a case; it was difficult to spot carcinoma but there was a tiny focus of it.

Thomas Mentzel: An interesting case, but unfortunately, I could find the carcinomatous component.

Markku Miettinen: Gastric polyp with dysplasia, thank you for the syndrome description.

Liz Montgomery: Gastric juvenile polyposis cases are fascinating. I could not find the early invasion on my slide (I probably missed it) but there was a lot of dysplasia. We have anecdotally had a couple of these patients. In one, we initially did not find the mucosal invasive carcinoma component but we found a metastasis that prompted a more careful search for the invasive carcinoma component.

Santiago Ramon y Cajal: Remarkable case. Thank you very much Volkan. Certainly, there are features quite similar to Peutz-Jeghers polyps.

Juan Rosai: Great case, even if there was no invasive carcinoma in my slide. I wonder whether cases like this were included by Menetriere in his classic paper in 1888. His description of the type he called

polyadenomes polypeux sounds similar. If that were the case, this would not be "an emerging subset" but rather a "resurfacing subset", as it often happens in pathology. Wouldn't be fun to do a molecular genetic study on Menetriere's cases?

Manuel Sobrinho Simões: Very nice case of massive gastric juvenile polyposis (SMAD 4 related). Fátima Carneiro has recently seen a similar case of gastric juvenile polyposis with SMAD 4 mutation but, in her case, there was also involvement of the colon. We have never seen such a variant limited to the stomach.

Dominic Spagnolo: This is a spectacular case of juvenile/hyperplastic polyposis, SMAD4 associated. Were any of the MUC stains done to assess the variability in phenotype? I may have a similar case from 2007 that was sent to me from a colleague at another laboratory, and caused much nosologic difficulty at the time. Am not sure if it falls into this group. Dr Greg Lauwers also opined on that case. Will communicate with you separately about this.

James Strauchen: Thanks! I was not aware of this syndrome!

Lawrence Weiss: Very interesting. Another syndrome to learn. I have never seen this phenomenon before.

Eduardo Zambrano: Very interesting case. My impression was that of a hyperplastic polyp of the gastric foveolar mucosa. I have seen juvenile/inflammatory polyps of the colon, but was not aware that those related to SMAD4 mutations are more commonly seen in the stomach.

CASE NO. 2 – CONTRIBUTED BY DAVID BEN-DOR:

Phil Allen: Osteoblastic osteogenic sarcoma of the left mandible with very myxoid extension into the adjacent soft tissues in a patient now aged 21 with a previous history of retinoblastoma treated with radiotherapy when aged about one year. I don't think I have previously seen such extensive myxoid change in an osteosarcoma but the osteoblastic differentiation in the circulated slide from the soft tissue is unequivocal. I think this tumor differs histologically from myxoid chondrosarcoma of soft parts. The pattern in some areas is reminiscent of myositis ossificans but I agree that it is an unequivocal osteosarcoma with myxoid change.

Gerald Berry: Agree with diagnosis. We have struggled recently with 2 cases of osteogenic sarcoma of the gnathic bones. The histological changes were at both ends of the spectrum! As usual radiological assessment was helpful.

Michele Bisceglia: Osteogenic sarcoma of the left mandible, osteoblastic type, presenting as an extra-osseous myxoid tumor, in a patient with a history of retinoblastoma and radiation therapy in early childhood. A genetic predisposition to osteosarcoma is found in patients with hereditary retinoblastoma, due to mutation of the retinoblastoma gene RB1 on Chr. 13q14, so osteosarcoma is the most common second neoplasm in young patients with history of retinoblastoma, and maybe one might think of it when dealing with a second neoplasm in retinoblastoma patients. Additionally osteosarcoma in association with retinoblastoma can also be seen in Li Fraumeni syndrome due to germline mutation of the p53 (Chr. 17p13.1). Radiotherapy and chemotherapy are even independent risk factors for osteosarcoma, which increase even more the possibility of its occurrence after retinoblastoma is treated according to these modalities. Although retinoblastoma in your case can well be sporadic (in the sense of a non-heritable form of retinoblastoma), the very young age of the patient at the time of the diagnosis of retinoblastoma points to a hereditary form (in the sense of germline mutation), despite its unilateral occurrence (25- to 30% of RB1 mutation carriers have just unilateral retinoblastoma). Patients with heritable retinoblastoma have a highly much higher susceptibility to develop either spontaneously or after therapy a second cancer (usually a sarcoma in the pediatric age) in comparison to patients with non-heritable retinoblastoma. Finally your patient can still develop other new cancers during his life, if he will be a long-term survivor from now onward (with epithelial cancers being more frequent than sarcomas after 40 years of age)
(Refs. 1. Ottaviani G, Jaffe N. The etiology of osteosarcoma. Cancer Treat Res. 2009;152:15-32. 2. Turaka K, Shields CL, Meadows AT, Leahey A. Second malignant neoplasms following chemoreduction with carboplatin, etoposide, and vincristine in 245 patients with intraocular retinoblastoma. Pediatr Blood Cancer. 2011 Aug 8. doi: 10.1002/pbc.23278. 3. Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. J

Natl Cancer Inst. 2008 Dec 17;100(24):1771-9. 4. Araki Y, Matsuyama Y, Kobayashi Y, Toyokawa S, Inoue K, Suzuki S, Makimoto A. Secondary neoplasms after retinoblastoma treatment: retrospective cohort study of 754 patients in Japan. Jpn J Clin Oncol. 2011 Mar;41(3):373-9. 5. Fletcher O, Easton D, Anderson K, Gilham C, Jay M, Peto J. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst. 2004 Mar 3;96(5):357-63. 6. Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, Li FP, Fraumeni JF Jr. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol. 2005 Apr 1;23(10):2272-9.)

Ira Bleiweiss: Myxoid and chondroid and the calcification reminds me of chondroblastoma. The bone looks metaplastic and benign to me. I would not have thought of this as osteosarcoma, but, as you say, the extraosseous photos clearly show the diagnosis.

Tom Colby: Myxoid sarcoma consistent with osteosarcoma. I noted the peculiar calcification and stromal reaction but did not recognize it as osteoid. Nevertheless I think I was convinced this was malignant and think it is compatible with a pattern that could be seen in osteosarcoma.

Kum Cooper: The history is a great segue for the diagnosis of post-radiation osteosarcoma. However, without the history I also considered malignant mixed tumor and malignant myoepithelioma. Parenthetically about a year ago I saw a post-radiation (mediastinum) synovial sarcoma in a young woman 4 years after radiation for mediastinal Hodgkin disease. Needless to say she did not survive very long.

Ivan Damjanov: I would agree that this is an osteosarcoma. In retrospect and after the lengthy comments written by David it is easy to be smart. I realize that a small biopsy would not have been diagnostic.

Otto Dietze: I cannot remember a similar case of OS. The last one I have seen post irradiation was high grade osteoblastic in the mediastinum.

Hugo Dominguez-Malagon: Jaw osteosarcoma, osteoblastic type is the best choice. In the slide sent there are “myxoid” areas, calcified osteoid arising from the hypocellular stroma can be recognized, plus the fact that there is nuclear atypia and unbalanced mitotic figures. The image studies show an intraosseous osteoblastic and lytic lesion and an extraosseous extension. Useful image studies would be orthopantomography and occlusal x-rays because they can show the characteristic widening of the periodontal space.

Göran Elmberger: David, great case for many reasons! Observation of unusual manifestations of common tumors. Radiological-clinical correlation. Importance of recognizing clues from patient history. Most impressive I find your recommended method of sending out photos to multiple pathologists for low-level hypothesis generating consultation. The risk of sending up-front formal consultation including slides to one or a few consultants is that if you pick the wrong person in the wrong field of expertise the right diagnosis may never be found. Today we have better tools including whole slide scanning and web hosting emerging at more and more labs so just imagine how much we all could benefit of creating a consultative network amongst the members of the AMR seminar club. As a matter of fact this case gave me an impulse to dig out an old case still itching...

Jonathan Epstein: Interesting history.

Vincenzo Eusebi: The interpretation of the present lesion as myxoid osteosarcoma is in keeping with the story of previous radiotherapy. The histological features are misleading due to myxoid stroma. Nevertheless your work up of the case appears convincing for an osteosarcoma.

Giovanni Falconieri: Great case and superb discussion, David! I have a limited experience with bony tumors including those arising outside the bone proper. My first thought was of nodular fasciitis, yet on a better sight I could notice nuclear debris and apoptotic cells which, along to an excess of mitoses and atypical nuclei, made me more dubious. The best guess here would be myxoid spindle cell sarcoma, NOS.

Franco Fedeli: Osteogenic sarcoma of the left mandible, osteoblastic type, presenting as an extra-osseous myxoid tumor, in a patient with a history of retinoblastoma and radiation therapy in early childhood. Never heard of myxoid osteosarcoma. Thank you, David, for sharing this case with us. Maybe the combination of retinoblastoma and osteosarcoma could point to an underlying hereditary tumour syndrome, especially Li Fraumeni, and up to 3% of young patients with osteosarcoma harbor this syndromic condition.

Cyril Fisher: Osteosarcoma with subtle osteoid deposition, very difficult case.

Christopher Fletcher: In the head and neck region, when first seeing these appearances, I would initially have thought of a myoepithelial neoplasm, particularly given the strikingly reticular architecture. However, I can recollect seeing one or two other cases of osteosarcoma in the craniofacial skeletal that closely mimicked a myoepithelial neoplasm as here.

Andrew Folpe: Agree with osteosarcoma. The myxoid change does make it more difficult.

Jerónimo Forteza Vila: I agree with the diagnosis. It could be a giant cell variant.

Masaharu Fukunaga: David, what a great case! My impression was a radiation-induced sarcoma or reactive myofibroblastic proliferation. It is very difficult to make a diagnosis of osteosarcoma with the slide. Thank you very much for the detailed description and photos which exhibit a convincing osteoblastic osteosarcoma.

Thomas Krausz: Before reading the discussion and the whole history my main consideration was malignant variant of ossifying fibromyxoid tumor of soft tissue. However, I agree that the images of the subsequent intraosseous tumor represent an osteosarcoma.

Janez Lamovec: Mitotically active spindle cell proliferation in myxoid background with focally suggestive osteoid deposition. I think that I saw atypical mitoses. Fibromyxoid lesions in the jaws may be quite tricky, particularly in small biopsy specimen; many years ago we saw a somewhat similar lesion and didn't know what to do with it and Dr. Dahlin diagnosed it as osteosarcoma that turned out to be the right diagnosis.

Thomas Mentzel: Many thanks for this fascinating case showing only small foci of calcified, neoplastic bone structures.

Michal Michal: Interesting case. I have seen amazing soft tissue tumors defying any classification in patients with bilateral retinoblastomas.

Markku Miettinen: Agree on osteosarcoma, relatively well-differentiated.

Liz Montgomery: This is really difficult with all the myxoid material – I guess the retinoblastoma history and the radiographic findings make a solid case for an osteosarcoma.

Santiago Ramon y Cajal: Thank you very much David for this superbly described case.

Juan Rosai: Great case of post-radiation osteosarcoma. The fibromyxoid quality of the tumor is striking. By the way, anybody interested in seeing a display of the histologic diversity of osteosarcoma will enjoy the paper by Yunis and Barnes published on Pathology Annual 21(1): 121-141, 1986. In retrospect, a feature that suggests that this lesion is indeed an osteosarcoma is the presence of areas of calcification of the osteoid trabeculae that look very basophilic and vaguely resemble fungal hyphae, as Dr. Lauren Ackerman used to emphasize.

Manuel Sobrinho Simões: Agree with the diagnosis after reading the whole description. We belong to the group that would underdiagnose the lesion as "Ossifying fibromyxoid tumour"

Dominic Spagnolo: David, this gnathic osteosarcoma is frightening. Kevin Raymond's comments are so apt. A wonderful case, and thanks for the instructive and insightful discussion.

James Strauchen: Very instructive case! I did not appreciate that osteoid could look like that either!

Saul Suster: Very difficult case to diagnose without the history and the imaging studies! I seem to recall that for some reason, the few gnathic osteosarcomas I've seen before also showed prominent myxoid changes.

Lawrence Weiss: I had never seen this before, and I did not know what it was. This is a case to remember and learn from (before I get sued from one of these).

Eduardo Zambrano: I have seen one case of osteosarcoma of the gnathic bones with a histologic appearance similar to this case; however, in my case, there were several areas showing more classic features of osteosarcoma, including the presence of osteoid in close association with malignant osteoblasts.

As is more frequent than not, in my case radiographic films were also very helpful at arriving at the correct diagnosis, since they showed a destructive bone lesion with areas featuring a sunburst appearance. These cases can be quite challenging.

CASE NO. 3 – CONTRIBUTED BY OFER BEN-ITZHAK:

Phil Allen: Cutaneous leishmaniasis of the legs of a husband and wife, with pseudoepitheliomatous hyperplasia in the wife. I would never have seen the organisms in the wife's ulcer if I had not seen the myriads of organisms in the husband's. We see occasional cases in Australia, mainly in illegal immigrants from places like Baghdad (Baghdad boil).

David Ben-Dor: Quite a case- kol-hakavod as we say here (hats off). I would have signed the woman's biopsy out as severe acute inflammation with florid reactive epithelial changes (I appreciate the concern for carcinoma) – how you saw a few leishmania organisms in the midst of all that mess is beyond me, but as I just said, kol hakavod. The husband's slide is more obvious if you take the trouble to and think of looking for the bugs. I suppose the "busy" surgeons didn't think of drawing any epidemiological conclusions from seeing a husband and wife with apparently simultaneously developing lesions and ask for travel history (maybe they had driven down to Eilat, a resort town on the Red Sea at the southern tip of the country, which requires passing through the Arava wilderness where the infection is endemic, as Ofer pointed out). I sometimes get biopsies of chronic skin ulcers with the question of leishmania, usually concerning soldiers who are stationed in those areas. Anyway I'll start looking more carefully at slides of severely inflamed skin ulcers (or send them to you!!).

Gerald Berry: We see occasional cases of leishmaniasis in visitors to or from Central America but I must admit that I have never seen this degree of pseudoepitheliomatous hyperplasia. A spectacular case.

Michele Bisceglia: Cutaneous leishmaniasis with pseudoepitheliomatous hyperplasia (or : How husbands can help their wives). To be honest I could not recognize leishmania bodies in slide “A” or at least I could not differentiate them from karyorrhectic bodies. In section “B” the matter was easier. Extraordinary simultaneous occurrence of two “familial cases” on the same pathologist’s tray of slides. We see here around 1 case of leishmaniasis per year, affecting skin or other organs, such as bone marrow and spleen. Incidentally, we (as AMR members) have also two cases of leishmania lymphadenitis in our Archive of Seminars: the former (in epitrochlear lymph node) was contributed as a regular case by Joshua Sickel in Seminar #12 and the latter (in parotid lymph node) was contributed as a “follow-up case” by myself in form of two kodachromes which echoed at that time the case Sickel had previously contributed (the two kodachromes were subsequently digitized and now are appended in the AMR website as “follow up” to Sickel’s case by Bisceglia in the section of “Archives of images” [follow-up to case n. 18 of Seminar # 12].

Ira Bleiweiss: Wow. With all the non-stop flights between New York and Tel Aviv, I’m surprised we don’t see this here.

Tom Colby: Pseudoepitheliomatous hyperplasia associated with Leishmaniasis. I suspected that it was something like that on the wife’s biopsy but could not convince myself of the organisms which, as noted, are much more easily seen in the husband’s biopsy.

Kum Cooper: What a great diagnostic pitfall. Needles to say I fell for squamous cell carcinoma in slide A. Slide B (thanks to husbands) shows the best LD bodies I have seen in a long time. Thank you for this educational case. I recently saw a squamous cell carcinoma arise at the edge of a skin ulcer in a patient with chronic osteomyelitis (Marjolin's ulcer).

Ivan Damjanov: Husband's specimen is relatively easy, wife's specimen not so obvious, but taken together it all makes sense.

Otto Dietze: Without a Giemsa stain I probably would have missed the diagnosis, however we see leishmaniasis less than 1 per year.

Hugo Dominguez-Malagon: Nice Case of cutaneous leishmaniasis, it is endemic in southeast Mexico but as mentioned it should be suspected because the microorganisms are difficult to see in HE slides, closely resemble histoplasma.

Göran Elmberger: Good detective job! I guess not contagious from person to person but more of a common exposure thing. Very impressive pseudoepitheliomatous hyperplasia. Still after 10 years at the Karolinska cytology FNA service I sometimes find it very difficult to separate neoplastic from reactive cellular atypia. As you say necrotizing granuloma may be a tip. I guess the wife was biopsied in later more difficult to recognize stage of the infection.

Jonathan Epstein: We never see these. With all the neutrophils, it would be easy to overlook the organisms and mistake them for nuclear debris. Thanks for the case.

Vincenzo Eusebi: Typical and convincing cases of cutaneous leishmaniasis. We see cases like this in Bologna (Northern Italy). Cases are confined to a small area of the town and in spite of the several interventions by the local health, the infection still goes on. The area is close to the main University Hospital… That's life. I have found very pertinent the statement that " a high index of suspicion is needed to diagnose the disease in cases with rare organism" as this is what often happens.

Giovanni Falconieri: Two at the price of one! Yet pretty difficult, Ofer. To my eye the first impression of A is a pseudoepitheliomatous ulcer, perhaps due to some stasis dermatitis. The gentleman specimen and especially his particular history offer a hint. Challenging case(s)!

Franco Fedeli: Nice case. Slide "A" is a confirmation that everyone has to look carefully into the stromal part of the biopsy specimen, when a pseudoepitheliomatous hyperplasia is shown (we see misleading epitheliomatous hyperplasia overlying several types of cutaneous as well as mucosal diseases, both inflammatory [either infectious or just reactive] and neoplastic [granular cell tumor, Spitz nevus, Ki-1 anaplastic lymphoma, …].

Cyril Fisher: Cutaneous leishmaniasis in husband and wife! Great case(s).

Christopher Fletcher: These are very convincing examples of cutaneous leishmaniasis – although it is true that the diagnosis is much easier in the husband's biopsy! We see occasional cases in Boston because there is a large immigrant Brazilian population here.

Andrew Folpe: Totally cool. Our dermpath people were besides themselves with excitement. Thanks for sharing.

Jerónimo Forteza Vila: I agree with the diagnosis. The pseuocarcinomatous hyperplasia attracts the attention.

Masaharu Fukunaga: Thank you very much for a wonderful case. Dr. Ben-Itzhak, I have never seen leishmaniasis case. The comment is very informative. I am gland to file it. The initial impression was well differentiated squamous cell carcinoma.

Thomas Krausz: Great case. I probably would have missed the microorganisms on slide A.

Janez Lamovec: Very impressive. We don't see these lesions here. Thank you for the slides and discussion.

Thomas Mentzel: A nice case emphasizing the importance of reactive, pseudoepitheliomatous hyperplasia mimicking an epithelial neoplasm.

Markku Miettinen: Agree on pseudocarcinomatous hyperplasia w. Leishmania, difficult case.

Liz Montgomery: This is a great case. I am glad you educated us. I was in the US military and trained at Walter Reed where all the returning soldiers came so we saw a lot of late stage leishmaniasis that were easier to recognize but, for me, this was more subtle.

Santiago Ramon y Cajal: Remarkable case. Although it is described as endemic in Mediterranean countries in general it is a rare finding in Spain.

Juan Rosai: Fantastic case of cutaneous leishmaniasis. The parasites are very well seen in the biopsy from the husband (slide B), but not so well in the slides from the wife (slide A), in which there is instead a striking epithelial squamous proliferation. I guess it is logical to assume that this represents pseudoepitheliomatous hyperplasia secondary to the leishmaniasis, but I would not completely rule out the

alternative possibility of an invasive squamous cell carcinoma arisen in a long-standing ulcer due to the parasite. I'm pretty sure I would have called this lesion a squamous cell carcinoma if the parasite had not been there.

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: Very nice example of cutaneous Leishmaniasis, thank you. We see about 2 – 3 cases annually, I suspect the majority occurring in patients who have arrived as refugees from regions where there is high prevalence.

James Strauchen: Fabulous case! I have seen one case in a tourist returning from Israel. There is also a literature on visceral leishmaniasis as an opportunistic infection in HIV/AIDS.

Saul Suster: This brought back fond memories from when I was a resident at the Tel-Hashomer Hospital in Tel-Aviv, where we used to see one of these at least once a week!

Lawrence Weiss: Finally, a case I can diagnose. I remember the case Josh Sickel presented, from lymph node.

Eduardo Zambrano: Fascinating. I have never seen a real life case of cutaneous leishmaniasis.

CASE NO. 4 – CONTRIBUTED BY GERALD BERRY:

Volkan Adsay: Great case. The adenomatoid tumor-like vacuolar pattern was the main reason I concluded that this was a malignant mesothelioma.

Phil Allen: Localized malignant mesothelioma, epithelioid type with pseudo-glandular pattern, right chest wall. Our very own 'localized mesothelioma' guru, Doug Henderson, pointed out that parts of the tumor resemble an adenomatoid tumor. His differential diagnosis rested between a peculiar adenomatoid tumor with solid areas vs a localized malignant mesothelioma. I myself was struck by the large number of pseudo-lipoblasts as well as the pseudo-glands but forgot all about an adenomatoid tumor. The two-year tumor free follow-up is encouraging.

David Ben-Dor: If this was say in the adrenal or epididymis would you call it a malignant adenomatoid tumor (which may be an oxymoron)?

Gerald Berry: My case. No recurrence to date.

Michele Bisceglia: Localized malignant mesothelioma, epithelioid type, pseudoglandular pattern. Very rare case. Thank you, Gerry, for showing this case to us. Histologically in some way and in my view (due to all those vacuolations) this tumor could even be called malignant adenomatoid tumor.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis of localized mesothelioma.

Kum Cooper: I always thought that localized mesotheliomas were papillary, well differentiated and circumscribed (and described in both the paratesticular and pleura cavity). Thank you for the education.

Ivan Damjanov: Agree-epithelioid mesothelioma.

Otto Dietze: Nice case, I have seen a similar one in the peritoneum a few years ago.

Hugo Dominguez-Malagon: Agree with the diagnosis of mesothelioma, resembles an adenomatoid tumor but atypia is evident.

Göran Elmberger: Great case. As you say highly unusual case with localized presentation, unusual histological subtype and so far benign follow-up. I am just a bit curious where we draw the line against adenomatoid tumor - a benign entity. We do see some cellular atypia but what about infiltration, necrosis,

proliferation and outcome? 9p21 deletion? I found one reference by Umezu et al on microcystic localized malignant mesothelioma accompanying an adenomatoid tumor-like lesion but their case invade parietal pleura, had a high proliferative rate and recurred after surgery indicating malignancy...

Jonathan Epstein: Looks like adenomatoid tumor with malignant cytology.

Vincenzo Eusebi: Nice case, I agree. The few localized cases of mesothelioma I have seen had no clear cut history of asbestos exposure.

Giovanni Falconieri: Great case! Thanks for this submission. The pseudoglandular/follicular and microcystic changes are remarkable. We drain cases from an area with a mesothelioma epidemic due to the major shipyards in the Trieste area but I do not recall cases being so localized and pseudoglandular to such an extent.

Franco Fedeli: Localized malignant mesothelioma, epithelioid type, pseudoglandular pattern. Very rare case.

Cyril Fisher: Unusual variant of localized mesothelioma I am not familiar with.

Christopher Fletcher: The combination of a pseudoglandular growth pattern as well as the localized nature of this lesion would pose a very considerable diagnostic challenge, although the cytomorphology would certainly fit well with mesothelial cells and hopefully would prompt appropriate immunostains etc.

Andrew Folpe: Agree with mesothelioma.

Jerónimo Forteza Vila: Differential diagnosis could stand for a spindle cell carcinoma and for a synovial sarcoma. I agree with the diagnosis.

Masaharu Fukunaga: Thank you for the beautiful case of localized malignant mesothelioma of the pleura, Dr Berry. We rarely have the localized type here.

Thomas Krausz: Agree with diagnosis. The adenomatoid pattern with the numerous intracytoplasmic mucin-containing (hyaluronic acid) vacuoles and the localized natura of the tumor may cause diagnostic confusion.

Janez Lamovec: In more peripheral areas, the cells are more reminiscent of mesothelial cells but otherwise this appears as a true glandular tumor.

Thomas Mentzel: Thanks for this impressive example of rare localized epithelioid malignant mesothelioma containing numerous vacuolated tumour cells.

Michal Michal: Adenomatoid tumor-like mesothelioma! I have just seen very similar case sent to from Russia (Skt. Petersburg). The case I saw was a 8 cm large mass!

Markku Miettinen: Agree on malignant (localized) mesothelioma, with adenomatoid tumor-like features.

Liz Montgomery Thanks for this lesion. At low magnification I thought of adenomatoid tumor but high-magnification discloses more atypical features. Very nice epithelioid mesothelioma.

Santiago Ramon y Cajal: Beautiful case. Thank you, Gerald.

Juan Rosai: Great case of localized mesothelioma. It almost looks like the malignant counterpart of an adenomatoid tumor, which is not too surprising when one realizes that the latter is a form of mesothelioma, to the point that Pierre Masson called them mesotheliomas of the “genital sphere” (I wonder which “spheres” he had in mind). Some areas of the tumor also reminded me of the microcystic variant of type A thymoma.

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: I agree it has to be considered a localized malignant mesothelioma. It has distinctly adenomatoid tumour-like features and is similar to another case reported as "microcystic" in 2002 (Pathol Int 2002;52:416-22. Microcystic variant of localized malignant mesothelioma accompanying an adenomatoid

tumor-like lesion. Umezu H et al). Colleagues will also be aware of Saul's recent publication of diffuse meso with AT-like features.

James Strauchen: Very instructive case! I though areas were reminiscent of an adenomatoid tumor.

Saul Suster: Very interesting case. We published a similar case several years ago arising in the anterior mediastinum which we interpreted as an adenomatoid tumor (Plaza J et al. Cystic adenomatoid tumor of the mediastinum. Am J Surg Pathol 28:132-138, 2004). The tumor was well-circumscribed and non-invasive, looked like Swiss cheese grossly, and histologically was identical to this case except there were no solid or sheet-like cellular areas. The patient is still alive without recurrence after 8 years. I guess given the large size of this lesion, the solid areas and the presence of focal nuclear pleomorphism and atypia the diagnosis of localized mesothelioma is warranted for the present case. We also recently reported our experience with diffuse pleural mesothelioma with adenomatoid tumor-like growth pattern (Weisserfeld A et al. Malignant mesothelioma with prominent adenomatoid features: a clinicopathologic and immunohistochemical study of 10 cases. Annals of Diagnostic Pathology; Vol.15: 25-29, 2011), which should not be an unexpected pattern in such tumors given the close kinship and mesothelial derivation of both adenomatoid tumor and malignant mesothelioma. However, all our cases were clearly invasive and diffuse.

Lawrence Weiss: Nice case, and not all that unusual. It has a mesothelioma feel to it, with little stroma or inflammatory cells in many areas.

CASE NO. 5 – CONTRIBUTED BY MICHELE BISCEGLIA:

Volkan Adsay: I personally also think hemangioblastoma is a very good diagnosis for this case.

Phil Allen: Richly vascularized benign mesenchymal hemangioblastoma-like tumor of soft tissues, subcutis, left thigh. I have seen at least two peripheral hemangioblastomas of soft tissue and they did not look quite like this tumor. I agree that it is benign but I don't know what it is.

David Ben-Dor: Very interesting thought- can these be stand-alone lesions not related to the familial/genetic syndrome? It would be interesting to send it to a neuropathologist who sees these tumors on a more regular basis.

Gerald Berry: Given the limited molecular experience of extra-axial HGB I think Dr. Rosai's designation as "richly vascularized benign mesenchymal hemangioblastoma-like tumor of soft tissue" is a good one. We do not have any experience with the extra-axial variants.

Michele Bisceglia: My case. Peripheral extraneural hemangioblastoma. Richly vascularised, benign mesenchymal hemangioblastoma-like tumor of soft tissue. Forgot to add in my case description that after getting negative results from molecular analysis we had the opportunity to study this tumor with electron microscopy. EM documented the tumor cells as being of mesenchymal nature with tracts of basal lamina on the external cell surface, and abundant glycogen particles, intermediate filaments, and rough endoplasmic reticulum in the cytoplasmic cell compartment. Notably occasional electron-dense granules of secretory type were also noticed in some tumor cells; lipid droplets were not demonstrated. In conclusion: this tumor is intriguing and difficult to classify completely because: *i.* light microscopy and immunohistochemistry would suggest the diagnosis of HGB; *ii.* EM seems to militate against HGB (even if it may just indicate a more evident neural differentiation); and iii. molecular testing in this case was indefinite.

Ira Bleiweiss: Agree with hemangioblastoma. I've never seen an extraneural one. Very pretty case.

Tom Colby: Agree with diagnosis of hemangioblastoma. I must admit that I did not think of that because of the location but once the light went on it burned brightly. Great discussion.

Kum Cooper: Michele, I am intrigued by the plexiform vasculature, univacuolated cells (S-100+) and patchy myxoid stroma. My question is did you try FISH for t(12:16)? Apart from this "wildcard" suggestion I have never seen a hemangioblastoma outside of the CNS!

Ivan Damjanov: Vascular tumor—I could not go further. Maybe it is a hemangioblastoma, but we had a case that turned out to be inhibin positive and finally presented with CNS tumor. If your case has no VHL stigmata it is not a typical the diagnosis of hemangioblastoma remains still just a possibility.

Otto Dietze: I was not aware of the immunophenotype of this tumor.

Hugo Dominguez-Malagon: It looks to me as a Hemangioblastoma of the pre-molecular era. Unless a new classification arises subtyping as "hemangioblastoma-like" those not related to VHL mutation.

Göran Elmberger: Difficult case. I have no personal experience with neural hemangioblastomas but I do see the immunophenotypical and morphological similarities with published series. A lot goes back to the specificity of the immunos and this is always difficult to evaluate second hand without extensive familiarity with the specific laboratory. I do see HPC like vessels and intratumoral mature fat. This makes me wonder about if this could be fitted into the category of SFT-HPC or some odd variant of lipoma spindle cell type. Actually all those tumors show some immunophenotypical and to me morphological overlap. Subcutaneous, thigh, female... I truly don't know.

Jonathan Epstein: Don't really think it looks like hemangioblastoma. Too spindled and no foam cells. Looks HPC or SFT.

Vincenzo Eusebi: If I had seen a case like this within the cerebellum I would have called it hemangioblastoma without immuno. Being subcutaneous I would add CD34 to your antibodies list, in the remote possibility of an angioblastic solitary fibrous tumour.

Giovanni Falconieri: Challenging case, Michele. I have no better idea to offer. Thanks for this contribution and the discussion as well.

Franco Fedeli: Peripheral extraneural hemangioblastoma, richly vascularised, benign mesenchymal hemangioblastoma-like tumor of soft tissue. As for me this tumor looks more cellular than the classic neuraxial form of hemangioblastoma, even if the microvacuolated stromal cells are reminiscent of the stromal cells that one sees as the main characteristic of that tumor. EM analysis might be helpful.

Christopher Fletcher: We see a few examples of peripheral hemangioblastoma each year but I do not recollect ever seeing such a case in the limb. To be honest, I do not find the usual microvacuolated cells to be really convincingly demonstrated in this lesion and, like Juan Rosai, I have some doubts about the diagnosis. On H&E, I would have favored the possibility of a solitary fibrous tumour. It would be interesting to know the results of (retrospective) inhibin staining as well as CD34.

Andrew Folpe: Looks like an HPC/SFT to me.

Jerónimo Forteza Vila: Complicated case. I don't think I would have thought that entity.

Masaharu Fukunaga: I agree soft tissue hemangioblastoma. Personally I have never signed out a soft tissue case. Thank you very much for the detailed information, Michele.

Thomas Krausz: Diagnostically difficult case. I must admit that I did not think about the possibility of hemangioblastoma until I was reading your discussion. I was considering a cellular variant of hemangiopericytoma/solitary fibrous tumor. Going back to the case I appreciated more the microvacuolated cells, but I am still not convinced about the diagnosis of hemangioblastoma as the vacuolated cells are not as distinct as the stromal cells I have seen in the cases of cerebellar hemangioblastomas. Is CD34 positive on the tumor cells?

Janez Lamovec: I am not sure. It is very similar to hemangioblastoma but not quite the same. The location is very unusual. However, I don't know how to call this lesion but it appears benign.

Thomas Mentzel: Many thanks for this interesting case. I`ve seen only very few examples in typical anatomic locations but not in soft tissues. What is the best morphological clue on H&E for this difficult diagnosis ? How specific are the mentioned immunohistochemical results ?

Michal Michal: Hemangioblastoma. When there are a lot of S-100 positive vacuolated stromal cells with atypia, such case may closely simulate a liposarcoma in soft tissues.

Markku Miettinen: Favor solitary fibrous tumor/hemangiopericytoma with a lipomatous component. I did not see CD34 data. I would doubt hemangioblastoma in peripheral, extra-axial soft tissues.

Liz Montgomery: Hmmm. I wondered about good old fashioned solitary fibrous tumor/hemangiopericytoma. I assume that CD34 was negative though it was not mentioned.

Santiago Ramon y Cajal: I think that would be important to check whether inhibin is positive or not, although I agree with the hemangioblastoma-like features. Thank you, Michele, for sharing with us these puzzling and educational cases.

Juan Rosai: I did not know what this lesion was when Michele sent it to me some time ago, and I don't know what it is now. I agree with him that it has hemangioblastoma-like features, but I cannot be sure that is an example of the real thing, as opposed to some type of low grade sarcoma.

Manuel Sobrinho Simões: I totally missed the diagnosis because I did not even know the entity. My non-educated guess was "peculiar solitary fibrous tumour" (I feel embarrassed but that is the truth).

Dominic Spagnolo: I don't have a better suggestion, Michele. It strongly resembles capillary hemangioblastoma. Has oncogenic osteomalacia been excluded?

James Strauchen: Thank you for the excellent discussion of hemangioblastoma!

Saul Suster: This looks like a solitary fibrous tumor to me. You should try CD34, but even if it's negative, I would still diagnose this as SFT (CD99 and bcl-2 were positive, according to your notes).

Lawrence Weiss: I am not qualified to opine on the question as to this represents a hemangioblastoma or a hemangioblastoma-like lesion, but it looked like a hemangioblastoma to me. You did not mention results of CD34 staining.

Eduardo Zambrano: Extraneural (peripheral) hemangioblastoma sounds good to me.

CASE NO. 6 – CONTRIBUTED BY MICHELE BISCEGLIA:

Volkan Adsay: Rosai-Dorfman (sinus histiocytosis with massive lymphadenopathy).

Phil Allen: Classical Rosai-Dorfman disease, neck and mediastinal lymph nodes, with some systemic symptoms treated by chemotherapy and autologous bone marrow transplantation. I have difficulty understanding the logic behind the bone marrow transplantation when the pretransplant chemotherapy was only partially effective and the disease was apparently limited to cervical and mediastinal lymph nodes.

David Ben-Dor: I agree that it's very nice to see a histologically classical example of an uncommon entity in a typical location (for a change). I'm not sure how easy it would be to make the diagnosis unless one were to take pains to notice that the inflammatory cells were within the cytoplasm of the macrophages- otherwise it could be misdiagnosed as "reactive lymphadenitis". I would have enjoyed your summarizing the histology. Is the marked plasmacytosis seen in the parenchyma typical of this condition?

Gerald Berry: Looks like classic Rosai-Dorfman disease. Seems like extraordinary therapy for what appears to be rather innocuous clinical disease.

Ira Bleiweiss: Agree.

Tom Colby: Agree with diagnosis of RDD. Lovely case. I can't remember but I might have submitted a case of RDD of the lung to the AMR group. It was a case that Juan also presented at the 50th Annual Penrose Meeting in Colorado. It incidentally had a large number of IgG4-positive plasma cells, the significance of which remains to be fully clarified.

Kum Cooper: A tribute to Dr Rosai! Michele there are foci of necrosis which can be attributed to the chemotherapy; however, necrosis has been described in RDD in the literature. Further, I have seen a case with co-incidental mycobacterial infection and RDD in Africa (where I saw many more cases). Here in Vermont I have only seen RDD in the skin in a couple of cases. So I would do a Z-N stain on this case to rule out mycobacterial infection.

Ivan Damjanov: Rosai-Dorfman disease-agree. Nice review. Apparently one of the more popular submissions

Otto Dietze: Convincing histology, I have the problem that clinicians sometimes don't believe us a negative diagnosis of RDD in cases with massive sinus histiocytosis despite negative immunostains.

Hugo Dominguez-Malagon: Beautiful classic example of Rosai Dorfman (when I was a resident it was also known as "Sinus histiocytosis with massive lymphadenopathy") and the illustrations were similar to the actual case.

Jonathan Epstein: Classic.

Vincenzo Eusebi: Agree, RDD in a lymph node.

Giovanni Falconieri: Once in a while, I can say it, Michele: I have recognized it! Great example of RDD in classic location. I did not know, however, that aggressive chemotherapy and bone marrow transplantation are offered in some cases.

Franco Fedeli: A beautiful example of Rosai-Dorfman disease, a classic type in a classic location. Although I can notice a few scattered necrobiotic foci of the lesional tissue, in association with little leukocytoclasia, still I do not know which the significance of such finding is. Again any significance to the fact that the histiocytic proliferation is focally present even in the intersinusal cords of nodal parenchyma.

Cyril Fisher: RDD, nice example and interesting analysis and history of incidence in AMR seminars!

Christopher Fletcher: Beautiful Rosai-Dorfman disease for sure – I have never previously heard of these lesions being treated aggressively with chemotherapy and bone marrow transplantation.

Andrew Folpe: Rosai-Dorfman.

Jerónimo Forteza-Vila: I agree with the diagnosis. It is the typical case with sinusoidal pattern, emperipolesis and plasmocytosis.

Masaharu Fukunaga: A beautiful case of nodal RDD. The detailed clinical information and the reviews are very informative.

Thomas Krausz: Beautiful example.

Janez Lamovec: Most characteristic example of Rosai-Dorfman disease.

Thomas Mentzel: A wonderful and classical case!

Markku Miettinen: Agree on Rosai-Dorfman disease.

Liz Montgomery: Lovely classic Rosai-Dorfman disease.

Juan Rosai: Typical case of Destombes-Azoury disease, the entity usually inaccurately designated as Rosai-Dorfman disease (an inaccuracy which Ron Dorfman and I hope will perdure). This particular case shows neutrophilic microabscesses, a feature which is not too uncommon but which we did not emphasize sufficiently in our original report. By the way, some of you may have seen an obituary in the June 15, 2011 issue of the New York Times about Dr. James Rahal, an "infectious-disease specialist" working at Cornell having died of Rosai-Dorfman disease, simply referred to in the article as "a rare disorder". I guess he could not figure out the etiology either. As you know, it is very unusual for patients to die of this condition, but when the disease is systemic it may happen (as it may in Langerhans' and other forms of histiocytosis).

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: Beautiful case of nodal Rosai-Dorfman disease. Thanks, Michele.

James Strauchen: Very nice case of Rosai-Dorfman disease! What was the idea behind using rituximab?

Saul Suster: Classical example of Rosai-Dorfman disease.

Lawrence Weiss: Classic case, histologically.

Eduardo Zambrano: Very nice example of RDD.

CASE NO. 7 – CONTRIBUTED BY MICHELE BISCEGLIA:

Phil Allen: Metastatic basosquamous carcinoma, cervical lymph nodes with extracapsular spread, presumably from a repeatedly recurrent, primary, basal cell carcinoma of the skin of the nose with no squamous differentiation. There was no squamous differentiation in the skin tumors, but the squamous differentiation is easily seen in the secondaries, while the basal cell differentiation is minimal. This raises the possibility of an undiscovered, occult primary in the deep tissues of the head and neck. In some instances, the primary is not apparent for several years after the appearance of nodal metastases while in other cases, it is never discovered.

David Ben-Dor: To be honest, these look to me more like poorly differentiated squamous cell carcinoma. There is extensive clear cell changes in the first specimen (7a) while the slide from the lymph node dissection (7b) shows more squamoid features. There is also bluish mucinous material mixed with the necrotic debris- this may be part of the stromal response but can I be sure that it isn't epithelially derived? Without the clinical history I wouldn't have thought of a metastasis from a basal cell carcinoma because I don't convincingly see features of that lesion here- if this is a metastasis from the previous B.C.C. then this would reflect significant malignant transformation. But there is a focus in the lymph node slide showing stromal retraction and poorly developed palisading but I didn't notice this generally. The clear cell changes with some suggestion of vacuolar change bring up the possibility of sebaceous carcinoma- I don't know if this has any predilection for the skin of the nose given the abundance of sebaceous glands in that situation.

Gerald Berry: Agree. The few cases that we have of metastatic BCC are to the periparotid region or to the lung. Nice discussion.

Ira Bleiweiss: Squamous cell ca to me, not basal.

Thomas Colby: Agree with diagnosis. The unusual, yet known to all of us, of metastatic basal cell carcinoma. I have several cases in the lung.

Kum Cooper: Thank you, Michele.

Ivan Damjanov: Basal cell carcinoma-nice discussion.

Otto Dietze: Fortunately, I cannot remember a patient with metastasizing basal cell carcinoma in our hospital.

Hugo Dominguez-Malagon: The tumor has some peculiarities like nodular fasciitis-like stroma, keratinization in nests (more or less abrupt), and few clear cells with foamy cytoplasm. I wander if some of the metastasizing BCC may represent other entities with basal-like features including sebaceous carcinoma, NUT carcinoma and other entities?

Göran Elmberger: That's an important case. Just reviewed a case of our own a couple of weeks ago when we had a case of pulmonary metastasis from a metatypical BCC. Initially the lobectomy specimen was signed out as SCC of the lung and an EGFR mutational analysis with negative findings was performed. Fortunately we review all cases in multidisciplinary rounds and then the diagnosis was changed. The skin tumor occurred 5 years previously at the left temporal region. Two attempts at surgical resection were unsuccessful and left positive margins. Post-op external RT was administered. The tumor was of aggressive metatypical subtype (squamous differentiation) and revealed a highly aggressive growth pattern including extensive perineural growth. The metastasis looked very similar and correlative IHC was identical including immunohistochemical signs of p53 mutation and molecular identification of the same p53 gene mutation. Morphology and IHC in favor of BCC.

Jonathan Epstein: At least in the recurrence looks squamous or basosquamous.

Vincenzo Eusebi: Atypical looking baso-squamous metastatic carcinoma. What a case.

Giovanni Falconieri: Nice case, Michele, a warning that with BCC things do not go smooth in 100% of cases and anyone of us can be so lucky to pick up that 0,001% that goes bad in time. Thanks for the thorough review of the literature and the comment update!

Franco Fedeli: Subcutaneous metastasis from (cutaneous) basal cell carcinoma with squamous cell differentiation. I agree. Indeed, this is a very rare occurrence. Interesting features are worth noting: microscopic foci of tumor necrosis, foci of (?postnecrotic) cystification, and scattered globi of weakly eosinophilic likely amyloidotic material among tumor cells as occasionally seen in basaliomas.

Cyril Fisher: Metastasizing basosquamous carcinoma.

Christopher Fletcher: Personally, I feel a little safer not living in the same town as Michele! The pathologic material in San Giovanni Rotondo seems often to be extraordinary and terrifying.

Andrew Folpe: Aggressive basal cell carcinoma.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: This case is also very nice. The review is informative. Thank you Michel, again. I have a case of BCC with multiple recurrences and died of metastatic disease of transforming to carcinosarcoma.

Thomas Krausz: Highly educational case. Before reading your excellent discussion I was struggling to establish the line of differentiation of this metastatic tumor, beyond squamous, and was considering myoepithelial/salivary primary. I hope next time I will remember the possibility of metastatic BCC in my differential.

Janez Lamovec: Very rare occurrence. We saw it once or twice.

Thomas Mentzel: Although we see quite a high number of basal cell carcinomas every year, we`ve never detected a rare metastasizing case, many thanks for this case we well.

Markku Miettinen: Carcinoma with basaloid features. Clinical correlation needed for primary, could be skin.

Liz Montgomery: In isolation it looked like squamous cell carcinoma to me.

Juan Rosai: This is the kind of basal cell carcinoma which has been called metatypical, basosquamous and basaloid. In contrast to the usual basal cell carcinoma of skin, it is a highly invasive lesion associated with stromal desmoplasia which can be very aggressively locally and at the metastatic level. In other words, it tends to behave like the basaloid carcinomas of the upper aero-digestive tract and the anal canal.

Manuel Sobrinho Simões: Very nice case. I made the (wrong) diagnosis of basaloid squamous-cell carcinoma (whatever this means ...)

Dominic Spagnolo: Exceptional case of metastasizing cutaneous basisquamous carcinoma, Michele. I am aware of one case here of metastasizing BCC but can't recall whether that had squamous features too. Thanks.

James Strauchen: Very unusual case! I have seen one BCC metastatic to lung.

Lawrence Weiss: Instructive case.

Eduardo Zambrano: I see some evidence of sebaceous differentiation in this case. Although rare examples of basal cell carcinoma with sebaceous differentiation have been reported in the literature, I wonder if this case could represent a sebaceous carcinoma, especially given its highly aggressive clinical course.

CASE NO. 8 – CONTRIBUTED BY THOMAS COLBY:

Phil Allen: Poorly differentiated, AE1/3, EMA, desmin, and estrogen receptor positive malignant round cell tumor with positive SS18 gene rearrangement by immunofluorescence and positive TLE-61, posterior chest wall beneath the inferior angle of the scapula. I would be reluctant to group this tumor with conventional monophasic or biphasic synovial sarcomas at this stage and I doubt that we can apply established synovial sarcoma prognostic figures to this case. I don't think I have seen one like it before and I suspect we need to see more similar cases to discover all the clinicopathological features before lumping it with synovial sarcoma.

David Ben-Dor: If I'm not mistaken, the positivity for HMB45 in what is now called PEComas was first picked up on the basis of an immunostain mistakenly ordered by a resident. So you may be on to something big.

Gerald Berry: I must admit that the ER would have led me down the proverbially garden path and I would not have considered synovial sarcoma! A great case to learn from.

Michele Bisceglia: Tom, in regard to your query about the anomalous desmin and ER expression in SVS, here are two pertinent paragraphs from two different papers: 1. In regard to desmin expression, one can read that in a series of renal SVS "*Limited immunohistochemical studies showed vimentin positivity in 5/5 cases, desmin was positive in 4/6 cases, MYF4 showed focal weak nuclear positivity in 1/4 cases, but MyoD1 was negative in all cases (0/5). PGP9.5 was focally, strongly positive in 4/5 cases and p53 was strongly positive in 3/6 cases. Cytokeratin, using the antibody CAM5.2, was uniformly negative within the tumor cells. Finally, CD56 was focally positive in 1/6 tumors, whereas all other markers were negative including NB84a (4/4), CD34 (5/6), CD99 (5/5), and WT1 (6/6 cases).*" (Argani P et al. AJSP 2007;31:1459-68). **2.** In regard to the ER expression in a series of soft tissue and bone tumors so evaluated biochemically "*Six of the 33 tumors (18%) contained low levels of ERP ranging from 19 to 73 fmol/mg as determined by the dextran-coated charcoal method."* (Weiss SW et al. Lab Invest. 1986;54:689-94**)**.

Ira Bleiweiss: I also thought about Merkel Cell, but given the findings, I suppose synovial sarcoma is correct.

Thomas Colby: My case. Looking forward to comments from the rest of the group.

Kum Cooper: Thank you Tom. I too thought of proximal E-S as my first differential diagnosis. Did you do CD34 and INI-1; although I am not debating the FISH nor TLE-1!

Ivan Damjanov: SS18 shows that this small blue cell tumor is a synovial cell carcoma.

Otto Dietze: I believe that positive SS18 rearrangement is the most important fact for this diagnosis.

Hugo Dominguez-Malagon: The case illustrate that malignant cells can show many "aberrant" expressions, lineage "infidelities" and molecular "promiscuities".

Göran Elmberger: Morphology and results of molecular studies are conclusive. Molecular rules in the field of soft tissue pathology… Can't explain ER or desmin. Did people check for receptors systematically? Out of the box findings can be surprising. Takes a pulmonary pathologist and a clerical error to detect! Today our IHC is so sensitive quite unexpected findings occur. You should check AR and PR too..

Jonathan Epstein: Agree. Nice example.

Vincenzo Eusebi: I acknowledge the immuno & cytogenetic results. I do not know how I would have called the present tumour. Probably I would have asked for a second opinion. Difficult case.

Franco Fedeli: Poorly differentiated synovial sarcoma with anomalous expression of desmin (and I guess ER). Desmin as well as ER expression must be very unusual in synovial sarcoma. I never seen a case of synovial sarcoma as positive for desmin, and I never immunostained a synovial sarcoma for ER.

Giovanni Falconieri: Tough case, Tom. Desmin positivity combined with the small cell morphology would have certainly misled me as well. Thanks for this teaching case.

Cyril Fisher: The immunophenotype and FISH finding indicate synovial sarcoma and RT-PCR would be of interest to identify the SSX partner gene subtype. Interestingly in relation to the desmin, the amount of cytoplasm is unusual for PDSS.

Christopher Fletcher: Remarkable case indeed and a very tough diagnosis to make in the absence of molecular confirmation. Personally I think that estrogen receptor positivity is incredibly non-specific and is a common finding in a very wide array of tumors, most often having little or no biologic significance. I can recollect seeing very occasional/rare cases of synovial sarcoma which were desmin positive and I believe that Cyril Fisher mentioned this possibility in a review many years ago in Ann Diagn Pathol (although I cannot access the journal right now as my office is a construction site!).

Andrew Folpe: I forgot about this case- it's certainly a very interesting one. I guess I'd just comment that desmin is "just another intermediate filament", and so it can be expressed anomalously in a variety of things. Anomalous neurofilament expression is relatively common in synovial sarcomas- how common desmin is, I don't know, since I've never studied it systematically. All the other data certainly points right at synovial sarcoma.

Jerónimo Forteza Vila: Immunohistochemistry and FISH study do not allow for diagnosis doubts, which histologically can only be conjectured.

Masaharu Fukunaga: It is very interesting and challenging. My first impression was extraskeletal osteosarcoma or rhabdomyosarcoma.

Thomas Krausz: Agree with diagnosis. ER and desmin positivity in synovial sarcoma is new to me in synovial sarcoma. However, expression of various aberrant markers has been documented in some other mesenchymal tumors when they become higher grade.

Janez Lamovec: SMA and MSA may be occasionally positive in synovial sarcoma but I don't know about desmin or ER.

Thomas Mentzel: To be honest I would not think on synovial sarcoma on H&E, however, poorly differentiated synovial sarcoma may show a very unusual immunophenotype, and also desmin expression has been reported in these neoplasms.

Markku Miettinen: Malignant small round cell tumor, impossible to define by histology only. Could be synovial sarcoma, based on the SS18-split.

Liz Montgomery: Nice case. I did not realize that dot-like desmin expression could be a feature of poorly differentiated synovial sarcoma.

Santiago Ramon y Cajal: Striking case. Based on the molecular studies, the diagnosis is the right one. I think that we are still missing many biological characteristics of these poorly differentiated tumors.

Juan Rosai: I guess we will have to accept the diagnosis of synovial sarcoma in view of the molecular genetic results, although it sure does not look like any morphologic variant of this tumor I know.

Manuel Sobrinho Simões: Agree with the diagnosis. I (we) do not have enough experience to comment on the desmin expression and strong positivity for ER.

Dominic Spagnolo: Agree with poorly differentiated synovial sarcoma. Desmin has rarely been reported in monophasic SS (don't know about poorly differentiated, as in this case). ER also was shown in the "old" days by dextran charcoal method and immunoassay though not by IHC. Given the better retrieval techniques now, it would be interesting to see how often this may occur.

James Strauchen: Nice case of poorly differentiated synovial sarcoma confirmed by FISH. Don't know what the desmin and ER mean. The WHO book states unequivocally that desmin is absent, but that actin or other muscle markers may occasionally be present.

Saul Suster: I agree with the diagnosis of synovial sarcoma. We've seen cases previously that were initially mistaken for Merkel cell carcinoma when in superficial or subcutaneous locations. I have never encountered ER or desmin positivity in these tumors.

Lawrence Weiss: I am going to guess that there is not much data on ER in synovial sarcoma, and I have none. I have no recollection of anomalous desmin expression.

Eduardo Zambrano: Synovial sarcomas are known to express certain myogenic markers, particularly calponin but, to my knowledge, desmin expression is rather unusual (ca. 5% of cases). Certainly a case for molecular analysis.

CASE NO. 9 – CONTRIBUTED BY GORAN ELMBERGER:

Volkan Adsay: Great case. I will make sure to show it to our residents for our unknown conference.

Phil Allen: Sclerosing polycystic adenosis parotid gland. The contribution of this rare condition, which I don't think I've seen before, is greatly appreciated.

David Ben-Dor: Well, I dunno. Very tricky. The cells are the ultimate in blandness. The presence of myoepithelium surrounding the glands is comforting, but in the salivary gland unlike the breast or prostate, malignant proliferations can consist of both (re. epithelial-myoepithelial carcinoma). There is obviously non-neoplastic parenchyma at the periphery of the sections which is separated from the neoplasm by fatty tissue. While the tumor seems to be keeping its distance from the benign parenchyma it intrudes on the fat in an irregular infiltrative pattern which is disconcerting. The back to back arrangement of the glands is also troubling. In the midst of the tumorous small acinar proliferation there are dilated cystic structures which are obviously benign- are they an integral part of the tumor or are they islands of residual benign parenchymal structures resulting from tumor invasion? I also found scattered (singly or in very small groups) serous acinar salivary cells mingling with and blending into the tumorous acini- is this intimate relationship proof of benignancy or can it be the result of the tumor invading into the benign gland? Maybe this is an acinar tumor deriving from the larger salivary ducts rather than from the acinar parenchyma?

Gerald Berry: Agree, nice case.

Michele Bisceglia: Sclerosing polycystic adenosis (SPA) of parotid gland. Nice case.

Ira Bleiweiss: Never heard of it.

Thomas Colby: A new entity for me. I thought the lesion was distinctive but probably would have gone down the low-grade salivary gland adenocarcinoma route left if left to my own devices.

Kum Cooper: Thank you Goran. This is a great educational experience as I have read about these lesions before but not seen a case (or perhaps missed it previously!). I have a current case that I think resembles this lesion but is in the mid-line at the base of the tongue. I await the excision of my case to compare with your case. Much thanks.

Ivan Damjanov: Thanks for teaching me about sclerosing polycystic adenosis of the salivary glands.

Otto Dietze: I know this only from the literature, I have not seen this before.

Hugo Dominguez-Malagon: I should confess that I missed the diagnosis because of the absence of apocrine-like cells and intracytoplasmic hyaline globules.

Göran Elmberger: My case. Hope you agree. Just saw an interesting tumor resembling case 9 superficially. I may probably present it to you later. That case I believe represent an non-clear cell variant of epithelial myoepithelial carcinoma ex SPA. If I am right may be the missing link! As you know SPA has recently changed its status to a true neoplastic lesion based on Humara assays and cases of DCIS arising in SPA being described. To my knowledge a bona fide case of invasive carcinoma ex SPA has not yet been described or at least published. If someone of you have a second case we might join forces.

Jonathan Epstein: Never have seen this but looks analogous to florid usual duct hyperplasia of breast.

Vincenzo Eusebi: I do not know how to call this lesion. There is duct ectasia together with nodular epi myoepithelial benign looking proliferation. No evidence of the acinic and apocrine- like cells which are a feature of SPA.

Giovanni Falconieri: Never seen in my practice, just in a few slide seminars (I guess one of the last held by Mario Luna here in Italy in 2006), and if seen I am afraid I missed it - spectacular case. Thank you Goran for this piece of cake, a collectible item.

Franco Fedeli: Sclerosing polycystic adenosis (SPA) of parotid gland. Nice case, well-documented.

Cyril Fisher: Sclerosing polycystic adenosis. I have no previous experience of this. It is a very pretty slide, many thanks.

Jerónimo Forteza Vila: Interesting case; had had seen none.

Andrew Folpe: Extremely difficult. I thought this was some type of low-grade salivary gland carcinoma. Thanks for enlightening me.

Masaharu Fukunaga: Sclerosing polycystic adenosis, it is new to me. It looks like breast lesion. Thank you very much for sharing the wonderful case.

Thomas Krausz: Agree with diagnosis. The literature data on the monoclonal nature of this type of lesions is surprising in the context of histology (organoid nodular adenosis with two cell types etc).

Janez Lamovec: Quite a few similarities with the analogous breast lesions.

Thomas Mentzel: A wonderful case with collagen rosettes!

Michal Michal: I am not sure that this is a case of sclerosing polycystic adenosis. Sclerosing polycystic adenosis of salivary glands looks like sclerosing cystic change of the breast with oxyphilic-apocrine features. This lesion seems to me to much closer to ductal adenoma of salivary glands (Weinreb I. et al. Histopathology 201057:707-715) than sclerosing polycystic adenosis.

Markku Miettinen: Adenoma with cystic features.

Liz Montgomery: Thanks for this. It looks like sclerosing adenosis in the breast!

Santiago Ramon y Cajal: Beautiful case, Goran. Thank you!

Juan Rosai: I always suspected that the entity originally described as sclerosing polycystic adenosis of salivary glands was in reality a neoplastic process, and looking at this case reinforces my impression. Some of the cases I have seen had a degree of cytological atypia in the ducts that one could not avoid calling carcinoma in situ.

Manuel Sobrinho Simões: I was not able to make any diagnosis besides suspecting it might have a myoepithelial nature.

Dominic Spagnolo: Nice example of sclerosing polycystic adenosis. Thanks.

James Strauchen: Thank you for this very instructive case! I was unaware of this entity!

Saul Suster: Never seen this before. Cannot imagine a more appropriate and fitting name for this condition.

Lawrence Weiss: Beautiful histology. I would bet EBV has nothing to do with this lesion.

CASE NO. 10 – CONTRIBUTED BY JONATHAN EPSTEIN:

Volkan Adsay: I find it fascinating that these intraductal carcinomas can resemble mammary comedocarcinomas (as had already been noted by Dr. Rosai). In fact, this particular case also closely resembles the salivary duct carcinoma of the head and neck region. Great case.

Phil Allen: Extensive intraductal carcinoma of the prostate with separate minute foci of Gleason's score 3 + 3 = 6 infiltrating adenocarcinoma. I trust that invasive prostate adenocarcinoma can never make its own high molecular weight keratin as it spreads.

David Ben-Dor: Now that Dr. Epstein has joined the group, I look forward to having my experience in and understanding of prostatic and urogenital pathology in general being significantly enriched. I've seen cases of this entity but in needle biopsies and not in RP. The aggressive nature of the disease may make them ineligible for surgery- was this patient operated on in Hopkins or outside? There's a nice cuff of soft tissue surrounding the organ so it seems that the surgeon knows what he's doing. I saw a few scraps of tumor in some peripheral smooth muscle (is this capsule?) but these look like mechanical displacement more than invasion.

Gerald Berry: Agree. The discussion was very helpful in clarifying the controversies.

Michele Bisceglia: Extensive intraductal carcinoma of the prostate (IDC-P) with separate (not shown) incidental minute foci of Gleason score 3+3=6 adenocarcinoma. Probably I would have missed this case, calling it infiltrating cribriform acinar adenocarcinoma. Will be well keeping this in mind and rely on immuno from now onward.

Ira Bleiweiss: Agree. Looks like breast in prostate.

Thomas Colby: Agree with diagnosis. Spectacular example.

Kum Cooper: Thank you, Jon, for that beautiful rendition of IDC-P. Welcome to the club!

Ivan Damjanov: Agree.

Otto Dietze: I have seen a case of (infiltrating) comedocarcinoma a few months ago, and my first impression was that this one might be a similar one; however I am convinced from your diagnosis.

Hugo Dominguez-Malagon: Beautiful case of intraductal carcinoma of the prostate, and excellent discussion, thank you.

Göran Elmberger: Important distinction for obvious reasons. Was also thinking on analogy with breast ADH-LGDCIS-HGDCIS. What is the implication of comedo-type necrosis? IDC-P? In the breast we do have some help from ancillary testing with IHC; CK5, ER, PgR, MIB1 and HER2 besides the basal/ME-markers for distinguishing infiltration. It would be tempting to see if one could have any success with CK subtypes, proliferation markers, AR, P504s, ERG to make this crucial distinction somewhat less stressing for us non-uro pathologists... Sometimes I am dreaming of a unified nomenclature for precursor lesions in all organs...

Vincenzo Eusebi: Nice case. Thank you.

Giovanni Falconieri: Extraordinary start up case, Dr. Epstein. Thank you for this submission. Needless to say, I have nothing to add to your comment. Of course, welcome to the club.

Franco Fedeli: Extensive intraductal carcinoma of the prostate (IDC-P) with separate (not shown) incidental minute foci of Gleason score 3+3=6 adenocarcinoma. Educational case. Thank you. And thanks for enlightening the differential between IDC-P and the other entities, both invasive (such as invasive cribriform acinar carcinoma and ductal carcinoma of prostate) and intraepithelial (i.e., HGPIN).

Cyril Fisher: Prostatic intraductal carcinoma, absorbing and helpful discussion. Welcome to the Seminar.

Christopher Fletcher: Truly a florid example of intraductal carcinoma of the prostate – many thanks for the detailed and educational discussion.

Andrew Folpe: I would have called this Gleason 5, comedocarcinoma. I've always wondered if many of those were really in-situ, but my GU people kept telling me to call them Gleason 5. Thanks!!

Jerónimo Forteza Vila: I agree with the diagnosis. Interesting case.

Masaharu Fukunaga: Welcome, Dr. Epstein. This is a very beautiful case and I have never seen one before. The comments and DD are very informative.

Thomas Krausz: Highly educational case. Thank you very much for the superb discussion.

Janez Lamovec: My problem with terminology in regard to analogous breast lesions is that IDC in the breast denotes infiltrating duct carcinoma while DCIS is ductal carcinoma in situ what is called IDC-P in the prostate. As I understand it, IDC-P would be similar to what we call high nuclear grade DCIS in the breast.

Thomas Mentzel: Thanks a lot for the case and for the interesting discussion, showing nicely the similarities of intraductal neoplasms of the breast and the prostate. We only can hope that differences in terminology (ductal carcinoma in situ *versus* ductal intraepithelial neoplasia, and intraductal carcinoma of the prostate *versus* high-grade prostatic intraepithelial neoplasia) will come to an end in near future!

Markku Miettinen: Agree on high-grade PIN with comedonecrosis. Did not see definitive invasive elements.

Santiago Ramon y Cajal: Excellent case and discussion!

Juan Rosai: It is amazing how this intraductal carcinoma of the prostate resembles intraductal carcinoma of the breast with cribriform features. I think this is yet another example of the striking morphologic, phenotypic and functional similarities that exist between the breast and the prostate both at the normal and the pathologic level.

Manuel Sobrinho Simões: Some people made the diagnosis of adenocarcinoma and others of intraductal carcinoma (I guess no one made "both" diagnoses).

Dominic Spagnolo: Great example of prostatic intraductal carcinoma with nice discussion and practice points. Thanks, and welcome to the club.

James Strauchen: Thank you for this instructive case! The analogy to breast cancer is interesting. It is remarkable how inconsistent the nomenclature is across organ systems for pre-invasive lesions. Some are considered carcinomas (e.g. DCIS of breast, papillary TCC of bladder) others not (HGPIN, colonic adenomas).

Saul Suster: Great case! Superficially resembles infiltrating cribriform carcinoma of the breast.

Lawrence Weiss: This is a wonderful example of how immunohistochemistry has turned our world upside down. From Gleason pattern 5 to intraductal carcinoma, all with the demonstration of a basal layer by immunohistochemical stains.

CASE NO. 11 – CONTRIBUTED BY GIOVANNI FALCONIERI:

Volkan Adsay: Great case. Some areas of this tumor reminded me of the mesenchymal hamartoma of the liver. The immature but bland appearance of the tumor cells, distinctive capillarization, clusters of thick-walled vessels, myxoid appearance of stroma with vacuolization, as well as cystic degeneration are all also seen in mesenchymal hamartoma of the liver. I wonder if this case might represent pulmonary counterpart of that phenomenon.

Phil Allen: What about a CD34 negative intrapulmonary lipomatous hemangiopericytoma (solitary fibrous tumor)?

David Ben-Dor: Beautiful case of Falconieri-Suster, tumor of the lung!

Gerald Berry: By default PEComa seems to be the best fit. I presume a metastasis has been excluded.

Michele Bisceglia: Stromal tumor-NOS or clear cell tumor NOS. I definitely cannot be of any help or advice. Sorry, Falco. I suppose this tumor was positive at least for vimentin. Why not to try EM analysis on paraffin embedded tissue?

Ira Bleiweiss: ? No idea.

Thomas Colby: Don't know what this is. I would truncate Saul's diagnosis of "clear cell tumor of unknown etiology" to simply "tumor of unknown etiology." I doubt that this is malignant and the funny little spindle cells have a resemblance to some of the cells seen in hamartomas and to the (usually focal) spindle cells seen in alveolar adenomas. Sometimes the cells in hamartomas will show positivity with GFAP but I certainly wouldn't use that as any sort of specific marker.

Kum Cooper: Falco, I have no better ideas!

Ivan Damjanov: Spindle cell lipoma or a low grade mesenchymal malignancy.

Otto Dietze: I believe that clear cell tumor is the best diagnosis. To my opinion HMB-45 staining is less often positive in PEComas than we expect it.

Hugo Dominguez-Malagon: Very strange tumor, I believe most cells have a histiocytic or macrophage phenotype, my problem is how to name it.

Göran Elmberger: Difficult case. I find it difficult to accept as clear cell tumor of the lung (PECOMA) without supportive IHC evidence. I note dominating stromal differentiation including fat but I also see some epithelial ductular component in the peripheral region under the attenuated bronchiolar mucosa. The question is whether these glands are part of the tumor moving us in the direction of biphasic pulmonary tumors or SGT or if there is a subtle infiltration going on by the stromal tumoral cells. I guess I am in favour of a biphasic benign tumor. Could this be an uncommon variant of pleomorphic adenoma? I would try more IHC focused on sensitive markers of ME cells and try to characterize the ductular epithelial component. SGT's of bronchial mucosa can be TTF1+! Any history of tumor in other organs?

Vincenzo Eusebi: I also think that the lesion would be a stromal tumour benign. No better diagnosis.

Giovanni Falconieri: My case. Waiting for your valuable comments, folks! BTW follow up is negative.

Franco Fedeli: Stromal tumor-NOS or clear cell tumor NOS. Very difficult case.

Christopher Fletcher: I regret that I do not recognize this lesion at all – benign spindle cell neoplasm would be the best that I can do.

Andrew Folpe: I'd be concerned about a metastatic sarcoma, perhaps one resected some time ago, and would work on getting better clinical history.

Jerónimo Forteza Vila: It doesn't occur to me what could provide additional information. In case to have more material, ultrastructural study could be interesting.

Masaharu Fukunaga: I think clear sugar tumor most likely although all immunostains were negative.

Thomas Krausz: On H&E I would favor solitary fibrous tumor with adipocytic differentiation. ? repeat CD34 on some other blocks. I also thought about juxtaglomerular cell tumor but in view of the presence of adipocytes, it is unlikely.

Janez Lamovec: Spindle and epithelioid clear cell tumor, benign. This is not very helpful but that far I can go.

Thomas Mentzel: For me the lesion looks like an unusual stromal tumour with some mature adipocytic cells and scattered inflammatory cells. A PEComa-like lesion is not present in my opinion.

Markku Miettinen: Unclassified, gave some consideration into an intrapulmonary solitary fibrous tumor variant.

Liz Montgomery: I have no idea what this is but it looks benign.

Santiago Ramon y Cajal: I do not know either. My first impression was a benign mesenchymal tumor and I was wondering some subtypes of hamartomatous tumors. It would be relevant to know the follow-up.

Juan Rosai: I don't know what this lung lesion is.

Manuel Sobrinho Simões: No idea. The best we could come up with was PEComa *versus* inflammatory myofibroblastic tumor.

Dominic Spagnolo: I too wondered about clear cell sugar tumor but it is does not seem to be that. I have no idea what it is. Histiocytic/dendritic markers all negative??

James Strauchen: Looks a lot like case 5! Hemangioblastoma of the lung?

Saul Suster: I still don't know what this is. In looking at this a second time, it does look rather similar to case No. 5 in the same seminar.

Lawrence Weiss: No clue.

CASE NO. 12 – CONTRIBUTED BY FRANCO FEDELLI:

Phil Allen: Epithelioid angiosarcoma of the left adrenal gland. It looks pretty good to me but will Bruce and Saul accept it? I am not too fussed by the keratin staining, but I have stronger feelings about joining this tumor with angiolymphoid hyperplasia with eosinophilia and epithelioid hemangioendothelioma into a pathology "family."

David Ben-Dor: On initial review of the slide, the tumor cells looked more syncytial rather than forming vascular spaces which are obviously irregular and poorly formed so for me it's a very nice pickup from which the confirmatory immunohistochemistry followed. It's interesting that WT-1 was one of the markers used to confirm vascular origin- at the beginning this was touted as a marker of serous or mesothelial derivation. When we started using it here and I saw that it was staining blood vessels I assumed it was in error. This point was discussed by Michele Bisceglia in articles he shared with me and also brought up at the meeting in Istanbul. Some of the compressed adrenal cells at the periphery of the tumor form single files which is curious but obviously irrelevant in the larger context.

Michele Bisceglia: Epithelioid angiosarcoma of the adrenal gland. Have met the acquaintance of this tumor in this location after the publication of a series of such cases by Bruce Wenig in 1994 (AJSP. 1994;18:62-73). Since then have encountered 3 cases of adrenal angiosarcomas (2 personal cases and a consult case, which had been diagnosed as anaplastic carcinoma).

Gerald Berry: Agree.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis. I had an epithelioid angiosarcoma of the adrenal gland present as lung metastases and I erroneously called it metastatic carcinoma because it was so epithelioid but subsequent studies confirmed angiosarcoma, primary in the adrenal gland.

Kum Cooper: Nice epithelioid morphology. I recently saw a case in the liver of a young 30-ish old man.

Ivan Damjanov: Fits with the diagnosis of epithelioid angiosarcoma. Initially I thought it was a pheochromocytoma, but the longer I examined the more I agreed with you.

Otto Dietze: Epithelioid angiosarcoma, even without immunostains the morphology is convincing from the H&E aspect.

Hugo Dominguez-Malagon: Agree with the diagnosis of epithelioid angiosarcoma, thank you.

Göran Elmberger: Nice case. Epithelioid and vasoformative. According to literature metastatic AS to the adrenal gland also occurs... Dx of exclusion.

Jonathan Epstein: Classic.

Vincenzo Eusebi: Typical epithelioid keratin positive angiosarcoma.

Giovanni Falconieri: Totally agree with your assessment and interpretation. Great case, Franco.

Cyril Fisher: Epithelioid angiosarcoma of adrenal, very nice example

Christopher Fletcher: Epithelioid angiosarcoma of adrenal. Indeed it seems that essentially all angiosarcomas in the adrenal have epithelioid morphology, which is remarkable. In my experience, epithelioid angiosarcomas at visceral locations and in deep soft tissue are far more often keratin positive than those occurring in the skin, which may explain the discrepancy between the two publications cited.

Andrew Folpe: Angiosarcoma.

Jerónimo Forteza Vila: I agree with the diagnosis. Very nice case.

Masaharu Fukunaga: Welcome, Franco. Thank you very much for the beautiful case, I had never seen an epithelioid angiosarcoma of the adrenal gland.

Thomas Krausz: Agree with the diagnosis of angiosarcoma.

Janez Lamovec: I have seen at least one case of this type of angiosarcoma of the adrenal before; almost identical to this one.

Thomas Mentzel: What a fascinating case, many thanks!

Markku Miettinen: Agree on epithelioid angiosarcoma involving adrenal.

Liz Montgomery: What a beautiful deep angiosarcoma.

Santiago Ramon y Cajal: Rare and striking case. Thanks!

Juan Rosai: Great case of epithelioid angiosarcoma of the adrenal gland. The huge acidophilic nucleoli are a very good clue of the diagnosis, as Vincenzo Eusebi and I realized when working on epithelioid angiosarcoma of the thyroid gland.

James Strauchen: Wild case!

Saul Suster: Agree with diagnosis of epithelioid angiosarcoma – beautiful case!

Lawrence Weiss: Beautiful case. Adrenal cortical carcinoma tends to be keratin negative, and particularly CK7 negative.

Eduardo Zambrano: Very nice case. My initial impression was that of an adenocarcinoma metastatic to the adrenal gland.

CASE NO. 13 – CONTRIBUTED BY MASAHARU FUKUNAGA:

Phil Allen: Female adnexal tumor of probable Wolffian in origin, right broad ligament. I don't see enough of these to permanently imprint the patterns on my memory. This one will help. Thanks for the contribution, Masaharu.

David Ben-Dor: A beautiful example of a quite rare lesion. Sometimes this comes up in the d.d. of what turn out to be more common entities so it's nice to have a classical example to be able to refer to in the future. Sad to say but in the future Masaharu may be sharing with us some very interesting examples of pathology resulting from the tragic nuclear reactor accident.

Gerald Berry: Agree.

Michele Bisceglia: Wolffian tumor of the broad ligament (female adnexal tumor of probable Wolffian origin). Very beautiful case as well as rare case. Thank you, Masa, for sharing this case with us. We have now 3 FATWO cases in our seminars (after the case from M Michal, case 10 in Seminar # 32, and the

other one from PW Allen, case 1 in Seminar 49). Incidentally there are also on record 2 FATWO-like endometrioid carcinoma of the salpinx (respectively contributed by J Sickel in Seminar # 33 and by M Bisceglia in Seminar # 35 as a "follow-up case" to the previous Sickel's case.

Ira Bleiweiss: Wow.

Thomas Colby: Agree with diagnosis.

Kum Cooper: FATWO. Thank you Masa.

Ivan Damjanov: Agree-FATWO.

Otto Dietze: Most cases I know from the seminar, the only one in our files was from the vagina.

Hugo Dominguez-Malagon: Beautiful example of FATWO, thank you Masaharu.

Göran Elmberger: Very good example of FATWO. Thanks.

Jonathan Epstein: Wonderful example.

Vincenzo Eusebi: Female adnexal tumour of probable Wolffian origin.

Giovanni Falconieri: Nice case, Masaharu. We do not see ob-gyn specimens in our department so it is good once in a while to boost up my memory.

Franco Fedeli: Wolffian tumor of the broad ligament (female adnexal tumor of probable Wolffian origin). Nice and rare case. Focally this tumor shows pseudoendometrioid features.

Cyril Fisher: FATWO, one for the collection!

Andrew Folpe: Very nice case. Thanks for submitting.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: This is my case and a very classical case.

Thomas Krausz: Very nice, classic example.

Janez Lamovec: Very characteristic FATWO! Thank you.

Thomas Mentzel: Thanks for this case of a rare entity.

Markku Miettinen: Agree on adnexal Wolffian-like tumor.

Santiago Ramon y Cajal: Thank you, Masaharu. Very interesting case.

Juan Rosai: : Very nice case of Wolffian duct tumor (FATWO). When this entity was first presented at a Journal Club I made a fool of myself by saying that I thought it was just another variant of sex cord-stromal tumor. I should have known better than going against Bob Scully's opinion.

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: A beautiful example of FATWO. Thank you, Masa.

James Strauchen: Thank you! I have only seen these presented at conferences!

Saul Suster: Not my area; thank you for the education.

Lawrence Weiss: Another beautiful case. Textbook.

CASE NO. 14 – CONTRIBUTED BY THOMAS KRAUSZ:

Volkan Adsay: I agree entirely that this is a salivary gland type tumor. I would regard this as low grade malignant. Some areas reminded me of mucoepidermoid carcinoma with eosinophilia of the thyroid gland. Focal prominence of eosinophils is interesting in this regard.

Phil Allen: Recurrent (x2) salivary gland type low-grade epithelial-myoepithelial carcinoma, left main bronchus. I have not had much experience with these tumors in salivary glands, let alone the lung, but I think Thomas' suggested diagnosis is correct.

David Ben-Dor: My two cents- the suggested diagnostic terms are low grade epithelial myoepithelial carcinoma or adenomyoepithelioma. Curiously the latter term refers to a benign tumor in the breast; in the WHO lung blue book (I have the one from 2004; has it been superseded?) it's used synonymously for epithelial myoepithelial carcinoma (as Thomas did) but also in the entry for pleomorphic adenoma it's listed as one of "benign salivary gland like tumors". The question is whether the recurrence is evidence of the lesion's malignancy or reflects the problematic removal of the tumor previously.

Gerald Berry: I would classify this as a mixed tumor of the bronchus. The designation of low grade seems appropriate based on multiple recurrences but has the patient had a definitive bronchoplasty/sleeve resection procedure or just endobronchial resections?

Michele Bisceglia: Salivary gland type tumor, most consistent with low-grade epithelial-myoepithelial carcinoma (low grade adenomyoepithelioma). Thomas, as you say this is difficult to classify. I would say that based on HE only this tumor seems impossible to better diagnose other than a low grade malignant epithelial tumor; however, after knowing the immunoprofile you described I would agree on a (strange) epithelial-myoepithelial tumor.

Ira Bleiweiss: Neat.

Tom Colby: Low-grade carcinoma consistent with salivary gland origin and I think low-grade epithelial-myoepithelial carcinoma is entirely reasonable.

Kum Cooper: Thank you, Thomas. Agreed salivary gland type tumor with epithelial and myoepithelial features. Carcinoma since the stroma is desmoplastic.

Ivan Damjanov: I am not sure if this is a vary, very, very low grade malignancy or a benign tumor. Favor benign.

Otto Dietze: I favor low grade epithelial myoepithelial carcinoma due to the infiltrative growth pattern; however, I have not seen this tumor in a bronchus before.

Hugo Dominguez-Malagon: I think it is malignant, agree with epithelial-myoepithelial carcinoma. Another possibility is mucoepidermoid carcinoma.

Göran Elmberger: Thomas first I want to tell you that I agree completely on your remarks on WHO 2004 classification on SGT of the bronchus. Even further I also think the WHO classification on SGT 2005 is often very difficult to apply on bronchial derived SGT. They are just hard to fit in any of the existing categories. The tumor you now present to us is definitively one of those problem cases. Then I would like to point out that the markers you cite as positive indicating ME differentiation, i.e.; p63, S100 &CK 5/6 are not very specific for ME cells. They also could mark basal cells or squamoid cells. I would like to see some evidence of myogenic differentiation before I feel convinced. From a morphological standpoint I see luminal-ductular differentiation and some possibly intermediate-squamoid differentiation in the peripheral parts. No convincing mucocytes. Stroma is desmoplastic and with lots of eosinophils. As is often the case with endobronchial tumors you get these piecemeal biopsies of only intralesional quality. This hampers ones ability to ascertain the malignant potential of the tumor. In the present case I would suspect a low-grade malignancy based on cytology, mitotic index, desmoplastic stroma and history. In summary: if you could show me convincing ME differentiation in peripheral parts along with convincing luminal differentiation in central parts preferably with a IHC double stain such as CK18/SMMS1 I could go along with your diagnostic suggestion of epithelial-myoepithelial ca LG. Adenomyoepithelioma I somehow reserve for breast and it also sounds awfully benign... Given the epidermoid sclerosing eosinophilic appearance I could not resist performing molecular markers for sclerosing mucoepidermoid carcinoma CRTC1-MAML2 even if that is deep fishing. If you get a catch it could be big! If ME differentiation after myogenic markers is not well developed

one could still consider ADCA NOS or possibly LG adenosquamous ca. Did you know that some bronchial SGT marks with TTF1? A potential pitfall.

Jonathan Epstein: Agree.

Vincenzo Eusebi: I agree with the interpretation of invasive epi-myoepithelial carcinoma. Luminal cells have eosinophilic granular cytoplasm and I bet they are either apocrine or oncocytic or both. This sort of carcinoma certainly recur, as the present case, but also can give metastases which are resistant to chemo and radiation therapy.

Giovanni Falconieri: I completely agree, Tom. Low-grade but definitely malignant. Great case for collection, thank you!

Franco Fedeli: Salivary gland type tumor, most consistent with low-grade epithelial-myoepithelial carcinoma (low grade adenomyoepithelioma). Difficult to subtype. However, taking into account all the morphological and immunohistochemical features I agree with a low-grade epithelial-myoepithelial carcinoma.

Christopher Fletcher: Thomas – I like your suggestion of a low grade epithelial-myoepithelial carcinoma, although I would claim no expertise at all with unusual lesions such as this in the bronchus.

Andrew Folpe: Looks low-grade malignant. I guess I'd wonder about something related to mucoepidermoid, with the mucin, but it's not right for that either.

Jerónimo Forteza Vila: I agree with the diagnosis. Nothing to add.

Masaharu Fukunaga: This case is very difficult to classify. It also likes like mucoepidermoid carcinoma.

Janez Lamovec: In most areas it is difficult to separate myoepithelial from luminal cells but in some foci the biphasic structures are quite evident. I couldn't find any certain mitosis. The recurrences may be due to incomplete excisions but you may be right that this is a low grade carcinoma.

Thomas Mentzel: Given the clinical and morphological features the diagnosis of a low-grade neoplasm similar to what is seen in salivary glands seems the best (until larger series of cases are collected allowing a better distinction between benign and obvious malignant neoplasms).

Markku Miettinen: Low-grade carcinoma variant.

Juan Rosai: I agree that this is a salivary gland type tumor. Low grade epithelial-myoepithelial carcinoma seems like a good name for it.

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: I can't think of a better designation than your low grade adenomyoepithelioma. In my section there are a reasonable number of intracytoplasmic mucin vacuoles and also foci of squamous (nonkeratinizing) differentiation. The spindle stroma is intriguing, and reminded me of metaplastic thymoma.

James Strauchen: Certainly looks like a bronchial salivary gland type tumor but hard to classify!

Saul Suster: I would regard this as a low-grade mucoepidermoid carcinoma. We published our experience a couple of years ago with 5 cases of epi-myoepithelial carcinomas of the lung with Cesar Moran (Hum Pathol 40:366-374, 2009), and they didn't look anything like this. Many types of salivary-gland tumors have a myoepithelial cell component, yet that has not been the basis for labeling them as epi-myoepithelial. Our tumors showed a much more prominent myoepithelial cell component that clearly stood out along the outer layer of the glandular structures, most of them forming a layer of clear cells that contrasted with the darker luminal cells. Intracytoplasmic mucin was not a feature in any of those cases.

Lawrence Weiss: In one area, it infiltrates like a low-grade salivary gland carcinoma. Your diagnosis is as good as any.

CASE NO. 15 – CONTRIBUTED BY ALBERTO MARCHEVSKY:

Volkan Adsay: Very nice case. We have recently seen similar cases that closely resembled splenic tissue. There are some cells in the vascular channels that made me wonder about extramedullary hematopoesis in this particular example as well.

Phil Allen: Multiple anastomosing hemangiomas in end-stage renal disease, left kidney. I will be interested to hear if any of the Club have previously seen multiple anastomosing hemangiomas.

David Ben-Dor: There is very dramatic thyroidization in this slide, to the extent that my first impression was that this was a thyroid tumor. There are obliterated glomeruli but you have to look for them. The tumor nodules are circumscribed but not perfectly so and in places the lesional tissue uncomfortably approaches the native benign tissue structures. The cells lining the vascular structures are very bland without atypia but the former are irregular and seemingly anastomose which is disquieting. So it's nice that someone already did the brainwork and came up with an entity under which to classify this lesion. Wasn't the radical surgery performed in this case overdoing it? Are abnormal kidneys prone to the development of this lesion?- a previous case recently submitted by Cyril Fisher occurred in a patient with ANCA vasculitis (though he didn't specify whether the kidney was directly affected); this isn't stated at least in the abstract of the Montgomery reference.

Gerald Berry: Agree.

Michele Bisceglia: Anastomosing hemangiomas of the kidney. Never seen one before outside AMR club (Cyril Fisher contributed the first one in Seminar # 59 [his case n. 12]).

Ira Bleiweiss: ? New one for me.

Thomas Colby: Agree with diagnosis, once I was made aware of the diagnosis. I have not seen this lesion before.

Kum Cooper: Wow, another Liz and Jon tumor!

Ivan Damjanov: Anastomosing hemangioma of the kidney—I have never seen one before.

Otto Dietze: I agree. In my opinion differential diagnosis of low grade malignant vascular tumor is very difficult, especially if someone is not aware of this entity.

Hugo Dominguez-Malagon: Anastomosing hemangioma of the kidney. In some areas it shows fibrin, slits with fragmented erythrocytes, and old hemorrhage. Is it a neoplasm or a reparative process?

Göran Elmberger: Very nice case. Fits excellent with original descriptions. A must know lesion considering ddx! Even in a lymph node... That is strange for a benign neoplasm as well as the infiltrative growth. Infection? Kaposi-like inclusions? LAM-like behaviour...

Jonathan Epstein: Since our original publication, have seen in addition to more cases in the kidney, cases occurring in the ovary as well. Am J Clin Path 2011; 136:450-7.

Vincenzo Eusebi: Anastomosing angioma of the kidney.

Giovanni Falconieri: Thank you, Dr. Marchevsky, for this valuable contribution, another pretty example of an exotic tumor right after Dr. Fisher submission for AMR 59 (case 12). Welcome to the club!

Franco Fedeli: Anastomosing hemangiomas of the kidney. Nice case. A new entity and a new entry for me.

Cyril Fisher: Anastomosing hemangioma. This is more fibrous than the example I submitted in AMR 59/12, illustrating the range of appearances. A further series including ovarian cases has just been published by Dr Epstein's group in Am J Clin Pathol. 2011;136:450-7.

Christopher Fletcher: Agree entirely with anastomosing hemangioma of kidney. We have seen quite a number of these lesions also in perirenal soft tissue.

Andrew Folpe: Anastomosing hemangioma. Nice case.

Jerónimo Forteza Vila: At first impression, if could be a malignant vascular tumor. It is a very interesting case for making the differential diagnosis. We had never seen a case of this significance. An interesting aspect from the AMR is that it provides the opportunity to see some cases you may have never seen before, that at most you know from the literature.

Masaharu Fukunaga: Welcome, Dr. Marchevsky. Thank your very much for the beautiful case. Multiple lesions are very interesting and they may be associated with the end stage kidney

Thomas Krausz: Agree with diagnosis. I have seen only one example before.

Janez Lamovec: There is a recent paper on this entity by Dr. Epstein group in August issue of AJCP. Thank you to complement it.

Thomas Mentzel: An interesting example of multifocal so-called anastomosing hemangioma, and it seems that these lesions are seen only in the genitourinary tract.

Markku Miettinen: Agree on capillary hemangioma variant. Tumor has some resemblance to "glomeruloid hemangioma".

Liz Montgomery: Thanks for sharing another one of these cute tumors. They seem to be all over the genital tract and kidneys.

Santiago Ramon y Cajal: Great and educational case.

Juan Rosai: So that's how anastomosing hemangioma of the kidney looks like! It seems to me that the appearance of this tumor (which is indeed spleen-like) is pretty different from the one that was shown as an example of the same entity in a previous seminar.

Manuel Sobrinho Simões: Agree with the diagnosis.

Dominic Spagnolo: Beautiful anastomosing hemangioma. I had only recently seen the latest 8 cases published in Am J Clin Pathol in September by Dr Epstein and colleagues (3 in the ovary, 5 in the kidney). Thanks for the slide, and welcome to the club!

James Strauchen: Thank you! I was unaware of this as an entity!

Saul Suster: Other than for the two seminar cases I've never noticed this before. Thank you for sharing this great case and welcome to the Club!

Lawrence Weiss: This is the first case I have ever seen. Thank you for sharing.

Eduardo Zambrano: Nice example of anastomosing hemangioma.

CASE NO. 16 – CONTRIBUTED BY THOMAS MENTZEL:

Volkan Adsay: For a myxoid mesenchymal neoplasm of this kind, based on the cellularity, I still wonder if it may not be more appropriate to regard this lesion as a very low-grade ("one half" or "0.5") myxoid sarcoma.

Phil Allen: Atypical (vascular and cellular) intramuscular myxoma, ?recurrent, left lower leg in Mazabraud's syndrome. I can only recall seeing one previous case of Mazabraud's syndrome. The intramuscular myxoma I saw initially was histologically typical, without any cellular or vascular areas, and as in this case, was initially thought to be recurrent. On careful questioning of the surgeon, he conceded that the tumor was adjacent to, but separate from, the site of one of many previous intramuscular myxomas. I teach my trainees that intramuscular myxomas never recur. When they do, the diagnosis is wrong (juxta-articular myxoma or myxofibrosarcoma) or the patient has Mazabraud's syndrome.

David Ben-Dor: The issue as to how reliable a history of recurrences is for basing a diagnosis of malignancy seems to come up repeatedly. Was the patient screened for bone lesions?

Gerald Berry: Yet another new entity that I have learned from the AMR Seminar! Nice case.

Michele Bisceglia: Recurring myxoid fibroblastic neoplasm. This is an educational case. Also the first case of intramuscular myxoma which has been circulated so far. Thank you, Thomas.

Ira Bleiweiss: Another syndrome I've never heard of.

Kum Cooper: Intra-muscular cellular myxoma. Much too cellular for the usual intra-muscular myxoma but not enough atypia/pleomorphism for myxofibrosarcoma. Mazabraud syndrome: learn something new everyday! Thank you, Thomas.

Ivan Damjanov: Low grade malignant myxoid tumor.

Otto Dietze: Thank you. I was not aware of this before and thought of low grade myxofibrosarcoma.

Hugo Dominguez-Malagon: My impression was low grade fibromyxoid tumor, but the molecular studies are conclusive.

Göran Elmberger: Interestingly this association seems to have been described by Folke Henschen in 1926. He was the first professor at the Karolinska Pathology Department after we moved to the present location. Obviously he was a colourful professor and there are many histories around his person. One tells that he fell off his bike on his way to job and broke his neck. He immediately realized what has happened took his head in a firm grip and shouted to the people approaching to stay away since he broke his dens… We have a beautiful fresco where you can see him in the far right. Last SGT course in Stockholm.

Jonathan Epstein: Histology typical with interesting molecular findings.

Vincenzo Eusebi: Very interesting case and thank you for Mazabraud syndrome of which I did not know the existence.

Giovanni Falconieri: I am not familial with the myxoid universe, and of course I totally ignored the entity at issue. My basic instinct tells me that this is benign to low-grade, but difficult for me to say more. Nonetheless, thank you, Thomas, for trying to educate me.

Franco Fedeli: Recurring myxoid fibroblastic neoplasm. Nice case, interesting clinical history and informative clinico-biologic data.

Cyril Fisher: An interesting case of myxoma unusually recurring, as seen in Mazabraud syndrome.

Christopher Fletcher: Whenever a morphologically bland intramuscular myxoma (or cellular myxoma) is said to 'recur' it is always worth considering the possibility of multicentricity (and hence Mazabraud syndrome), since local recurrence in tumors of this type is extremely infrequent.

Andrew Folpe: Myxoma.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: It looks like cellular myxoma in Mazabraud syndrome. It's very new to me. Thank you very much for the wonderful case.

Thomas Krausz: Very interesting case considering the clinical and molecular context. What a coincidence, we have a similar case currently (patient with multiple myxomas, awaiting molecular studies).

Janez Lamovec: To me this lesion appeared almost neurofibroma-like. I heard of Mazabraud syndrome but have never seen a case.

Michal Michal: Patients with GNAS mutation may have other interesting lesions. We have recently seen four patients with a point mutation in exon 1 of the GNAS gene having various skin and soft tissue lesions (osteoma-like , calcinosis circumscripta –like, calcifying aponeurotic fibroma-like lesion and others. *Kacerovska D, Nemcova J, Michal M, Kazakov D. Am J Dermatopathol 2008:30:417-424*)

Markku Miettinen: Cellular intramuscular myxoma.

Elizabeth Montgomery: Wow, the history is so dramatic but the lesion just looks like a myxoma! Thanks for sharing this rare example.

Santiago Ramon y Cajal: Excellent case.

Manuel Sobrinho Simões: I made the (wrong) diagnosis of low grade myxofibrosarcoma.

Dominic Spagnolo: Recurrent cellular myxoma in Mazabraud's syndrome. Never seen this before – thank you.

James Strauchen: Intramuscular myxoma. Was not aware of Mazabraud syndrome before. Thank you!

Saul Suster: Was not even aware of Mazabraud syndrome! Thank you for the education, Thomas.

Lawrence Weiss: Intramuscular myxoma was my first thought. Another new syndrome to learn.

Eduardo Zambrano: My impression was that of a cellular intramuscular myxoma. Very interesting follow-up and confirmation of GNAS mutation in this patient with Mazabraud syndrome.

CASE NO. 17 – CONTRIBUTED BY ELIZABETH MONTGOMERY:

Volkan Adsay: Great case. Especially the vascular pattern also reminded me of those rare cases that occur in the vulva/vagina and Nucci and Fletcher had termed as "cellular angiofibroma" although those cases are usually CD34 negative. I wonder if Dr. Fletcher also thought there is some resemblance between these entities.

Phil Allen: Pedunculated solitary fibrous tumor with giant cells, oesophagus. There are some giant cells in my slide. I am reluctant to be provocative but this looks just like the sinonasal-type hemangiopericytomas described by Thompson and two eminent members of this Club in Am J Surg Pathol 27:737-749, 2003. Should we let CD 34 negative hemangiopericytomas in the nose live on equal terms and in peaceful coexistence with the more sweetly smelling solitary fibrous tumor, who has already seen off giant cell angiofibroma, or should we encourage our poor old hemangiopericytomatous friend to join his illustrious creator in the grave?

Gerald Berry: I continue to be amazed at the novel locations that the SFT is reported.

David Ben-Dor: I assume that the statement that the esophageal location of a 27 cm mass was "fun" was meant for the pathologist (and maybe the surgeon who appreciated the challenge) but not for the patient. I wonder how the size of this lesion was in comparison with the liposarcoma of the esophagus that Paul discussed at previous meetings- the photos he showed looked like something from a freak show. To be honest (and I'm in no position to challenge your authority) I appreciated the stromal cellularity but the

vessels looked more round and regular than staghorn like and while there are areas of fibrosis I wasn't sure about there being thick collagen bundles to an appreciable extent. But I believe your diagnosis without the immuno. The giant cells showed up nicely.

Michele Bisceglia: Solitary fibrous tumor with areas of giant cells (giant cell angiofibroma/giant cell rich solitary fibrous tumor). Nice case.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis.

Kum Cooper: Thank you, Liz. Unusual site. Classic morphology.

Ivan Damjanov: I would buy this diagnosis probably better than the descriptive giant cell angiofibroma.

Hugo Dominguez-Malagon: Solitary fibrous tumor, unusual location but classic histology.

Göran Elmberger: Nice case. Certainly not the first expectation in esophagus. Nice variation between fibrous/hypocellular and cellular areas. In a few areas good portion of multinucleated stromal cells.

Jonathan Epstein: Typical histology in unusual site.

Vincenzo Eusebi: Esophageal SFT with giant cells, very nice case.

Giovanni Falconieri: Agree with SFT, location is pretty unusual but not surprising. Giant cells are quite remarkable in this particular case. Thank you for this contribution.

Franco Fedeli: Solitary fibrous tumor with areas of giant cells (giant cell angiofibroma/giant cell rich solitary fibrous tumor). Nice case.

Cyril Fisher: SFT with giant cells (just a few in my slide) in unusual location! Nice example.

Christopher Fletcher: Solitary fibrous tumour with small 'giant cell angiofibroma'-like foci. It was cases such as this that taught me that giant cell angiofibroma was not a discrete 'entity', although that first series of cases which we published consisted exclusively of giant cell angiofibroma-like elements and it was remarkable that all were located in the orbit. In any event, I was duped for sure and I have not made the diagnosis of giant cell angiofibroma in many years.

Andrew Folpe: Nice example of SFT with giant cells.

Jerónimo Forteza Vila: Brings up the differential diagnosis with the inflammatory fibroid polyp.

Masaharu Fukunaga: I agree giant cell angiofibroblastoma. A wonderful case, thank you.

Thomas Krausz: Superb example.

Janez Lamovec: We've seen quite a number of SFTs but never one in the esophagus.

Thomas Mentzel: Many thanks for sharing this really classical example of SFT with giant cell angiofibroma-like areas arising in an unusual clinical setting.

Markku Miettinen: Agree on solitary fibrous tumor (with giant cell angiofibroma-like features).

Santiago Ramon y Cajal: Although I like and agree with the diagnosis, is relevant the differential diagnosis with an inflammatory fibroid polyp.

Juan Rosai: Good case of the giant cell-rich variant of solitary fibrous tumor. This polypoid lesion of the esophagus can reach a huge size. Dr. Ackerman used to tell about a patient from the Ozarks who regurgitated this tumor at will, chewed it up, and swallowed it back into the esophagus. Eventually he agreed (with a great deal of reluctance) to have it removed, after which – to quote again Dr. Ackerman, "he went back to the Ozarks, where he belonged".

Manuel Sobrinho Simões: I agree with the diagnosis.

Dominic Spagnolo: Typical giant cell angiofibroma in a funny location – very pretty.

James Strauchen: Giant cell angiofibroma/solitary fibrous tumor! I was unaware of cases in the esophagus!

Saul Suster: Nice case of solitary fibrous tumor with giant cells. Dr. Moran described this finding several years ago in a review paper on these tumors in the pleura (Moran CA et al. Semin Diagn Pathol 9:169-180, 1992). What I find particularly unusual for this case is the location; I have never seen one in the wall of the esophagus!

Lawrence Weiss: Classic, unmistakable histology, but what is it doing there. I guess it can be anywhere.

Eduardo Zambrano: Solitary fibrous tumor/giant cell angiofibroma. Unusual location.

CASE NO. 18 – CONTRIBUTED BY CESAR MORAN:

Phil Allen: Elastofibroma, location not clear. Is this elastofibroma of the pleura or was it extrapleural, in the typical subscapular location? Elastofibroma dorsi may occasionally be bilateral.

David Ben-Dor: From my own experience, these can be missed and confounded with fibrosing tumors if the elastic tissue is overlooked.

Gerald Berry: Agree.

Michele Bisceglia: Elastofibroma. Cesar, I understand this tumor is of intrathoracic location, a very unusual site of occurrence. Can you confirm?

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis. I assume this was not within the chest cavity. I am not sure how mesothelioma enters into the histologic differential here.

Kum Cooper: Thank you, Cesar.

Otto Dietze: Typical case of elastofibroma, even without an elastic stain.

Hugo Dominguez-Malagon: Elastofibroma, the "beads" of fragmented elastic fibers are very apparent.

Göran Elmberger: Yes. I didn't get the location. Typical or intrapulmonary?

Jonathan Epstein: We used to see these not infrequently and haven't seen them as much in the last 15-20 years. Not sure why.

Vincenzo Eusebi: Elastofibroma in an unusual location.

Giovanni Falconieri: Agree, Cesar, elastofibroma, don't have better ideas.

Franco Fedeli: Elastofibroma. Typical case in an unusual location.

Christopher Fletcher: Perfect example of elastofibroma.

Cyril Fisher: Elastofibroma. Was this in a typical subscapular location?

Andrew Folpe: Elastofibroma.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: Elastofibroma. There are many cases in Okinawa, Japan.

Thomas Krausz: Classic example, the clinical history makes it even more interesting.

Thomas Mentzel: The typical changes of the elastic fibres are seen nicely.

Markku Miettinen: Agree on elastofibroma.

Liz Montgomery: What a nice bread and butter elastofibroma.

Santiago Ramon y Cajal: Agree. Thank you, Cesar.

Juan Rosai: It looks like an elastofibroma, all right, but I could not figure out the exact location of this mass from the description. It didn't sound it was located in the periscapular region, which of course is the classic site.

Manuel Sobrinho Simões: I agree with the diagnosis.

Dominic Spagnolo: Agree with elastofibroma. Am not sure exactly where this lesion was to occasion the confusion with mesothelioma. It was nice catching up with you down under, Cesar.

James Strauchen: Nice one!

Lawrence Weiss: Beautiful case. It was the first lesion I learned from an AFIP slide box of soft tissue tumors that I had ordered when I was a first year resident.

Eduardo Zambrano: Elastofibroma.

CASE NO. 19 – CONTRIBUTED BY SANTIAGO RAMON Y CAJAL:

Volkan Adsay: Agree entirely. Beautiful example of IPMN with low-grade dysplasia, branch duct type, and gastric-foveolar phenotype.

Phil Allen: Intraductal papillary mucinous tumor, head of pancreas. I can't see any invasion in my slide. We must blame the radiologists for giving us these pathological curiosities, which never used to trouble us in the good old days of 30 years ago.

David Ben-Dor: There is nuclear crowding and hyperchromasia consistent with the diagnosis. This is analogous in my experience to discriminating between a mucinous cystadenoma and borderline tumor in the ovary.

Gerald Berry: Agree with IPMT. I find these cases challenging and multiple sections and often leveled sections are needed.

Michele Bisceglia: Intra-ductal papillary mucinous tumor of pancreas with low grade dysplasia. Beautiful example, Santiago. And thank you for the CT imaging study.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis.

Kum Cooper: IPMN. Focal possible borderline features. No evidence of invasion. Thank you ,Santiago.

Otto Dietze: I believe that invasion would require stroma desmoplasia and / or nerve sheet involvement.

Hugo Dominguez-Malagon: Agree with the diagnosis of pancreatic intraductal papillary mucinous tumor (IPMT), nice case.

Göran Elmberger: IPMN beautiful case with IM and low-borderline dysplasia (borderline intraductal papillary-mucinous neoplasm). I guess pancreas is a difficult organ not like the breast, prostate and salivary

glands where the basal/ME cells tend to help us with regard to invasiveness. More like the mucinous tumors of the ovary. Does the concept of expansile invasive growth apply in the pancreas?

Jonathan Epstein: Classic example.

Vincenzo Eusebi: Intraductal papillary mucinous tumor.

Giovanni Falconieri: Agree, Ramon, nice case. Thank you for this contribution.

Franco Fedeli: Intra-ductal papillary mucinous tumor of pancreas with low grade dysplasia. Beautiful case. I agree with a low grade dysplasia.

Cyril Fisher: Intra-ductal papillary mucinous tumor of pancreas with low grade dysplasia, without definite invasion.

Christopher Fletcher: Textbook IPMN – perfect for teaching purposes – many thanks!

Andrew Folpe: Agree with IDPM. I don't see high grade dysplasia or invasion.

Jerónimo Forteza Vila: I agree with the diagnosis.

Masaharu Fukunaga: Intraductal papillary mucinous adenoma. There seems to be no atypia.

Thomas Krausz: Agree with diagnosis.

Janez Lamovec: Intraductal papillary mucinous tumor. Agree.

Thomas Mentzel: Many thanks for this recently described entity. On the given slide I found the degree of atypia (dysplasia) very low.

Markku Miettinen: Agree on pancreatic intraductal mucinous neoplasm.

Liz Montgomery: Thanks for the nice intra-ductal papillary mucinous neoplasm.

Juan Rosai: Nice case of intraductal papillary mucinous tumor with low grade dysplasia. I guess this the same lesion which is called Panin when involving smaller ducts.

Manuel Sobrinho Simões: I agree with the diagnosis.

Dominic Spagnolo: Nice example of MCN of pancreas. I agree there is no invasive carcinoma in this section. Thank you.

James Strauchen: Nice example of intraductal papillary mucinous tumor!

Lawrence Weiss: Nice case.

Eduardo Zambrano: Intraductal papillary mucinous neoplasm of the pancreas.

CASE NO. 20 – CONTRIBUTED BY DOMINIC SPANGOLO:

Phil Allen: Cutaneous myeloid sarcoma (aleukemic myeloid leukemia cutis), left chest wall. One must admire the menagerie of acronyms that have escaped into the discussion. I count myself lucky, Dom, that I am not a lymphologist.

David Ben-Dor: That's quite a remarkable workup and explanation. It may be "annoying" only in the sense that it shows how little I know about this topic. It's remarkable how much theoretical complexity there is to a cellular proliferation which on the surface looks rather simple histologically.

Gerald Berry: Thank you for the discussion. I find the recent entity of blastic plasmacytoid dendritic cell neoplasm to be fascinating, in part on account of its name!

Michele Bisceglia: Cutaneous myeloid sarcoma ("aleukemic" myeloid leukemia cutis), consistent with acute myelomonocytic leukemia (AMML). A very instructive case and a source of reference when dealing with cutaneous localization of myeloid neoplasms. Thank you, Dom.

Ira Bleiweiss: Agree.

Thomas Colby: Agree with diagnosis (based on the immunohistochemistry). Without that I was assuming this was some sort of lymphoreticular malignancy, probably of myeloid etiology based on the H & E. Superb discussion (way beyond my elementary level of hemepath these days).

Kum Cooper: Thank you, Dom...no annoyance at all. The old UCHL-1 (also a T-cell marker) stained myeloid cells too.

Ivan Damjanov: Consistent with AMML—nice write-up, sorry I have nothing meaningful to add.

Otto Dietze: My first impression from the H&E was M5 due to the distinct monocytoid appearance of tumor cells (and a similar case in our institute a few weeks ago).

Hugo Dominguez-Malagon: Cutaneous myeloid sarcoma, I agree with the diagnosis.

Göran Elmberger: Thanks for updating me. Great discussion.

Jonathan Epstein: Nice case. Thanks for the detailed summary.

Vincenzo Eusebi: I would have labeled the present case as cutaneous myeloid sarcoma and then shown it, for further refinements, to Stefano Pileri, who works next door to me.

Giovanni Falconieri: Challenging case, Dom. May be that the last case I saw was during my residency > 35 years ago. Yet that was much easier since widespread, not localized, in terminal AML seen at autopsy. Thank you for the thorough and enlightening discussion regarding IHC pitfalls.

Franco Fedeli: Cutaneous myeloid sarcoma ("aleukemic" myeloid leukemia cutis), consistent with acute myelomonocytic leukemia (AMML). Interesting case. The discussion is a valuable treatise on this topic.

Cyril Fisher: Leukemic infiltrate in skin, very informative discussion. Many thanks, Dom.

Christopher Fletcher: Very convincing example of myeloid sarcoma. I still often find it hard to recognize the blastic plasmacytoid dendritic cell neoplasms and am grateful that I have excellent colleagues in hematopathology.

Andrew Folpe: I couldn't imagine adding anything to this write up. Wow.

Jerónimo Forteza Vila: I agree with the diagnosis. With this hematolymphoid morphology it is always necessary to rule out the possibility of granulocytic or myeloid sarcoma.

Masaharu Fukunaga: Cutaneous myeloid sarcoma. It is a challenging case. Thank you very much for submitting this wonderful case and very informative comments.

Thomas Krausz: Agree with diagnosis. Thank you very much for the excellent and comprehensive discussion.

Janez Lamovec: Myeloid sarcoma; very erudite and educative discussion. Thank you.

Thomas Mentzel: Thanks for this wonderful case and the detailed discussion especially about the interesting topic of CD4+/CD56+ cutaneous haematological neoplasms.

Markku Miettinen: Agree that work-up supports blastic extramedullary myeloid tumor, although histologically could go as diffuse large (B-cell) lymphoma.

Liz Montgomery: Thanks for this instructive example of cutaneous myeloid sarcoma and for your excellent discussion (presumably the handout you used for the conference – feels like we got the

conference for free!); it seems that making the diagnosis of leukemia in the skin and soft tissues is often a matter of thinking of it and not going down a foolish diagnostic garden path.

Santiago Ramon y Cajal: Thank you Dominic, these kinds of cases are always fun in retrospect and scary prospectively. Very nicely put together, thanks!

Juan Rosai: Spectacular case of cutaneous myeloid sarcoma. This is such a characteristic lesion, but one which is often missed (at least by me) because one simply does not think of it.

Manuel Sobrinho Simões: We thought it was a haematological neoplasm but we completely missed the diagnosis (our first differential diagnosis would be in the lymphoma area).

Dominic Spagnolo: My case. She remained well for 6 months maintained on Etoposide. One month ago presented again, now unwell, rash and found to have circulating blast cells. Bone marrow trephine and aspirate showed transformation to AML. No further treatment is planned.

James Strauchen: Nice example of myeloid sarcoma in the skin!

Saul Suster: Nice example of myeloid sarcoma – thanks for the excellent discussion, Dom.

CASE NO. 21 – CONTRIBUTED BY EDUARDO ZAMBRANO:

Phil Allen: Cranial fasciitis of childhood, right maxilla, with post-operative recurrence. I don't think this is a desmoid tumor nor diffuse infantile fibromatosis (lipofibromatosis) nor myofibromatosis. As far as I am aware, there have been no large pathology series since Lauer and Enzinger's original description in Cancer 45: 401-406, 1980 and they only reported nine cases. Lauer mentions, but does not illustrate, the densely collagenized areas. Since leaving the AFIP 41 years ago, I think I have only seen one other case of cranial fasciitis and certainly none that have recurred. However, I have seen one or two examples of referred, genuine, nodular fasciitis (not myxofibrosarcomas, desmoids, cutaneous histiocytomas nor DFSP) that have recurred locally, excluding those that I saw at the AFIP, but I see about one nodular fasciitis every 2 months in consultation. I think the long-term prognosis of the current “tumor” should be excellent.

David Ben-Dor: I'm sorry if I'm dumbing this down, but is there a practical difference between the two proposed entities?- obviously both would have to be removed to the maximal extent and the patient carefully followed.

Gerald Berry: Would defer this one to the soft tissue experts in the group.

Michele Bisceglia: Low-grade myofibroblastic neoplasm. Agree, and would call this tumor as a low-grade myofibroblastic sarcoma with keloidal features of the maxillary bone. EM would be of great value in establishing myofibroblastic differentiation.

Ira Bleiweiss: If this were in breast, I would say myofibroblastoma.

Thomas Colby: Agree with that group of neoplasms: myofibroblastic, myofibroma, etc.; will wait to hear what the heavyweights say.

Kum Cooper: Morphologically it looked benign to me...akin to metaphyseal fibrous defect or non-ossifying fibroma. Clinically it is obviously more aggressive.

Ivan Damjanov: To me it looked like a dentigerous tumor and I thought that it was benign, but a recurrence may prove me wrong. I would be interested in a longer follow-up if available.

Otto Dietze: I cannot offer another diagnosis, esp. in this age group.

Hugo Dominguez-Malagon: Radiographically it looks like an extensively destructive lesion, and the rapid recurrence confirms the aggressiveness. It could be a fibroblastic osteosarcoma with myofibroblastic differentiation (there are hyaline trabeculae resembling osteoid and “trapped” bone spicules). Another possibility is a desmoplastic fibroma that can be very destructive.

Göran Elmberger: Eduardo, sorry no experience. Did you rule out myoepithelial differentiation?

Jonathan Epstein: Looks more fasciitis.

Vincenzo Eusebi: I would agree with myofibroblastic neoplasm. Keloid like fibrous bands are frequently associated to myofibroblastic proliferations.

Giovanni Falconieri: Difficult case, Eduardo. I am not too familiar with pediatric soft tissue lesions. I may say that there are features indicating a low-grade/UMP lesions.

Cyril Fisher: Infiltrative myofibroblastic lesion without obvious nuclear atypia but the principal concern is low grade myofibrosarcoma of which a subset occur in the jawbones in childhood.

Christopher Fletcher: This myofibroblastic lesion is certainly difficult to classify with certainty. Some areas almost resemble nodular fasciitis, but the hyaline collagen bundles would not fit so well in that regard – nor would the history of recurrence, although occasional incompletely excised examples do sometimes recur locally. The pattern of infiltration through bone is worrisome. It would not be surprising if this tumour recurred again.

Andrew Folpe: Your diagnosis seems as good as any.

Jerónimo Forteza Vila: Child fibromatosis of desmoids type seems the best option. It is a complicated case.

Masaharu Fukunaga: Thank you very much, Eduardo, an interest and difficult case. I agree with your diagnosis. It could be myofibromatosis.

Thomas Krausz: Diagnostically difficult case. I think in the background there is matrix/osteoid deposition so I would favor low-grade fibroblastic osteosarcoma.

Janez Lamovec: I would go along with your diagnosis of low-grade myofibroblastic sarcoma and wonder what experts will say.

Thomas Mentzel : Given the presence of numerous tissue fragments I`ve found it very difficult to make the diagnosis of low-grade myofibroblastic sarcoma in this young patient. Morphologically, the lesion shows some features of nodular fasciitis: however, the given history does not fit really.

Markku Miettinen: Benign myofibroblastic neoplasm with nodular fasciitis-like features, ? cranial fasciitis.

Liz Montgomery: The lesion is certainly myofibroblastic but has peculiar morphology- ?myofibroma?

Santiago Ramon y Cajal: Agree with your diagnosis. The differential diagnosis with myofibromatosis is challenging.

Juan Rosai: I would have included in the differential diagnosis a benign fibro-osseous lesion in the family of fibrous dysplasia.

Manuel Sobrinho Simões: Agree with your diagnosis because we were not able to go further (in a sort of local voting I got several tentative diagnoses varying from ossifying fibroma to congenital fibrosarcoma or even congenital well-differentiated osteosarcoma).

Dominic Spagnolo: I have made heavy weather of this lesion and don't recognize it as a "named" entity specific for this site. It is a destructive lesion behaving like a sarcoma. I considered a well differentiated low grade fibroblastic osteosarcoma, but in the end was not convinced of malignant osteoid. A low grade myofibroblastic sarcoma is where I ended up.

James Strauchen: Areas resemble nodular fasciitis or cranial fasciitis.

Saul Suster: Agree that it looks very low-grade and reactive, but the history of recurrence and destruction of bone would make me very worried about calling this benign. Low-grade myofibroblastic sarcoma seems like a more prudent approach. It's already recurred once!

QUIZ CASE #1 – CONTRIBUTED BY MANUEL SOBRINHO SIMOES:

Volkan Adsay: This being a quiz case, I guess I won't feel shy to propose some potentially off-mark zebra diagnoses: I thought this could be a metastatic carcinoma into a follicular variant of papillary carcinoma (tumor-to-tumor metastasis which endocrine neoplasia are known to have the ability to do, and we have seen examples of, in the thyroid). I think the lesion at the periphery is a thyroid follicular neoplasm, and some of the nuclear features seem to qualify as PTC. If it is really metastasis, consideration would include acinar or adnexal/salivary gland tumors among others. Another possibility that I would have investigated with immunohistochemistry would be to rule out a mixed follicular-medullary carcinoma, because the pattern/cytology of the tumor cells in the middle of the tumor made me wonder about medullary differentiation.

Phil Allen: Microfollicular adenoma, thyroid. I'm no thyroidologist but something has made me very conservative. I regard as benign all histologically bland follicular thyroid lesions that are not extensively invading vessels and surrounding tissues. If they metastasize, I am prepared to be proven wrong but I have not seen enough cases yet to fall into that error. As for fine needle aspiration, the error rate amongst the relatively inexperienced South Australian thyroid cytologists is so high that I could not support the test locally. In Hong Kong where there are many more papillary carcinomas, the thyroid aspiration cytology accuracy is much higher than it is here.

David Ben-Dor: I assume this is of thyroid follicular origin- a fetal adenoma?- sounds too simplistic to be true.

Michele Bisceglia: Encapsulated thyroid tumor in a 70-year-old male. ?? Mixed follicular neoplasm (follicular adenoma and [encapsulated] follicular variant of papillary carcinoma).

Thomas Colby: Looks like may be two cell populations, and I would need to study some special stains.

Kum Cooper: SETTLE? although it looks very epithelioid!

Otto Dietze: Paraganglioma?

Hugo Dominguez-Malagon: Parathyroid adenoma vs. follicular adenoma.

Göran Elmberger: Follicular variant of papillary thyroid carcinoma with predominant solid growth pattern? Combined papillary and medullary carcinoma need to be excluded with calcitonin stain.

Giovanni Falconieri: At first guess, I would choose follicular tumor, UMP, perhaps with incipient capsular invasion. Thank for this instructing and challenging case, and welcome to the club.

Franco Fedeli: Follicular adenoma of the thyroid versus mixed follicular tumor (follicular adenoma plus foci of a papillary carcinoma component?)

Jerónimo Forteza Vila: I think that it is a small cell tumor, with basaloid appearance and in which two other components appear clearly differentiated: the more peripheral one has characteristics of follicular adenoma, whereas the other seems to be a papillar carcinoma (follicular variant). It is a tumor with three appearances that I find hard to assign a name.

Masaharu Fukunaga: Welcome, Dr. Manuel Sobrinho Simoes. I favor follicular adenoma.

Janez Lamovec: ?Hypercellular follicular adenoma, ?FT-UMP

Markku Miettinen: Follicular adenoma with atypical features. Did not find vascular invasion.

Santiago Ramon y Cajal: A quite challenging case, with a myriad of patterns, oncocytic, nuclear changes,.. I can guess why the FNAB was not conclusive. I look forward to hear the wise comments of Manuel.

Juan Rosai: I am afraid I cannot comment on this case, being that it was sent to me by Manuel Sobrinho and that it will be published in a forthcoming issue of the International Journal of Surgical Pathology, with a very imaginative proposal regarding its nature.

MANUEL SOBRINHO SIMOES: See comments below.

Clinical History: Encapsulated, 3.2x3.0x0.6cm thyroid tumor in a 70-year-old male. No history of radiation exposure, nor family history of any type of thyroid pathology. A total thyroidectomy (38g) was performed after non-conclusive FNAB.

Macroscopic and Histologic Findings: Besides the 3.2cm, whitish encapsulated nodule in the upper pole of the right lobe, there was a brownish encapsulated 2.0 cm nodule in the left lobe.

Histologically, the nodule in the right lobe was an encapsulated tumor-in-tumor composed by three lesions morphologically different. The most peripheral lesion, which showed features of follicular adenoma (FA) with a microfollicular growth pattern, was present in nearly 90% of the nodule circumference and, occasionally, also between the intermediate and the main central lesion. There were no signs of capsular or vascular invasion. The intermediate lesion displayed the typical features of follicular variant of papillary thyroid carcinoma (FVPTC) and was present in approximately 50% of the nodule circumference. The third (central) lesion constituted the bulk of the nodule and presented a solid pattern of growth with scattered tubular structures filled with a PAS diastase resistant material. This central lesion was composed of monotonous epithelioid cells with oval nuclei and eosinophilic cytoplasm, and exhibited a prominent peripheral palisading. At variance with the other lesions, in which we did not detect any mitosis, the central lesion had 4 mitoses *per* 10/HPF. We did not observe in the central lesion any colloid-type material nor evidence of necrosis or vascular invasion. The nodule in the left lobe was a follicular adenoma. The remaining thyroid parenchyma was apparently normal.

ISH for thyroglobulin and calcitonin performed in the main lesion did not detect any positivity in the central component. The results of the immunostains are summarized in Table1.

Mutations of *BRAF* and *N-RAS* were searched in the FVPTC, in the central lesion and in the normal appearing thyroid parenchyma of the left lobe. PCR amplification of hot spot regions of these genes showed a Q61R *N-RAS* mutation in the exon 2 of both the FVPTC and the central lesion; no *N-RAS* mutations were detected in the normal appearing thyroid parenchyma. The study was not possible, for technical reasons, in the FA. No mutations were identified in the exon 15 hot spot of *BRAF* gene. *RET/PTC* translocations were searched in the central lesion but the results were inconclusive due to technical reasons.

TABLE 1. Immunohistochemical study of the three lesions.

	Differential expression		
Primary antibody	**FA**	**FVPTC**	**Central lesion**
Cytokeratins AE1AE3	F	+	F
Cytokeratin5	-	-	+
Cytokeratin7	+	+	+
Cytokeratin19	-	+	+
Cytokeratin20	-	-	-
TTF-1	+	+	-
Thyroglobulin	+	+	-
Calcitonin	-	-	-
Chromogranin A	-	-	-
Synaptophysin	-	-	-
p53	-	-	-
p63	-	F	+
CEA	-	-	+*
S100 protein	-	-	-
SMA	-	-	-
Vimentin	F	+	-
Galectin 3	-	F	F
CD5	-	-	-
Ki-67	<1%	<1%	5%

FA, follicular adenoma; FVPTC, follicular variant of papillary thyroid carcinoma;
* Expression in luminal surface of the cysts; +, diffuse positive; -, diffuse negative; F, focal positivity;
TTF-1, thyroid transcription factor 1; CEA, carcinoembryonic antigen; SMA, smooth muscle actin.

Final diagnosis:
Tumour-in-tumour-in-tumour
Follicular adenoma/adenomatous lesion
Follicular variant of papillary carcinoma
Tumor with basaloid differentiation and solid cell nest features

Discussion: Tumor-to-tumor metastasis, mainly to FA or to FVPTC, is a rare phenomenon that should be considered as a possibility in the presence of complex thyroid lesions showing bi- or triphasic morphological and immunohistochemical features. The occurrence of FVPTC apparently within a FA has been documented by several authors but the same does not hold true with the central lesion seen in our case. The possibility of this central lesion representing a metastasis in a preexisting thyroid tumor was made unlikely by the negative clinical and radiologic findings and by the follow-up, which did not reveal the existence of any neoplasia outside the thyroid gland. The alternative hypothesis of a poorly differentiated/ undifferentiated thyroid carcinoma was ruled out by the morphologic and immunohistochemical features.

Having ruled out the above listed hypotheses, we evaluated the possibility of the central lesion representing a tumor arising from ectopic intra-thyroid tissue such as salivary gland, parathyroid and thymus. Although there were basaloid cells with peripheral palisading suggesting a basal cell tumor of salivary gland type, the negativity for S100 protein, smooth muscle actin and vimentin, as well as the absence of any remnants of normal salivary gland tissue do not support this hypothesis. The histological appearance and the absence of chromogranin A do not fit an intra-thyroidal parathyroid adenoma. Finally, our tumor did not have features of any of the thymus-derived tumors described by Chan and Rosai.

A primary tumor-in-tumor with unusual features was finally considered, after having excluded the other possibilities. The morphologic features of the central lesion are similar to those observed in solid cell nest (SCN) main cells. The cells of both lesions are epithelioid/basaloid, with oval nuclei and eosinophilic cytoplasm, and displaying in both instances a solid pattern with cystic/tubular structures filled with a mucin-like PAS-diastase positive material. The immunohistochemical profile observed in the central lesion is also similar to that of SCN: positivity for AE1AE3, CK5, CK7, CK19, p63, CEA and galectin 3, and negativity for TTF-1, thyroglobulin, calcitonin and CK20.

The morphologic features of the lesion (monomorphic and highly proliferative) and the presence of a mutation of the *N-RAS* oncogene support our assumption that this lesion should be considered a neoplasm

rather than a hyperplasia. Its malignant potential remains to be established, as the patient follow up is too short.

It remains also to be clarified the putative relationship between the basaloid central lesion and the FVPTC, as well as between the latter and the FA. The fact that the basaloid component was surrounded by a FVPTC and shared with it a Q61R *N-RAS* mutation supports a histogenetic relation between these two lesions. An analogous finding was reported by Cameselle-Teijeiro *et al*, who reported a *BRAF* mutation in a case of SCN hyperplasia with a contiguous papillary microcarcinoma, the mutation being present in both components. (For a more detailed discussion of the case please see Eloy et al. Tumor-in-Tumor of the Thyroid With Basaloid Differentiation: A Lesion With a Solid Cell Nest Neoplastic Component? Int J Surg Pathol 19:276-80, 2011).

Dominic Spagnolo: Welcome to the club! I favor poorly differentiated carcinoma (not particularly "insular") developing from encapsulated follicular variant papillary carcinoma. I don't see definite vascular or capsular invasion. Without the papillary CA component I would also have considered a mixed medullary/follicular carcinoma.

James Strauchen: Mucoepidermoid carcinoma of the thyroid.