

COMMENTS TO AMR SEMINAR #46

CASE NO. 1 – CONTRIBUTED BY DR. DAVID BEN-DOR

Phil Allen: Clear cell oncocytosis of parotid, presumably bilateral. A most instructive case. I have not seen it before.

Gerald Berry: Agree. Great case. I have seen microscopic oncocytosis with and without clear change but this is the first case of florid oncocytosis causing bilateral enlargement that I have encountered. The FNA would be challenging!

David Ben-Dor: My case. A similar case of oncocytic hyperplasia with clear cell change was presented by Dr. William Westra in the weekly departmental slide seminar of Johns Hopkins University from the first week of September which is posted on the internet. The same issues that I brought up were discussed by him, though that case involved a completely resected gland and not a small biopsy as I was confronted with.

Michele Bisceglia: Parotid clear cell oncocytosis. Nice case and very nice discussion. Definitely a difficult diagnosis. Never seen a similar case; have only seen 1 case of oncocytoma, one case of oncocytic carcinoma, and one case of the usual eosinophilic type of nodular oncocytic hyperplasia. Thus I am particularly grateful to David for his case which seems to complete the spectrum of the oncocytic disease process. "Clear" cell oncocytosis/oncocytoma seems to be a paradoxical process, since by definition oncocytes are cells with eosinophilic and granular cytoplasm. According to Ellis GL (in the paper quoted by David) the clear cytoplasm seen by light microscopy is primarily due to artifact and accumulated intracytoplasmic glycogen and that by electron microscopy and histochemistry (PTAH) it is demonstrated that mitochondria are the preponderant cytoplasmic organelle. The clue to diagnosis is probably represented by the (even few) usual eosinophilic cells which may stay interspersed among the clear cells or by clear cells which while appearing mainly clear also have peripheral rims of eosinophilic cytoplasm. Immunohistochemistry to antimitochondrial antigen (mES-13) should play a crucial role for diagnosis.

Ira Bleiweiss: Agree. I definitely would have been suspicious for a metastasis of renal cell ca. The normal (scattered, on my slide) parotid acini and ducts argue against the metastatic diagnosis. I would have worked it up in the same way you did. Nice exemplary case.

Tom Colby: Agree with diagnosis; I probably would have gone down the renal cell route, but agree with the ultimate diagnosis. Based on this relatively small biopsy it would be difficult to exclude a portion of (bilateral) oncocytomas (causing enlargement) as opposed to diffuse involvement of the gland.

Kum Cooper: What an educational experience, David. And how did we ever manage in years gone by without immunohistochemistry! Was good to catch up with you in the Czech Republic.

Ivan Damjanov: To me this looks like a tumor and I would call it oncocytoma with clear cell changes. But, like you, I would make sure that there is no primary in the kidney.

Vincenzo Eusebi: : I agree on the oncocytic lesion, benign. The name to give to the condition depends on the extent of the lesion (s). Entrapment of residual glandular tissue, lobulated structure and lack of nuclear atypia, are all features consistent with oncocytic benign lesions.

Giovanni Falconieri: Quite unusual. Thanks for this contribution and the extensive discussion.

Cyril Fisher: Oncocytic/clear cell change, most unusual and distinctive appearance and interesting discussion, many thanks.

Christopher Fletcher: What an impressive case – since clear cell change is a recognized feature of oncocytomas at this site, then it seems perfectly reasonable to have a clear cell variant of oncocytosis but I have very little personal experience in this context. Many thanks.

Andrew Folpe: Interesting lesion. I had not seen clear cell change quite so extensive in the parotid before.

Jeronimo Forteza-Vila: I agree with your diagnosis. Thank you for this interesting case.

Allen Gown: David had shared this case with me earlier, as noted. Fascinating case!

Thomas Krausz: Highly educational case. I haven't seen clear cell diffuse oncocytosis before. Before reading the discussion, metastatic renal cell carcinoma certainly was my first consideration.

Thomas Mentzel: Many thanks for sharing this unusual clear cell lesion with scattered eosinophilic cells and for the detailed and very helpful discussion.

Markku Miettinen: The uniformity of the process and lack of any normal tissue would lead me to believe that this is a neoplasm, one composed of clear cells and oncocytes, of parotid ductal origin.

Elizabeth Montgomery: I would certainly have thought of renal cell carcinoma and am thus grateful to you for educating me about parotid clear cell oncocytosis. I am relieved that the immunohistochemistry can be helpful in separating the two; probably cheaper than scanning the kidney!

Joshua Sickel: Metastatic renal cell carcinoma until proven otherwise. This is an amazing case. One of the senior colleagues in our group remembered a case he encountered in the early 80's which was sent to a prominent ENT pathologist, who was certain the patient had a renal primary. Clinical work-up was negative and this peculiar diagnosis was subsequently invoked.

Dominic Spagnolo: Agree with clear cell oncocytosis - a very nice example thank you, and nice discussion. Have seen similar before.

James Strauchen: Spectacular example of clear cell oncocytosis!

Lawrence Weiss: Agree. Nice discussion. Nothing more needs to be said.

CASE NO. 2 — CONTRIBUTED BY: DR. GERALD BERRY

Phil Allen: . Histiocytoid cardiomyopathy, male aged 11 months. Yet another condition that I have not seen before. Thanks for the contribution.

David Ben-Dor: In a totally different context, from the point of view of location and morphology this reminds me of the myocytolytic changes described in subendocardial infarction seen in patients with multivessel disease. Is there any logic as to why the histiocytoid cells appear specifically in the subendocardial region?

Gerald Berry: My case. The patient continues to do well after transplantation.

Michele Bisceglia: Histiocytoid cardiomyopathy. Thank you, Gerry, for sharing this rare case with us. Just would like to say that the original hypothesis for this process as a disease of the specific myocardial conduction system was first indicated by an Italian group (Amini M, Bosman C, Marino B. Histiocytoid cardiomyopathy in infancy: a new hypothesis? Chest. 1980; 77(4):556-8).

John Chan: Another collector's item (histiocytoid cardiomyopathy) from Gerald Berry's collection of very uncommon cardiac lesions (which I rarely or never encounter)!

Tom Colby: A new entity for me.

Kum Cooper: Thanks Gerry for this lovely example which complements the desmin CMO. If the theory is that these are Purkinje cell in origin then calretinin may help in this regard (similar to the suggestion that cardiac myxomas may be derived from neural fibres based on this immunopositivity).

Ivan Damjanov: Agree. Never seen one, and will probably never see one in my life.

Vincenzo Eusebi: : Histiocytoid cardiomyopathy. Thank you; the first I see on a glass slide.

Giovanni Falconieri: Thanks for filling another gap of my ignorance.

Cyril Fisher: What a striking appearance, I have not seen this before.

Christopher Fletcher: Many thanks for sharing this rare case – by chance, my fellow and I have been reading recently about histiocytoid cardiomyopathy because we encountered a morphologically somewhat similar lesion in an adult – which actually turned out to be a cardiac myxoma with oncocytic change. I am delighted, now, to have seen a genuine example of this strange disease.

Andrew Folpe: Great example. I am fortunate that our pediatric pathologist, Bahig Shehata, has an interest in this and has educated me a bit on this. Thanks.

Jeronimo Forteza-Vila: I think cells are not histiocytoid in origin although their morphologic features are similar to them. I think that a good diagnosis could be "Purkinje cell hamartoma".

Allen Gown: I have never seen a case of this before; thanks, Gerald!

Thomas Krausz: Haven't seen this before. Some of the cells resemble the vacuolated cells of rhabdomyoma.

Thomas Mentzel: Unfortunately, I've got a very pale slide (?)

Markku Miettinen: Histologic impression would be rhabdomyoma, multifocal. Is it possible that "histiocytoid cardiomyopathy" is related to cardiac rhabdomyoma or is a form of it?

Joshua Sickel: Great case. Thanks for the wonderful discussion.

Dominic Spagnolo: Had not heard of histiocytoid cardiomyopathy before this before Gerry - thanks for the education. On the blind I was thinking some form of hamartoma. A quick look at the literature interestingly showed that oncocytosis may be present in other organs, and more recently, some mutations of mitochondrial cytochrome genes have been reported. What a fascinating lesion, whatever its nature.

James Strauchen: A new one for me! Thanks for this fascinating case!

Saul Suster: Wonderful case for our teaching collection! Had never seen this before. Congratulations on the excellent paper!

Paul Wakely: Thank you for all these beautiful and unusual cardiac cases you keep submitting to the club.

Lawrence Weiss: Wow, what a case!

CASE NO. 3 — CONTRIBUTED BY: DR. MICHELE BISCEGLIA

Phil Allen: Histologically benign cutaneous aneurysmal fibrous histiocytoma metastatic to a cervical lymph node, female aged 13. To my eye, this is absolutely indistinguishable from a benign aneurysmal cutaneous histiocytoma with hemosiderin areas. I seem to recall that the one metastasizing cutaneous histiocytoma that I saw in Australia some years ago dedifferentiated as it metastasized, but this metastasis is histologically benign. Congratulations on the scholarly workup, Michele.

David Ben-Dor: Another unusual case worked up in painstaking detail by Michele. Without an adequate history (which given that the patient has been treated in different facilities might be close to a miracle) this case would be nearly impossible to figure out. I hope for the sake of the patient that this process burns itself out.

Gerald Berry: A fascinating case. I have not seen this particular lesion previously but have always had it in the back of my mind when reviewing cutaneous fibrohistiocytic lesions.

Michele Bisceglia: Aneurysmal fibrous histiocytoma metastatic to a neck lymph node (primary on the scalp -cutaneous "benign fibrous histiocytoma, with cellular features"). I look forward to everybody's comments on this case. Have very few spared slides of the primary skin lesion (BFH with cellular features) as well as of the first local recurrence (almost an ordinary BFH) which will be sent on request to any skeptical members. Actually, very recently, since this case will be soon submitted for publication in AAP together with the case of Carlos Bacchi, and since my case is a bit convoluted as for the clinical history and the change in morphology from the primary to the metastasis in the parotid lymph node, I decided to send to Phil Allen the glass slides from the primary in the skin of the head and from the first recurrence. Allen handled my slides as he usually does with his consultation material. Here is Phil Allen's comments on my case after looking at the glass slides: *"Dear Michele, I have at last got around to the sections from this most unusual case. In my opinion, the 1993 section (96217-93) is a fragmented but histologically characteristic benign cutaneous histiocytoma which seems to be mainly intradermal but is extending down very close to the subcutaneous fat. The occasional multinucleate giant cells, the scattered pigment laden macrophages, the absence of any cellular atypia and the minimal mitotic activity all reinforce the impression of a histologically benign cutaneous histiocytoma. There is a small amount of necrosis in one of the fragments but I have seen a number of similar fragmented benign cutaneous histiocytomas with small foci of necrosis in consultation. As far as I can see, it is no different from the many other benign cases I have seen. There is nothing in the sections to suggest dermatofibrosarcoma protuberans, although I have not seen the CD34 or Factor 13A stain; the lesion does not have the features of a malignant fibrous histiocytoma or any other sarcoma and while occasional mitoses are apparent, there are no more than one usually sees in a benign cutaneous histiocytomas. The fragmented nature of the lesion suggests that it may not have been completely excised and I cannot see any aneurysmal components. The second accession, your number 3-86119, is less cellular but is an absolutely typical intradermal cutaneous histiocytoma (dermatofibroma) with no aneurysmal features. I would certainly never have expected this tumor to metastasize, although the recurrence rate of cutaneous histiocytomas excised in fragments is thought to be about 5%. I certainly have about 15 consultation cases of recurrent benign cutaneous histiocytomas in my files, all but one of which was referred because of a recurrence. One might argue that the aneurysmal component in the lymph node metastasis indicates that it could not have come from the previously excised primary or recurrent scalp tumours but there is no other primary site apparent and aneurysmal change is common in benign cutaneous histiocytomas. I believe the most likely explanation is that the 1993 lesion is the primary tumour. Metastases from a benign cutaneous histiocytoma must be extraordinarily rare, considering the extreme commonness of that skin tumour but I have one case in my consultation files that was referred because it had metastasized. I therefore accept your interpretation and believe this case must be published. .*

Ira Bleiweiss: Very strange. I've not seen anything like this (outside of the club, of course).

John Chan: Very unusual case of metastasizing aneurysmal fibrous histiocytoma. Focally (in areas without Touton giant cells), distinction from angiomatoid (malignant) fibrous histiocytoma can be very difficult, since a lymphoid rim (but not true lymph node as in this case) is also characteristic of the latter entity.

Tom Colby: Agree with diagnosis; we seem to have a theme of benign metastasizing lesions.

Kum Cooper: Michele, I enjoyed listening to you present this case "behind the computer" at the Czech Republic. Very much enjoyed the interaction with you!

Vincenzo Eusebi: Metastatic dermatofibroma. Thank you for the case and learned hand out.

Giovanni Falconieri: Great case, Michele. I still have vivid memories of your outstanding presentation at the Srni seminar of this intriguing case.

Cyril Fisher: If this is a lymph node, then metastasizing BFH with aneurysmal features, exceptional case. Thanks, Michele, for extensive commentary.

Christopher Fletcher: Indeed the appearances are very convincing for lymph node metastasis of aneurysmal fibrous histiocytoma – quite similar to several other cases which I have seen in the past. This phenomenon seems most often to be preceded by local recurrence. This topic was discussed extensively in the Comments to AMR Seminar #45.

Andrew Folpe: Very nice example of BFH with metastases. I have seen several of these, and there is nothing that would allow you to predict this behavior. Very complete write-up, as usual.

Jeronimo Forteza-Vila: I agree with this brilliant case.

Allen Gown: Thank you for that incredible write-up of this case. I hope I get to see another one of these in my lifetime!

Thomas Krausz: Thank you Michele for the most comprehensive discussion. It is ready for publication.

Thomas Mentzel: Thanks Michele discussing again this very rare case of metastasizing aneurysmal dermatofibroma arising in a young girl. Actually, we had the impression that dermatofibroma arising on the face is generally rare but associated with a more aggressive clinical course (Am J Dermatopathol 2001; 23: 419-426)

Markku Miettinen: Agree on lymph node metastasis of aneurysmal fibrous histiocytoma, very convincing example.

Elizabeth Montgomery: Thanks for showing us yet another example of "benign" metastasizing fibrous histiocytoma. As far as I can tell, these have yet to kill anyone, even with the addition of your new case.

Joshua Sickel: Another example of this strange phenomenon.

Dominic Spagnolo: The evidence is overwhelming for this being a metastasizing cutaneous fibrous histiocytoma - a typically excellent discussion Michele, thank you. I agree that the main differential would be angiomatoid fibrous histiocytoma - I agree with your points of distinction, but to be provocative, why could that entity also not metastasize to a node, and add to the list of "benign" metastasizing lesions?

James Strauchen: I also considered aneurysmal bone cyst and tendosynovial giant cell tumor.

Saul Suster: Very valuable case to have shared with the Club members. Michele presented this case at our recent International Arkadi M. Rywlin Anatomic Pathology Symposium in the Czech Republic and, as usual, did a wonderful and very convincing job in putting this case together.

Lawrence Weiss: Where do you get these cases? Very scholarly discussion

CASE NO. 4 – CONTRIBUTED BY: DR. BLEIWEISS

Phil Allen: Invasive adenosquamous carcinoma (low-grade metaplastic carcinoma), right breast. There is some squamous differentiation in my slide. Once again, I have not previously seen a similar case. Thanks for the contribution.

David Ben-Dor: This is certainly a fascinating and thought provoking slide. In the view of someone who sees far less than 1000 cases of breast cancer a year, the invasive elements are subtle and may be overlooked. I would hate to meet this lesion in a stereotactic needle biopsy. There is a lot of background inflammation- is this part of the lesion, due to previous needling, or just coincidental? In some places I might misinterpret the tumor elements as being reactive blood vessels. I can make out a focus of clear cut squamous differentiation involving a duct but I might have considered it reactive metaplasia (as in necrotizing sialometaplasia in the oral cavity) in light of the inflammation; are you sure its part of the tumor? Assuming that I was certain this was neoplastic I assume I would interpret it as tubular carcinoma (given my lack of familiarity with this entity). Given the p63 positivity, is there true glandular differentiation in this tumor or are the clefts in reality pseudolumina? I looked up this entity in Medline, and not surprisingly, found a recent contribution to the literature in (Czech) by Michal and his associate Alena Skalova (who gave a very informative update on

salivary gland cancer at the recent meeting in the Czech republic), and older articles by Rosen, who points out the homology between this tumor and sweat glands- actually here and there I can faintly visualize cuticles in some of the ducts. This case is food for thought or maybe anxiety (assuming I'm apathetic to the missile launchers pointed at us from our neighbors a few miles down the coast).

Gerald Berry: My first impression of this low-grade carcinoma was tubulolobular carcinoma, as I didn't see either squamoid differentiation or the "tadpole" arrangements.

Michele Bisceglia: Low-grade, invasive adenosquamous (metaplastic) carcinoma of the breast. Indeed a rare case. This tumor type would represent the starting-point for a debate in the terminology on breast tumor pathology: 1. since *metaplastic* is often synonymic with *sarcomatoid*, the example on theme demonstrates that metaplastic should be preferred to sarcomatoid -in fact this case is not sarcomatoid; 2. this case demonstrates that the terms *adenosquamous* and *mucepidermoid* cannot be intended as synonymic (as up to very recently some people did): in fact this case has nothing to share with the mucoepidermoid type; 3. last, we can say that there is a syringomatous variant of this tumor type (adenosquamous, low grade), i.e. the syringomatous variant (Suster S, Moran AC, Hurt MA. Cancer 1991; 67:2350-2355; Urso C. Pathologica 1996; 88:196-199), and that -in accordance with the myoepithelial derivation/involvement- this tumor may show adenomyoepitheliomatous features (Van Hoesen KH, Drudis T, Cranor ML, Erlandson RA, Rosen PP. AJSP 1993; 17:248-258; in this study, one tumor sized more than 3.5 cm gave rise to lymph node metastasis) or may arise in adenomyoepithelioma (Foschini MP, Pizzicannella G, Peterse JL, Eusebi V. Virchows Archiv 1995; 427:243-250).

John Chan: Agree with diagnosis, but I might have probably signed such cases out simply as infiltrative ductal carcinoma NOS.

Tom Colby: Agree with diagnosis; it's nice we don't have to struggle with these lesions on frozen section too much anymore.

Kum Cooper: Thank you Ira for this rare example of metaplastic carcinoma that I have not seen before.

Ivan Damjanov: Low-grade breast carcinoma, most likely as you said a low-grade metaplastic carcinoma.

Vincenzo Eusebi: Low-grade adenosquamous carcinoma (siryngoid carcinoma) of the breast. This type of tumor invades widely and is rarely completely excised in conservative treatments.

Giovanni Falconieri: Very difficult case Ira, in my slide I could not catch the clue until I found some metaplastic squamous nests with malignant cytology. Never seen something like that before, although I have never thought about it in my practice.

Cyril Fisher: Adenosquamous carcinoma, great slide.

Christopher Fletcher: I have never personally seen a low-grade adenosquamous carcinoma of breast such as this - thanks for the education!

Andrew Folpe: I had not seen a low-grade adenosquamous carcinoma of the breast before. Thanks for submitting this.

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

Allen Gown: The real question for me in these metaplastic carcinomas is whether they are manifesting squamous or myoepithelial differentiation. Virtually all the markers positive on these tumors do not distinguish between these possibilities.

Thomas Krausz: Agree with diagnosis. In places there is a "syringomatoid" growth pattern.

Thomas Mentzel: An interesting and rare form of low grade breast cancer, many thanks.

Markku Miettinen: Agree on sclerosing carcinoma, with focal squamous in situ component. Ca is probably of myoepithelial type, or one containing such elements.

Joshua Sickel: Nice example of a rare tumor. I've seen only a few cases in practice.

Dominic Spagnolo: A very nice case of low-grade adenosquamous/metaplastic carcinoma. In my slide it shows pronounced syringomatous features. We have recently encountered a similar case. Thank you.

James Strauchen: Nice case! P63 is also positive in other squamous carcinomas, so it may not necessarily imply myoepithelial derivation.

Saul Suster: This is indeed a very interesting case, of which I have seen several examples before. Given that Dr. Bleiweiss is a disciple of Dr. Peter Paul Rosen, I can certainly understand his preference for the terminology of "low-grade metaplastic carcinoma" for this lesion. However, I disagree with the blanket interpretation that these cases are carcinomas. Many years ago, Dr. Moran and I, together with a past member of this club, Dr. Mark Hurt, published a short series of identical cases that we designated as "syringomatous squamous tumors of the breast" (Suster S, Moran CA, Hurt MA. Cancer 67:2350-2355, 1991). The lesions we described were identical in every respect from the "low-grade metaplastic carcinoma" of Rosen. None of our cases have either recurred or metastasized after simple local excision. I have had the opportunity to see a few additional similar cases since the publication of that paper, and none of them have "come back to haunt me" either. An identical lesion was also described many years ago by Cyril Toker in the salivary glands,

and also interpreted as a phenomenon of benign syringomatous metaplasia (Syringomatous tumors of minor salivary gland origin. Hum Pathol 13:182-184, 1982). Although, undoubtedly, there must be a few such cases that do have recurrent or metastatic potential, the majority of such tumors behave no more aggressively than sclerosing adenosis or radial scars; indiscriminately designating them as "carcinomas" is therefore, in my opinion, wrong.

Lawrence Weiss: Beautiful case. In my experience also, this is an extremely rare neoplasm.

CASE NO. 5— CONTRIBUTED BY: DR. JOHN CHAN

Phil Allen: I'm not ashamed to claim that I have never seen this condition before. Adelaide is a clean living city and our pathologists are all above reproach. However, I must confess that my son is a young lawyer with no nose for trouble, but living in Hong Kong. Fortunately, he is presently in Milan doing a deal for John Chan's good friend and potential benefactor, Li Ka-Shing.

David Ben-Dor: I'm frustrated by the fact that many of the interesting cases which would merit discussion in this group come as small biopsies in which I assume that there isn't enough material to produce the required number of sections. This small biopsy proved me wrong. In places the epithelium looked transitional and without knowing the history or site I construed this as being from the urinary bladder showing nephrogenic adenoma. This case demonstrates how important a good history is and how difficult it is to get it. The conclusion is very apt.

Gerald Berry: I ran into the same problem recently on a case here. I did suggest serum ANCA studies nonetheless!

Michele Bisceglia: Cocaine-induced osteocartilaginous necrosis and mucosal ulceration/inflammation. Thank you for the case and the pathologic issue. Was not aware of this.

Ira Bleiweiss: Agree.

Tom Colby: Agree with diagnosis. There is a very nice reference from Italy that shows that the destructive lesions of cocaine abuse can actually be much worse than those associated with Wegener's: Medicine (Baltimore) 2001;80:391-404.

Kum Cooper: John, an amazing and instructional case! Thank you for raising my awareness to this entity.

Ivan Damjanov: Consistent with cocaine induced necrosis.

Vincenzo Eusebi: Nice case.

Giovanni Falconieri: The history is probably much more enlightening than the slide itself. The microscopic changes truly would suggest to choose amongst the "mid-line" entities.

Cyril Fisher: Septal necrosis due to cocaine, have never seen the histology of this before.

Christopher Fletcher: Great case – as you say, one always has to consider the wide range of weird things that patients do to themselves!

Andrew Folpe: Nice example of cocaine-induced nasal disease.

Jeronimo Forteza-Vila: I agree with your diagnosis.

Thomas Krausz: Highly educational case. Hopefully I will remember the cocaine-association in the next case of necrosis of "uncertain etiology".

Thomas Mentzel: An important differential diagnosis for rather unspecific necrotic and inflammatory changes in this location – we should think on this !

Markku Miettinen: Very difficult, could not get this without history. Certainly the cartilage could be misinterpreted as a potentially neoplastic element.

Elizabeth Montgomery: Very cool case. We see the footprint of cocaine abuse in the GI tract too. The usual story is ischemic colitis in someone young in whom we can find no explanation. We tell them we want to do an angiogram to see if they have vasculitis (polyarteritis nodosa) but that cocaine abuse can do the same thing. No one wants to have an angiogram so we finally get the history. (I thought all lawyers were cocaine abusers).

Joshua Sickel: Thanks for the great discussion.

Dominic Spagnolo: A very instructive case John - have not seen any cocaine-related pathology, and did not consider it in this case.

James Strauchen: Interesting! Our ENT people recently collected a series of these.. They found polarization for foreign material was sometimes a clue!

Saul Suster: Another fascinoma!

Lawrence Weiss: I saw the non-specific changes, and the possibility of cocaine never crossed my mind. Very instructive case.

CASE NO. 6 — CONTRIBUTED BY: DR. THOMAS COLBY

Phil Allen: Two separate, histologically benign, metastatic meningiomas, left lung near hilum and left upper lobe in a 49 year old female with a large, radiologically characteristic, asymptomatic, presumed intracranial meningioma. Yet another wonderful case with a superb discussion.

David Ben-Dor: It's interesting that the same issue of metastatic spread from an otherwise benign appearing lesion came up in the case presented by Michele in this seminar (I'm examining both in the same sitting). I wonder what the implications for the patient would be, especially since this and the other pulmonary lesion were discovered incidentally in a person in good health. I wonder if she would have been better off not getting that x-ray (just a day or two ago I saw an op-ed column in the New York Times questioning the utility screening using the cutting edge CT machines which can detect minute lung nodules).

Gerald Berry: Nice case for the teaching files. The discussion is very enlightening.

Michele Bisceglia: Metastatic (benign) meningioma. Just seen a couple of cases, but only in seminars. Thank you for the pathologic assessment of this issue. While on one hand I would like to add (benign) meningioma to the list of benign metastasizing tumors (see my contribution of case 3 to Seminar #46) I wonder if it is correct to grade ordinary meningiomas as grade I.

Ira Bleiweiss: Agree, beautiful case.

Kum Cooper: Metastatic meningioma to lung...another first for me Tom; thanks!. Was great being able to spend time and getting to know you in Czech Republic.

Ivan Damjanov: Nice example.

Vincenzo Eusebi: Meningioma. I totally agree with the discussion provided in the hand out. It is difficult to be sure about primary or metastatic meningioma in the lack of careful clinical information.

Giovanni Falconieri: Another common lesion in an uncommon place. How can we confidently draw a line between benign and malignant in a case like this?

Cyril Fisher: Meningioma, very nice case. Thanks for the additional picture.

Christopher Fletcher: A beautiful and very convincing example of metastatic ('benign') meningioma – we saw a very similar case just a few months ago. It is increasingly clear that, at least in some tumour types, metastasis must be more closely related to a specific genetic 'hit' which facilitates invasion/metastasis, rather than to any morphologic attribute which we can recognize.

Andrew Folpe: Wow. I'm happy to say that I did think of that, but really only because I expect AMR cases to be pretty far-out. I've seen a hemangioblastoma "metastasize" to the lung, but only after intracranial surgery.

Jeronimo Forteza-Vila: Psammoma body is the morphological clue for this diagnosis. Good case.

Allen Gown: It would have been interesting to see if molecular analysis would confirm the origin of the lung tumor(s) from the documented meningioma.

Thomas Krausz: Thank you for the excellent discussion.

Thomas Mentzel: Another example of a benign looking metastasizing neoplasm, many thanks.

Markku Miettinen: Meningioma with benign features, could not primarily think it as a metastasis but rather as "pulmonary meningioma". Very nice case. I remember having seen only one pulmonary meningioma before. This was a minute microscopic finding in the visceral pleura in a wedge resection specimen for low-grade marginal cell lymphoma.

Elizabeth Montgomery: Thanks so much for this metastatic meningioma. Once one thinks of it, it is suddenly obvious!

Joshua Sichel: Spectacular case!

Dominic Spagnolo: Agree with metastatic meningioma - nice case - thanks Tom.

James Strauchen: Nice example of metastatic meningioma! Classically postoperative and believed to be related to intraoperative manipulation of the tumor and tumor embolization.

Saul Suster: Yet another example of a "benign metastasizing" condition.

Lawrence Weiss: Yet another unbelievable case. At least I could recognize this one.

CASE NO. 7 — CONTRIBUTED BY: DR. GIOVANNI FALCONIERI

Phil Allen: Metastatic amelanotic malignant melanoma with osteoclast-like multinucleate giant cells, subcutis, anterior chest wall from nodular malignant melanoma, skin of back excised three years previously. I accept the suggested diagnosis because it does not look like any primary soft tissue tumor that I recognize, there is a history of malignant melanoma and osteoclast like giant cells have previously been described in metastatic malignant melanoma. I don't know what I would have said if I did not know about the history of melanoma.

David Ben-Dor: Melanoma is certainly logical from the cytologic point of view. I also found a few macrophages with brown pigment (always welcome in trying to substantiate the diagnosis of melanoma when immunohistochemistry isn't immediately available). I found a few cells with 4-5 nuclei but not the huge osteoclastic type with tens of nuclei. Is the keloidal collagen deposition seen in this case a feature of metastatic melanoma?- I don't recall seeing it (or paying attention to it) previously.

Gerald Berry: I have now learned about some of the different histologic variants of malignant melanoma from this case and Case 9! Thank you for sharing this case.

Michele Bisceglia: Recurrent melanoma associated with osteoclast-like multinucleated giant cell reaction. I was just making a list of tumors with osteoclast-like giant cell reaction, so melanoma is very welcome to be added to the rest of tumors (dermatofibroma, atypical fibroxanthoma, aggressive angiomyxoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, mesenchymoma,)

Ira Bleiweiss: I'm not convinced this is melanoma, although, of course melanoma can look like anything. It looks more histiocytic. did you compare it to the original melanoma? Was there any bone involvement?

John Chan: A difficult case of melanoma to diagnose without clinical history. Morphologically, the tumor cells lack the prominent nucleoli and focal cellular dehiscence commonly seen in melanoma.

Tom Colby: Agree with diagnosis.

Kum Cooper: Have seen this occasionally in melanoma, Falco. I would not do anymore. Great to see you in Czech Republic (and your son).

Ivan Damjanov: Without the history would anybody make the diagnosis on H&E slides?

Vincenzo Eusebi: Very nice case. Never seen osteoclast-like cells within melanoma.

Giovanni Falconieri: My case. The more I look at it, the more confused I get ...

Cyril Fisher: Melanoma with unusual osteoclast-like giant cells. They can be seen in clear cell sarcoma (though more wreath-like) but here there is a clear history of cutaneous melanoma (and HMB45 is negative).

Christopher Fletcher: In the context of the history provided, then indeed the appearances would seem to fit well with metastatic melanoma. In my personal experience, one may occasionally see an osteoclastic giant cell reaction in association with virtually any tumour type, although I have not taken particular note of this in melanomas so cannot provide any clear perspective in that regard. Whether this represents an idiosyncratic host response or whether, instead, it results from secretion of chemokines by the tumours in which these osteoclasts are seen is unclear, although the latter seems more probable.

Andrew Folpe: Melanoma with osteoclastic giant cells. I've seen this a few times. Serves to nicely reinforce Chris Fletcher's point about always seeking another diagnosis before diagnosing "malignant giant cell tumor".

Jeronimo Forteza-Vila: Thank you for this interesting case. Is there antecedent of previous radiotherapy?.

Allen Gown: Without the history of melanoma (or perhaps even with it), I think it's impossible to be certain about the diagnosis of melanoma, given the histology and the relatively nonspecific significance of S100 expression of and by itself.

Thomas Krausz: I do remember seeing osteoclast-type giant cells in rare cases of metastatic melanoma. However, before reading the history and the discussion I was considering a malignant variety of giant cell tumor of tendon sheath.

Thomas Mentzel: The osteoclast-like giant cells are mainly located around erythrocytes and represent a reactive phenomenon in my opinion.

Markku Miettinen: Considering the history and the nesting (and S100 +) this is very consistent with metastatic melanoma. Osteoclastic giant cells are unusual in my experience in peripheral melanomas, but they are a common feature in the intestinal clear cell sarcoma-like tumor (described by Zambrano et al. Int J Surg Pathol 2003;11:75-81); these tumors we see 1 case for every 300 GISTs.

Elizabeth Montgomery: Thanks for showing us another of the many faces of melanoma.

Joshua Sichel: I've never seen osteoclasts in a melanoma. Without the history, I favored a solid variant of epithelioid hemangioendothelioma.

Dominic Spagnolo: I found this difficult Giovanni, and while I guess it has to be melanoma, I find the pattern of growth and cytology unusual. I don't recall seeing osteoclastic type giant cells in melanoma before. The lack of other supporting immuno evidence for melanoma in this case is also disturbing. This is the sort of case I would examine ultrastructurally. One consideration that came to mind was atypical/malignant ossifying fibromyxoid tumor. CD57? GFAP?

James Strauchen: Interesting! Any relation to case 9? Without the history I might have considered other giant cell lesions, e.g. malignant giant cell tumor.

Saul Suster: Metastatic melanoma is the best interpretation, in my opinion. Osteoclast-type giant cells can be seen focally in a large number of tumors adjacent to areas of hemorrhage.

Lawrence Weiss: Looks like melanoma to me. I think that osteoclast-like multinucleated cells are underrated elements in a lot of different types of neoplasms, including lymphomas.

CASE NO. 8 — CONTRIBUTED BY: DR. ANDREW FOLPE

Phil Allen: Intranodal palisaded myofibroblastoma with calcified amianthoid fibres, (Susteroma), (left) inguinal lymph node. What a spectacular example! Thanks for the contribution.

David Ben-Dor: An inguinal lymph node with a spindle cell proliferation containing a lot of brown pigment in a patient who just by coincidence has a documented history of melanoma (in the calf of all places): lucky we have immunohistochemistry to figure these things out! I wonder if I could be so certain in this circumstance that the pigment wasn't melanin without performing a simple iron stain. I was familiar with this paper before I ever made contact with Saul, and it's nice to see an example of it with the proverbial amianthoid fibers. It's comforting that these rare entities actually do occur from time to time (and don't exist only in the literature).

Gerald Berry: I remember seeing a few cases that were sent to Dr. Dorfman after the publication of the initial reports in 1989. Beautiful example of intranodal palisaded myofibroblastoma.

Michele Bisceglia: Intranodal palisaded myofibroblastoma. Genuine case. Have seen 2 cases (the first from the groin and the other from the axilla). The first one occurred around the year when it was first described, which I called "intranodal schwannoma". Concerning this tumor type, I can't refrain from asking everyone in the club if they have any explanation for the fact that any time one mentions the authors who first described this entity they always forget to include also Lee et al. Lee et al described perfectly this tumor (abstract enclosed). Once I was told that possibly the most commonly referenced two groups (Suster and Rosai, and Weiss et al) described the tumor months in advance in comparison with Lee et al. But this is not the correct explanation: it was May 1989, also for Lee et al as it was for Suster et al and Weiss et al. Here is the Abstract (from the paper of Lee et al): Lee JY, Abell E, Shevechik GJ. [Solitary spindle cell tumor with myoid differentiation of the lymph node](#). Arch Pathol Lab Med. 1989 May;113(5):547-50. <<<< *Spindle cell tumors arising in the lymph nodes are very rare. We report the light microscopic, histochemical, immunohistochemical, and ultrastructural findings of an unusual solitary spindle cell tumor in a peripheral lymph node of a 45-year-old woman. Microscopically, the tumor was characterized by interlacing fascicles of uniform spindle cells with nuclear palisading and formation of Verocay bodies. Numerous erythrocytes were found interstitially. There were no mitotic figures or significant nuclear atypia. The ultrastructural findings of abundant myofilaments with dense bodies indicated myoid differentiation. The clinical and pathologic findings favored this being a benign tumor and could represent a unique example of "intranodal myofibroblastoma." The differential diagnosis includes neurilemoma, leiomyoma, and, more importantly, leiomyosarcoma, Kaposi's sarcoma, and other metastatic spindle cell tumors.*>>>>

Ira Bleiweiss: Agree. Never seen one.

John Chan: Beautiful collector's item (intranodal palisaded myofibroblastoma).

Tom Colby: Agree with diagnosis; this is an "O'Henry case": seems straightforward grossly but has a twist at the microscopic end.

Kum Cooper: Thanks Andy. Chris also described this tumor in the neck lymph nodes (I recall!).

Ivan Damjanov: Very nice example.

Vincenzo Eusebi: Intranodal palisaded myofibroblastoma.

Giovanni Falconieri: Wonderful example. I believe that we may start to call it Suster-Rosai disease, honoring the entity descriptors. Interestingly, a case has come recently to my attention where comparable features, including the amianthoid fibers, were present in a lung nodular lesion. I am trying to retrieve pertinent clinical information and spared tissue for a future AMR submission.

Cyril Fisher: A very pretty example of intranodal (palisaded) myofibroblastoma. I think these lesions are more commonly seen than their incidence in the literature suggests. Interestingly, although the lesional cells are usually desmin (and CD34) -negative/SMA-positive, their ultrastructure is more suggestive of smooth muscle than myofibroblastic differentiation.

Christopher Fletcher: Indeed a perfect example of palisaded myofibroblastoma of lymph node.

Andrew Folpe: My case. Not especially difficult, but a nice example, I thought.

Jeronimo Forteza-Vila: Thank you for this beautiful case.

Allen Gown: Nice example, Andrew

Thomas Krausz: Beautiful example.

Thomas Mentzel: A very nice example of an obvious rare entity.

Markku Miettinen: Really nice case of palisaded myofibroblastoma/inteanodal hemoprhrhagic spindle cell tumor described by Saul Suster and Sharon Weiss independently.

Elizabeth Montgomery: At first glance this indeed looks like a schwannoma but then one notes the node and the amianthoid fibers. The immunohistochemical stain results clinch your impression of intranodal myofibroblastoma. Thanks for sharing this case.

Joshua Sickel: Beautiful example of a Suster tumor.

Dominic Spagnolo: Beautiful example of intranodal palisaded myofibroblastoma - thanks.

James Strauchen: A classic! These may be misdiagnosed as Schwannoma if one doesn't realize one is dealing with a lymph node. The prediction for inguinal nodes is unexplained.

Saul Suster: Very typical example of this rare tumor. Dr. Bisceglia's point regarding proper credit for its description is well taken. Dr. Lee indeed should also be credited for the observation, which was published at the same time as the other two papers. Dr. Michal Michal has also published a few cases of his own of this entity with some very detailed ultrastructural observations, and so has Dr. Brian Eyden with conflicting results. It appears that the issue as to the exact nature of the lesion is still not settled. This gets into the sticky point of terminology. The term of "intranodal myofibroblastoma" as proposed by Sharon Weiss is the one that has gained popular favor, despite the ongoing controversy regarding the myofibroblastic origin. The temptation for creating an eponymic designation is also, of course, great, and indeed, has already been tried (see: Gal R, Siegal B, Siegal A: Intanodal "amianthoid" myofibroblastoma - Weiss-Suster's tumor. Cell Vision 2:129-131, 1995). Someone here proposed "Suster-Rosai disease" or "Susteroma". I would like to point out that at the time this paper was published, I was merely a fellow with Dr. Rosai and, thus, the unwitting recipient of the good fortune of being assigned this project by him. The merit for the original observation and the publication should go entirely to Dr. Rosai, to Dr. Sharon Weiss, and to Dr. Lee (in other words, keep me out of it; the idea of having my name associated with a disease gives me the creeps). I personally also favor the term of palisaded myofibroblastoma, although the lesion is neither palisaded, nor has the myofibroblastic origin been conclusively proven. But if an eponym were to be applied, it should be the "Rosai-Weiss-Lee tumor".

Lawrence Weiss: This lesion is as classic as you can get!

CASE NO. 9 — CONTRIBUTED BY: DR. MASAHARA FUKUNAGA

Phil Allen: Recurrent acral lentiginous osteogenic melanoma with no melanocytic differentiation, dermis and subcutis with skin ulceration, sole of left foot at base of the second toe. I have never seen one of these before either. In Australia, we see large numbers of cutaneous malignant melanomas on the trunk, limbs and face but very few acral lentiginous or subungual melanomas. Thanks for the erudite discussion.

David Ben-Dor: This is an amazing case. This looks so much like a mixed tumor to me and in places it looks bland enough that I wouldn't even be certain that it was malignant. The osteogenic activity is very focal and I don't see why it couldn't be part of a mixed tumor. Here again the history is crucial (lucky you got it!) along with immunohistochemical confirmation. But without the history I wonder how many pathologists would think of working this up for melanoma; after all the S100 positivity would be used to support the diagnosis of myoepithelial tumor. I agree that the tumor cells themselves are responsible for the chondroid and osteoid material as they are intimately associated with it. This case was presented at Srni along with an interesting case of Kum Cooper's of a soft tissue myoepithelioma presenting as a vertebral lesion highly suspicious for metastatic carcinoma, so this pattern can present itself in manifold and devious ways.

Gerald Berry: Another nice example of malignant melanoma that I was not familiar with before this submission.

Michele Bisceglia: Osteogenic melanoma. First one for me. Very interesting case.

Ira Bleiweiss: Wow! Certainly looks like a chondrosarcoma.

John Chan: Very unusual and difficult case of osteocartilaginous melanoma. Most areas look like a grade 3 chondrosarcoma. Focally, there are some packets comprising cells with cellular dehiscence, compatible with conventional melanoma.

Tom Colby: Agree with diagnosis; I probably would have gotten into trouble with this case if I had not known the history or done an HMB-45.

Kum Cooper: Thank you Masa. This case made a great presentation at the AMR Meeting in the Czech Republic. Was wonderful meeting you and the family again.

Ivan Damjanov: Incredible.

Vincenzo Eusebi: Very interesting case. Without the clinical story and taking into account immunohistochemistry, I would have called the lesion a matrix producing metaplastic carcinoma of sweat glands. I have the feeling that this tumor, that has appeared 16 years after the putative primary, is unrelated to the melanoma.

Giovanni Falconieri: Extraordinary case. I guess this is the second such case I come across. This case displays a prominent chondroid appearance.

Cyril Fisher: Wow, another amazing variant of melanoma. The HMB45 positivity becomes critical here.

Christopher Fletcher: The appearances in this specimen would fit best with a malignant myoepithelial neoplasm (mixed tumour), particularly in the context of the immunohistochemical results obtained – however, since the primary lesion at this site apparently shows typical features of melanoma, then indeed I suppose that this must represent a very unusual recurrence of the latter. Can we be certain that this does not represent a new (second) primary lesion, given the 14-year interval between excisions? I agree that HMB45 positivity would be unusual in a myoepithelial lesion – but EMA positivity in melanoma would seem equally infrequent.

Andrew Folpe: Another of the many faces of melanoma. Thanks for sharing such a rare case.

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

Allen Gown: Melanomas seem to have a unique and remarkable capacity for unusual 'transdifferentiation', as illustrated by this case.

Thomas Krausz: Amazing what melanoma can do.

Thomas Mentzel: A great case of a rare variant of malignant melanoma, many thanks for sharing.

Markku Miettinen: Malignant cutaneous mixed tumor/metaplastic carcinoma with osteosarcomatous elements would have been my first choice. These tumors could have S100, GFAP and EMA. However, HMB45 is puzzling and must raise the possibility of melanoma, although morphologically difficult to accept as such. Perhaps it is an unusual multidirectional carcinosarcomatous tumor with melanocytic differentiation.

Elizabeth Montgomery: What a fantastic case. Without the melanoma history, this seems really tough. I thought it was a myxoid chondrosarcoma at first but of course it was too atypical so then considered an extraskeletal osteosarcoma but was baffled that it was so superficial. The IHC certainly helped. Thanks for this great case and for your excellent summary of the literature.

Joshua Sichel: I agree, this resembles chondroblastic osteosarcoma. Melanoma would have never crossed my mind! Thanks for this extraordinary case and comprehensive discussion.

Dominic Spagnolo: Wow! Have never seen melanoma with osteocartilagenous metaplasia. Thanks Masa.

James Strauchen: Amazing! I have never seen or heard of this! Thank you.

Saul Suster: Have seen only a couple of cases of this condition before in consultation. Given the extensive chondroid differentiation and the cord-like and, in areas, pseudo-glandular arrangement of the tumor cells my first thought would have been for a soft tissue malignant mixed tumor as described by Chris Fletcher and his group. However, the HMB45 positivity coupled with the history certainly support the diagnosis of melanoma. Would have certainly not even thought of melanoma without the history!

Lawrence Weiss: I didn't even include melanoma in my differential diagnosis.

CASE NO. 10 — CONTRIBUTED BY: DR. ALLEN GOWN

Phil Allen: Malignant tumor, probably de novo desmoplastic malignant melanoma, dermis, right temple. I have always maintained that "all" superficial malignant (epithelioid) schwannomas are desmoplastic melanomas (Am J. Surg Pathol 13:358-373, 1989), particularly when they arise in sun damaged skin of the head and neck of fair skinned individuals.

David Ben-Dor: On histologic grounds I would think of a myoepithelial tumor. Assuming this were to be resected maybe a connection with a nerve could be identified?

Gerald Berry: I am not aware of any way to sort out these 2 lesions except in the setting of the patient with known neurofibromatosis. Our dermatopathologists usually favor melanoma and soft tissue folks favor MPNST!

Michele Bisceglia: Spindle cell melanoma versus epithelioid MPNST. From the clinico-pathologic notes I would favor malignant melanoma (mainly spindle): old age, sun-exposed area (temple), focal erosion, are all in favor of melanoma. Sometimes in spindle cell melanomas you cannot find overlying junctional activity or alternatively it may be so small that it can escape recognition, or even having been lost in the skin erosion. However I do not know either how to discriminate between the two. Not even EM would result in any help. Spindle cell melanoma lack melanosomes (you can detect lysosome-like granules only) and poorly differentiated MPNST <<are composed of undifferentiated spindle cells devoid of any ultrastructural markers of either Schwannoma perineurial cells. [.....] Diagnosis of these tumors is based on gross evidence of origin from a major nerve trunk and exclusion of another type of sarcoma, e.g., leiomyosarcoma, fibrosarcoma, SNVS, ... >>>> (from Erlandson's Textbook of EM of tumors).

However, this is not your problem only. I am taking the liberty (with Saul's consent) for enclosing so much from the literature on this subject, which would be useful for several of us.

Thus here I enclose 3 papers which extensively dealt with this problem, and they quote practically all the available literature on this issue. Enjoy them!

1) Diaz-Cascajo C, Hoos A. Histopathologic Features of Malignant Peripheral Nerve Sheath Tumor Are Not Restricted to Metastatic Malignant Melanoma and Can Be Found in Primary Malignant Melanoma Also [Letter]. AJSP, Volume 24(10), October 2000, pp 1438-1439: *"We read the interesting article by King et al. in a recent issue of the American Journal of Surgical Pathology concerning metastatic malignant melanoma with histopathologic features of malignant peripheral nerve sheath tumor (MPNST) (3). Microscopically, the tumors were described as a proliferation of atypical spindle cells arranged in fascicles that showed a peritheliomatous growth pattern, alternance of hypercellular and hypocellular areas, numerous mitoses, and foci of necrosis. A primary malignant melanoma was found in six of 16 cases. In four of the six cases, the primary tumor showed the conventional microscopic appearance of malignant melanoma. In the other two cases, the primary lesion displayed features of blue nevus and clear cell sarcoma, respectively. The absence of primary malignant melanoma with features of MPNST in the reported cases may lead readers to conclude that these unusual findings are present in metastases of malignant melanoma only. In the past years, a few cases of primary malignant melanoma with histopathologic features of MPNST have been reported (1,6-8). Neuroid differentiation has also been observed in some examples of desmoplastic malignant melanoma (2,5). In some cases, Schwannian characteristics were found only in the primary tumor and not in the metastasis. We have had the opportunity to study two cases of primary malignant melanoma reminiscent of MPNST. In both cases, immunohistochemical studies were necessary to establish the diagnosis. In one case, a 68-year-old man presented with a bleeding nodule located on his back. The lesion had been growing for at least 3 years. The clinical diagnosis was basal cell carcinoma. A biopsy followed by complete excision with free surgical margins was performed. The diagnosis of malignant melanoma, Clark level V, 1.9 cm in thickness according to Breslow was established. At this time, pulmonary and axillary lymph node metastases were detected. A biopsy from an axillary lymph node was performed. It showed neoplastic melanocytes arranged in nests alternating with fascicles of spindle-shaped melanocytes similar to those observed in the primary tumor. The patient died 15 months later of pneumonia. No autopsy was performed. In the second case, an 86-year-old woman presented for consultation because of an exophytic tumor that had been growing asymptotically for an undetermined amount of time. The tumor was excised completely under the clinical diagnosis basal cell carcinoma versus malignant melanoma. The diagnosis of spindle cell malignant melanoma, Clark level V, 1.5 cm thickness according to Breslow was established. Work-up for metastases was negative. Nine months later, a well-circumscribed nodule was removed from the scar of the previous excision and showed similar histopathologic findings. Because of the sharply demarcated borders, the lesion was interpreted as a cutaneous metastasis. Vascular spaces around the tumor were dilated and contained aggregates of neoplastic cells. Histopathologically, in both cases, the tumors were localized in the dermis and extended irregularly into the subcutaneous tissue, an uncommon finding in MPNST, which is mostly located deeply. Neoplastic cells were arranged in large fascicles as observed in MPNST, fibrosarcoma, and so on (Fig. 1A). They showed a peculiar orientation around blood vessels giving the impression that neoplastic cells herniate into the lumina. In some cases, neoplastic cells showed nuclear palisading suggesting neural differentiation (Fig. 1B). In both tumors, but not in the cutaneous metastasis of case no. 2, densely cellular areas alternated with less cellular ones. The cells showed spindle-shaped nuclei with pointed ends and, rarely, a wavy configuration. In both cases, despite focal ulceration, melanoma in situ was present, but otherwise no conventional areas of malignant melanoma were detected. [Fig. 1. (A) Case no. 1: large fascicles of spindle cells reminiscent of malignant peripheral nerve sheath tumor in malignant melanoma. (B) Case no. 1: nuclear palisading suggesting*

HMB45, on the other hand, which is a monoclonal antibody to group 100 proteins, has more specificity but less sensitivity. Whereas the majority of conventional melanomas exhibit strong staining with HMB45, in a study of 28 cases of DM done by Kay, et al., only 7% were HMB45+ and other studies reveal predominantly HMB45-negative DM tumors.

Melan-A, a melanocytic differentiation antigen, shows a similar staining pattern to S100 for melanocytes, only more specific than S100. Melan-A gives strong and diffuse staining of all the benign melanocytic lesions and most melanomas with less sensitivity for metastatic, spindle cell and desmoplastic melanomas.

Tyrosinase, an enzyme essential in early stages of melanin biosynthesis, is extremely sensitive to most melanomas, with little or no reactivity in DM. In the study by Kay, et al., out of 28 cases of DM, only 4 cases stained positive. A study of two cases of DM by Clarkson (2001) revealed positive staining of all cells with S100 and no staining with tyrosinase, Melan-A or HMB45, however, as you can see, the study was limited to only two cases of DM.

In a paper by Xu, et al., MAGE-1, a member of the melanoma antigen encoding gene family, was found to exhibit protein expression in malignant melanomas. Unfortunately, other non-melanocytic malignant tumors can also express MAGE, as well. For this reason, it has been recommended that a panel of these immunostains be used to determine the source and extent of tumor in these types of lesions.

Skelton, et al., from the AFIP reported on 128 patients in a large study group, 59% of whom had DM in the head/neck region. Typically, it had been noted that desmoplastic melanoma demonstrated a better prognosis than other melanomas. The exception to this observation would be those DMs located in the head/neck. While they reported a 61% 5 year survival rate for DMs invading to a depth of >4mm, these same tumors when located in the head/neck worsened the 5-year survival rate to 38%. It has been postulated that the reason for this is that the thin layer of the dermis in this area allows faster access to the bloodstream and lymphatics, as well as the fact that cosmetically, this region may not allow for the clinician to achieve such wide surgical margins as necessary. They identified other poor prognostic factors, to include positivity for tyrosinase, melan-A and SMA staining, as well as tumor size and tumor thickness.

Most DM tumors have been found to be Clark level IV or V, leading Kay, et al., to state that a Breslow measurement of tumor thickness would have more clinical importance than Clark level in this instance.

In a study by Busam and colleagues, 92 patients with either "pure" or "combined" DM from a single institution were studied between 1980 and 2002. Their purpose was to identify clinical and pathologic parameters that could be used as significant variables for disease-free survival. They found that it was important clinically to distinguish "pure DMs", where desmoplasia was prominent throughout the entire tumor (constituting > 90% of the invasive melanoma) from "combined DMs", in which desmoplasia is only a partial, usually minor component (densely cellular tumor foci without stromal fibrosis constituted > 10% of the entire tumor). They found through Kaplan-Meier curves and hazard ratios for prognostic parameters that pure forms were associated with longer disease-specific survival. Histologically, in the "combined" DMs, the non-desmoplastic dense cellular aggregates had more atypical nuclei, higher mitotic index and overall higher cellular density compared with "pure" DM. Also, more "combined" tumors than pure DMs were associated with ulceration, (24% vs. 16%.) Of four clinical and histologic parameters identified by statistical analysis: Clark level (P=0.005), subtype of DM (P=0.01), tumor mitotic rate (P=0.01), and tumor thickness (P=0.02), the effect of subtype had the strongest influence on survival in patients with deeply infiltrating (Clarks V) melanomas. Patients with a combined DM had a 3.5 times greater risk of an event such as death of disease or metastatic disease than those with pure DM. Regarding the controversy over the prognosis of DM, in Conley's studies, 5 of 7 patients had local recurrences, 3 had lymph node mets and 4 died of disease. This led the authors to conclude that DMs may be associated with a worse clinical outcome than conventional melanomas. In 1988, Egbert, et al, had 12 of 23 patients with DM have local recurrences and 3 of those die of disease, leading him to share Conley's conclusion. There was, however, never an adjustment for tumor thickness in these studies. Also in 1988, Walsh et al, after adjusting for tumor thickness, suggested that DM might be associated with a more favorable outcome. They reported the high incidence of local recurrences, but also noted longer survival in patients with DM compared to patients with conventional melanomas of similar thickness. However since Walsh's 1988 study, the waters have again been muddied, with a large study of 280 patients from the Sydney Melanoma Unit. Here, they did not detect a difference in survival rates between patients with DM vs. conventional melanoma. This might be, in part due to the fact that the patients studied in the SMU series had melanomas < 4mm in thickness, whereas in the Walsh studies, patients had tumor thicknesses of > 4mm. Busam postulates that the favorable prognostic impact may only be significant in those patients with thicker and more deeply infiltrating tumors, (i.e., Clarks level IV-V, and > 4mm in thickness).

In a second study by Busam, he emphasizes the importance of distinguishing DM from conventional melanomas. Underlying this is the fact that the clinical presentation of the two entities is so very different. Unlike conventional melanoma, most DMs are rarely diagnosed at early stage, and are >4mm at time of diagnosis. The majority of DMs are Clarks level IV or V at the time of diagnosis and 18-20% are ulcerated. A subset of DMs are neurotropic and exhibit prominent infiltration of peripheral nerves, with some evidence that these tumors are more aggressive than those without neurotropism, leading to DNM as a variant of DM, but data is conflicting. He goes on to point out that the histologic differential diagnosis of DM vs. other sclerosing lesions can be daunting at times. He recommends a panel of immunohistochemical stains including S100, 34BE12, SMA, desmin, gp100, Melan-A, tyrosinase, microphthalmia transcription factor and factor XIIIa to distinguish DM from entities such as sclerosing nevi, dermatofibroma, neurofibroma, fibrosarcoma, desmoplastic leiomyosarcoma, sclerosing sarcomatoid squamous cell carcinoma and MPNST. Importantly, evidence indicates that lymph node mets are much lower at presentation in patients with DM than in patients with conventional melanoma. DMs need to be completely excised, and due to the high incidence of nerve involvement, a wide excision is recommended, if aesthetically possible. As sentinel lymph node involvement is much less common in DM than conventional melanomas, the low yield of positive results would thus imply limited, if any prognostic value as far as risk stratification for patients with DM. For that reason, there is no potential benefit for this procedure, according to Busam, and it is no longer recommended in patients with pure DM. As for radiation therapy, while conventional melanomas have been shown to be radiation-resistant, there was a study at the University of California showing that post-op adjuvant radiation decreased the incidence of local recurrences, and was therefore recommended by the authors. The need for wide and deep margins, the response to adjuvant radiation, as well as the low frequency of mets to sentinel lymph nodes at presentation of DM, underscore the importance in distinction between DM and conventional melanoma as separate subtypes, each requiring different management.

In a paper by Jukic and Spencer, discussing a 71 year-old man with clear cell sarcoma of tendons and aponeuroses (CCS), they underline the importance of differentiating this entity from malignant melanoma (MM), Pecoma, follicular dendritic and interdigitating cell tumors (IDCT/FDCT), and malignant peripheral nerve sheath tumors (MPNST). They go on to elaborate on how the distinction can be made between first CCS, MM and MPNST, all of which are derived from neural crest, and all of which show S100 positivity. First and

perhaps most important, CCS has been shown recently to have a characteristic translocation, $t(12;22)(q13;q13)$, resulting in a fusion gene, *EWS/ATF12*, and is apparently pathognomonic for these tumors. Additionally, CCS usually presents in young adults with a slight female predominance and was described as a slow-growing, painful nodule of the (often) lower extremities, usually arising in deep tissues around fascia, tendons and aponeuroses. Over the course of years, it may spread to regional lymph nodes, lungs or bone. The 5-year survival rate is estimated at 48-67%, lower if widely metastatic at diagnosis. The three can usually be separated immunohistochemically by a panel of stains. To name a few, MPNST can be distinguished from MM and CCS, as it is negative for HMB45, Melan-A, and Tyrosinase, while the other two are positive. Likewise, MM and CCS can be distinguished by GFAP, as MM is usually weakly positive and CCS is negative. CCS is also positive for synaptophysin, while MM is negative and CCS can be positive for chromogranin, and MM is not. Pcomas do not express S100 reactivity. IDCTs/FDCTs are both negative for Melan-A and Tyrosinase, while CCS is positive for both, as are Pcomas. Other stains that were compared were NSE, CD56, MITF-1, CD68, Vimentin, EMA, CD117, SMA, Desmin, HHF35, CD35 and CD21. The authors go on to point out that misdiagnosis is a danger to the dermatopathologist regarding these tumors, and early recognition of lesions is paramount. They stress the importance of being aware of the number of differential diagnoses associated with these types of lesions and the wide array of techniques at one's disposal for identifying the correct entity.

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Ira Bleiweiss: I would favor spindle cell melanoma based on the nucleoli. I don't recall such prominent opennes in the few MPNST cases I've seen.

John Chan: Difficult if not impossible to distinguish between spindle cell melanoma and epithelioid MPNST. Given the clinical scenario and presence of some vacuolated cells containing red cells, I would also add angiosarcoma to the differential (even though CD34 is negative, perhaps CD31 can be tried as well).

Tom Colby: Given the location I would have to favor melanoma over MPNST but I too have often wondered that we probably separate these lesions arbitrarily when they are poorly differentiated.

Kum Cooper: An interesting problem Allen. What about EM?

Ivan Damjanov: I think that this is a melanoma.

Vincenzo Eusebi: Probably epithelioid PNST. Difficult to be sure.

Giovanni Falconieri: I vote for melanoma. Unless EM can be resorted, I do not consider MPNST on the top of the differential in a malignant tumor which is diffusely +ve for S100 only.

Cyril Fisher: Based on the cytology I favour melanoma, although as you point out there is overlap with MPNST (especially at the ultrastructural level).

Christopher Fletcher: In sun damaged skin of an elderly individual and given the focally somewhat nested architecture, then I would personally regard this lesion as a spindle cell melanoma. As Allen rightly says, spindle cell or desmoplastic melanomas are very often negative for the second-line melanoma antigens such as HMB45 and MART-1. In my experience, convincing examples of MPNST arising in skin are exceedingly rare and almost always represent malignant change in a pre-existing neurofibroma. The clinical course may help to prove the diagnosis in a case such as this, based on the pattern of metastasis, particularly if spread to lymph nodes occurs.

Andrew Folpe: Ulcerated dermal lesion, strongly S100 positive with a lymphocytic reaction? I'd go for "melanoma".

Jeronimo Forteza-Vila: I agree with the histological diagnosis.

Thomas Krausz: Examples of epithelioid MPNST I have seen before were less inflamed and more epithelioid. In a case like this, I would consider melanoma first (? Cutaneous met from another site or "lost" in situ component as a result of previous ulceration/regression).

Thomas Mentzel: As in other cases I've got a very pale slide, however, given the clinicopathological features and the reported strong expression of S-100 protein, I would favor malignant melanoma.

Markku Miettinen: Malignant spindle cell and epithelioid neoplasm, would have favored carcinoma [of cutaneous origin, more likely] by morphology, but readily accept malignant melanoma, same scenario often happens in practice. Lack of markers other than S100 is no detraction for a melanoma diagnosis, although junctional activity is not seen in the sections. Our convention is to diagnose this type of tumor as MPNSTs only when they arise in connection with neurofibroma, otherwise we put melanoma in the front.

Elizabeth Montgomery: To me, this looks more like melanoma than epithelioid MPNST since the tumor cells are more pleomorphic than those of my idea of epithelioid MPNST, plus there is a lymphoplasmacytic backdrop.

Joshua Sichel: The boundary between these lesions is rather blurry. What do the soft tissue expert's think?

Dominic Spagnolo: An age-old problem particularly in the head and neck area. On morphologic grounds I can't separate melanoma from epithelioid MPNST. Your immunoprofile in this case would favor MPNST. There is a school of thought that considers the 2 are probably related.

James Strauchen: The subepidermal involvement and solar changes might favor melanoma. I would have also considered AFX and spindle squamous cell carcinoma histologically, showing the importance of the immuno in cases like this!

Saul Suster: Favor melanoma in this case, despite the absence of melanocytic markers other than S-100. We reported a case of epithelioid MPNST of the skin several years ago (Suster S et al. Malignant epithelioid schwannoma of the skin. A low-grade variant of neurotropic melanoma? Am J Dermatopathol 11:338-344, 1989). I remember when we reported that case, the reviewers insisted that we not be dogmatic in the diagnosis of MPNST despite the fact that the histology was unlike any conventional melanoma and the tumor had a benign follow-up; hence the reason for the subtitle of the paper. In the present tumor the cells are too spindled, not terribly epithelioid, and really look good for neurotropic/desmoplastic melanoma, which are often negative for all melanocytic markers other than S-100.

Lawrence Weiss: Given the clinical setting, I think that it is probably melanoma and will behave as one. Collagen IV staining can be helpful in the distinction upon occasion.

CASE NO. 11 — CONTRIBUTED BY: DR. THOMAS KRAUSZ

Phil Allen: Retroperitoneal angiomyolipoma simulating liposarcoma. I once saw Enzinger nearly caught in this trap some 35 years ago. He had dictated an AFIP consultation case as a retroperitoneal liposarcoma but after a good night's sleep, he had more correct thoughts when he came to sign it out. In those days, there was no such thing as an HMB 45 stain, but Enzinger still managed to keep out of trouble.

David Ben-Dor: Thomas, I admire your logical analysis of this case. Renal tumors that present as retroperitoneal mesenchymal masses not obviously attached to the kidney can fool you. Years ago I had a needle biopsy of a retroperitoneal mass which the radiologist claimed grew to "touch" the kidney but couldn't be said to be derived from it. The histology was that of a spindle cell tumor which I called leiomyosarcoma despite the keratin positivity (which I conveniently ignored). The mass was resected and at its edge there was a small fragment of renal parenchyma which showed classical clear cell carcinoma in direct continuity with the spindle cell tumor. So renal masses can present as retroperitoneal tumors with a minimal connection to the kidney not obvious radiologically.

Gerald Berry: Agree. But would not have wanted to be the one on frozen section coverage!

Michele Bisceglia: Angiomyolipoma. This case was lacking in AMR series. We had a case from the opposite side of the spectrum, e.g., a case without adipocytic component, which I personally contributed in the past (AMR Seminar # 26, case 3) as a "retroperitoneal lymphangiomyoma versus (renal) angiomyolipoma without adipocytic component", of which subsequently had the opportunity to see further examples. The only case like yours, Thomas, of angiomyolipoma poor in myogenic cells I have seen was the case of adjacent gene syndrome of TSC-2/ADPKD-1 which I presented in Srni (2nd Intl AMR Meeting): in that case there were several (mainly small) "angioliomatous" lesions positive for melanocytic markers, but devoid of spindle "myogenic" cells. Of course classical angiomyolipomatous nodules were also present as were small cystic changes of the TSC type and classical cystic changes of the ADPKD type.

Ira Bleiweiss: Tough case, very poor in the myo component. Very instructive workup.

Tom Colby: Agree with diagnosis; but I too was initially fooled and have been previously fooled by fatty predominant AMLs.

Kum Cooper: Thomas, thank you for this superb instructional/educational case. I am certain that I would have called the frozen liposarcoma! Was good to see you and Suzie in the Czech Republic.

Ivan Damjanov: Good point.

Vincenzo Eusebi: Nice case of angiomyolipoma.

Giovanni Falconieri: I would be hesitant in calling this angiomyolipoma, yet I guess that this is the best microscopic interpretation that one can render. Undoubtedly a weird lesion in a bad place. Thanks Tom. It was nice to share fun with you in South Bohemia.

Cyril Fisher: Very good diagnosis of angiomyolipoma – there are even lipoblast-like cells. The HMB45 demonstrates this is the lipid rich variant.

Christopher Fletcher: A beautiful and very impressive example of adipocyte-predominant angiomyolipoma. I agree that the best clue, in separating this lesion from liposarcoma would be the focally evident plump perivascular cells as well as the occasional clusters of large pale-staining epithelioid cells.

Andrew Folpe: Agree with lipoma-like AML. In my experience these are frequently submitted with the question of WDL, based on the somewhat atypical appearing PEC. Thanks.

Jeronimo Forteza-Vila: I agree with this interesting case.

Thomas Mentzel: I've found the H&E section very difficult, because morphological features resemble atypical lipomatous tumour. However, the mentioned blood vessels and scattered myogenic cells surrounding vascular structures are a good clue for the diagnosis. I've seen recently a more typical example of angiomyolipoma, and found as well focal expression of melanocytic markers by lipogenic cells (probably due to pretreatment of slides ?)

Markku Miettinen: Agree on predominantly lipomatous angiomyolipoma, definitely a tumor that can be confused with well-differentiated liposarcoma.

Elizabeth Montgomery: Thanks for this nice example of angiomyolipoma.

Joshua Sickel: My first impression was well differentiated liposarcoma. Subtle case!

Dominic Spagnolo: Without the abnormal vessels and IPOXs, I would have struggled with this. I agree with angiomyolipoma. Thanks for the case.

James Strauchen: Nice example of a "subtle" angiomyolipoma!

Saul Suster: Very nice example of adipose-rich AML.

Lawrence Weiss: I plan on doing more immunostaining on my fatty tumors of the retroperitoneum. This case is highly instructive.

CASE NO. 12 — CONTRIBUTED BY: DR. THOMAS MENTZEL

Phil Allen: Variant of angiomyoma (vascular leiomyoma), ?subcutis, back of right foot. I have never seen the need to join this tumor in lexicological wedlock with glomus tumors, hemangiopericytomas or congenital generalized and localized fibromatosis (myofibromatosis). Perhaps I have been unduly influenced by the big series of vascular leiomyomas that was published by Professor Enjoji's group in Cancer about 20 years ago.

David Ben-Dor: Now that the concept of hemangiopericytoma has been laid to rest (after a good deal of arduous effort on the part of Dr. Fletcher) has it found a way to resurface as a myopericytoma?

Gerald Berry: Beautiful example of a lesion that I don't ever see. Are these related to myointimomas?

Michele Bisceglia: Intravascular myopericytoma. Nice case. As for case 7, I am collecting all tumor types characterized by intravascular growth or arising in the vessel lumina: as far as I know so far, I have in the list the following: neurothekeoma, pyogenic granuloma, myofibromatosis, infantile hemangiopericytoma, intravascular fasciitis, intravenous leiomyomatosis, giant cell tumor, and myopericytoma. Would be grateful if any of you would be so kind to remind me of any other such tumor.

Ira Bleiweiss: A new one on me.

John Chan: I find it difficult to distinguish it from an angioleiomyoma with intravascular growth. The foot/ankle location is also typical for angioleiomyoma (except for the intravascular growth).

Tom Colby: Agree with diagnosis. I have not heard of these lesions being intravascular but I note the reference in J Cutaneous Pathology.

Kum Cooper: Thanks Thomas. I have seen three cases in the last three months in Vermont!!

Ivan Damjanov: At the Euro Soc. Path congress you presided over a session where a similar case was shown! I just could not remember the name. My residents suggested that I do not go to meeting any more because I am too old to remember such fancy names—instead I should send one of them to Paris next time!

Vincenzo Eusebi: Nice case of intravascular myopericytoma.

Giovanni Falconieri: I guess that I have already seen this in my practice and mislabeled repeatedly it as angioleiomyoma. Thanks Thomas, for submitting this educational case

Cyril Fisher: Intravascular myopericytoma, beautiful example.

Christopher Fletcher: Beautiful case of intravascular myopericytoma – it is my subjective impression that perhaps 2 - 3% of myopericytomas are entirely intravascular, but that one may also see more focal involvement of vascular lumina in a higher proportion of cases.

Andrew Folpe: Very nice example of myopericytoma, apparently entirely intravascular. I've seen this with myofibroma, so I guess it makes sense that it happens with this as well.

Jeronimo Forteza-Vila: I did not know this entity.

Allen Gown: A lovely example of a very distinctive and unusual tumor

Thomas Krausz: Beautiful example. Amazing, how quickly myopericytoma as a real entity has established itself.

Markku Miettinen: Angioleiomyoma with a myopericytic component is my interpretation; this tumor is a hybrid between angioleiomyoma and purely myopericytic tumor [quite rare] having both well-differentiated vascular smooth muscle and rounded myopericytic components. The perfect circumscription of these tumors is explained by their origin from vessel wall to which they remain confined.

Elizabeth Montgomery: Thanks for sharing this nice case of intravascular myopericytoma/myofibroma.

Dominic Spagnolo: I agree with the diagnosis, but I do think this shows overlapping features with angioleiomyoma. There are well-formed small arteries/arterioles with organized smooth muscle in their walls, in addition to the more typical thin-walled vessels around which the myopericytic cells are arranged. Thank you for the case. I have not seen an intravascular lesion before.

Joshua Sichel: Beautiful example and nice discussion. I suspect I may have called this lesion angioleiomyoma in the past.

James Strauchen: Interesting! I would have considered angioleiomyoma.

Lawrence Weiss: Beautiful case!

CASE NO. 13 — CONTRIBUTED BY: DR. ELIZABETH MONTGOMERY

Phil Allen: . Juxta-glomerular cell tumor, kidney. I seem to remember having seen one of these somewhere before.

David Ben-Dor: To be honest I wouldn't have thought of this rare entity (should the young age and clinical presentation afford a clue?)

Gerald Berry: Nice example for the teaching files. Thank you.

Michele Bisceglia: Juxtglomerular cell tumor. Beautiful case. The first one for me. Yes, it looks like hemangiopericytoma in places. And in fact we are aware that sometimes ectopic renin-secreting tumor may occur (especially in the retroperitoneum: Weiss and Goldblum. Soft Tissue Tumors textbook; pag. 1015), which can be misinterpreted as soft tissue hemangiopericytoma.

Ira Bleiweiss: Agree. Nice case.

John Chan: Great case of juxtglomerular cell tumor. I find it difficult to tell whether the tubules represent part of the neoplasm or merely entrapped renal tubules.

Tom Colby: Agree with diagnosis. Lovely case.

Kum Cooper: I was considering a vascular tumor (hemangioendothelioma). Did you do any more vascular markers (even though the CD34 was negative)?

Ivan Damjanov: Nice case. Classical.

Vincenzo Eusebi: Thank you very much for showing this case of juxtaglomerular cell tumor. The first case I see.

Giovanni Falconieri: Great case! Thank you Dr. Montgomery for sharing with us this exceptional case

Cyril Fisher: A great rare case with wonderful EM pictures – a perfect example of the continuing value of EM for diagnosis!

Christopher Fletcher: Thanks for the beautiful and very typical example of this rare lesion.

Andrew Folpe: Totally cool. Definitely the best example I have ever seen. Thanks, Liz.

Jeronimo Forteza-Vila: I agree with your diagnosis. Very interesting case. Vascular lesion is an important feature of this tumor.

Allen Gown: I saw an example of a juxtaglomerular tumor a few years ago, and was able to confirm expression of renin by the tumor cells by sending the case to Dr. Patrick Bruneval, Laboratoire d'Anatomie Pathologique, Hopital Europeen G Pompidou, Paris.; Dr. Bruneval has antibodies to renin that can be used to identify renin-producing tumors, and is about the only person I could find anywhere that can do this by IHC.

Thomas Krausz: Agree with diagnosis. I have seen only one example before. I assume that the tubules filled by colloid-like secretion represent entrapment rather than tubular differentiation. As result, the tumor has a rather complex architecture.

Kum Cooper: Lovely example of JGA tumor. Thank you very much.

Thomas Mentzel: Many thanks for sharing an example of this rare entity.

Markku Miettinen: Would have considered this an unusual primitive epithelial tumor, after reading the story I believe that it is juxtaglomerular cell tumor. Never seen this before.

Joshua Sickel: Very nice case. We recently had a JXG tumor at the South Bay pathology society meeting.

Dominic Spagnolo: What a wonderful example of a juxtaglomerular cell tumor. My slide exhibits pretty much the full morphological spectrum these tumors can have. Thanks.

James Strauchen: A classic! I have never seen one "on the hoof"! Thank you.

Saul Suster: Have only seen one case previously, also in a slide seminar. Thank you very much for the contribution!

Lawrence Weiss: So much for my diagnosis of synovial sarcoma. Another unbelievable tumor.

CASE NO. 14 — CONTRIBUTED BY: DR. SANTIAGO RAMON Y CAJAL

Phil Allen: Malignant solitary fibrous tumor, pleura. I accept the suggested diagnosis, although I would be prepared to retract it, if told to do so by Saul. If my memory serves me correctly, I think he once said that the CD34 stain is negative in about 10% of solitary fibrous tumors.

David Ben-Dor: In the slide I received I couldn't locate the benign solitary fibrous tumor areas. The tumor cells look vacuolated- I suppose in light of the CD34 negativity it wouldn't be any more logical to bring up the possibility of an angiosarcoma. Cases are often presented to this seminar which require immunohistochemistry- ideally if the other members had access to a small piece of tumor they could try their own immuno stains (it would be very interesting to compare the results!) but this is totally impractical. Unfortunately this circumstance limits the ability to make meaningful comments. I assume that cytokeratins, EMA, and mesothelial markers (calretinin) were applied and were negative. I identified foci of vascular invasion.

Gerald Berry: I have seen a couple of low grade SFT undergo dedifferentiation to chondrosarcoma. This phenomenon is not very well documented in the literature.

Michele Bisceglia: I am not sure, Santiago, that this case is solitary fibrous tumor in nature. It certainly is malignant, and a tough case. ???????? might be mesothelioma. There are few malignant localized mesotheliomas which have been described. If immuno doesn't support the diagnosis of mesothelioma, likely EM would help. Am interested in other people's opinion.

John Chan: Agree with diagnosis of solitary fibrous tumor. On my slide, I do not see an overtly malignant foci.

Tom Colby: Probable malignant tumor, unclassified. To me this would be an unusual solitary fibrous tumor (benign or malignant). There is prominent vascularity with small vessels. It appears as though this may be parietal pleural in which case this may be more of a soft tissue mass bulging into the pleura. I would wonder about other markers, including CD31, keratins.

Ivan Damjanov: I thought that this is a vascular tumor, low grade malignancy, you choose the name.

Vincenzo Eusebi: I do not know what is this lesion.

Giovanni Falconieri: Difficult case. A mixed ropy collagen/hemangiopericytoid pattern can be recognized, yet the overall changes make me uncomfortable with any interpretation (? Malignant SFT, synovial sarcoma), unless we want to call this "sarcoma, NOS". I shall look forward to reading the opinion of the soft part experts. Thanks Santiago for this challenging contribution.

Cyril Fisher: Very difficult case. I am surprised that the benign area is CD34-negative.

Christopher Fletcher: Without more typical areas of solitary fibrous tumour and in the setting of CD34 negativity, it would be difficult to make a definitive diagnosis based on this one slide. I note the presence of highly cellular whorled structures, reminiscent of those sometimes seen in dedifferentiated liposarcoma. Also, some of the more hypercellular areas give the impression of perhaps having a vasoformative architecture. I would have difficulty in classifying this lesion based on this one slide and in the absence of additional immunostains.

Andrew Folpe: Agree with "sarcoma". I'm not sure there is any typical SFT on my slide.

Jeronimo Forteza-Vila: There are few vascular channels. I think it would be important to rule out a vascular tumor.

Allen Gown: While it's really an example of diagnosis by "association", it's even harder to justify an alternative diagnosis.

Thomas Krausz: I am not sure what this is. It does look different than the SFTs I have seen before. In places it appears vasoformative?

Thomas Mentzel: Unfortunately, I've got a very pale slide, and I can not make any sensible comment.

Markku Miettinen: Agree on low grade sarcoma. Cannot be sure of type. There are features raising the possibility of meningotheliomatous elements with dedifferentiated liposarcoma (first described by Nascimento et al. AJSP 1998;22:945). Has pseudoangiomatous and epithelioid foci, but cannot find quite convincing neoplastic adipocytes. The slide in my set did not contain solitary fibrous tumor-like areas.

Elizabeth Montgomery: Not sure what this is but also thought of SFT and hemangiopericytoma; the "inert" IHC might support the latter interpretation.

Joshua Sichel: Can you diagnose SFT in the absence of CD34 staining?

Dominic Spagnolo: I can't make a specific diagnosis here. The setting and the gross are all in keeping with SFT, and it does look malignant, but on this slide, and given the absence of immuno support, I can't get to malignant SFT. Am not sure what this is!

James Strauchen: Seems to have a biphasic pattern with epithelioid foci in addition to spindle cell and myxoid areas. I would have also considered a localized malignant mesothelioma or vascular tumor. Did you do mesothelial or vascular markers? BCL2 is another marker of SFT you might try.

Saul Suster: The features I see in the submitted slide could certainly be consistent with but not exactly typical of solitary fibrous tumor. The gross and clinical description, on the other hand, certainly is strongly suggestive of the diagnosis rendered (solitary, 37 cm/2,600 gm mass attached to the pleura!!!). The morphologic features are not those of an angiosarcoma of the pleura (no atypia, no necrosis). Besides, if this was angiosarcoma, it would be diffusely infiltrating all over the place instead of being "attached" to the pleura and the patient would have not survived long enough for the tumor to reach a size of 37 cm!. The focal meningothelial-like whorling, also reported in some "dedifferentiated" liposarcomas, is unusual, but I have seen similar features before in SFT. Besides, I am not aware of liposarcoma arising in the pleura. The fact that this tumor is malignant can be surmised from the sheer size of the tumor and the description by Santiago of areas displaying increased cellularity, mitotic activity and foci of necrosis. The negative CD34 does not bother me at all and in my opinion does not exclude the diagnosis of SFT. More than 20% of classical, bona-fide SFT's of the pleura that we've seen have been negative for this marker. I think this case needs to be studied more thoroughly. We would need to have a more detailed gross description of the lesion (i.e., was it infiltrative? did it involve the parietal or visceral pleura? was there involvement of the soft tissue in the chest wall?), see more sections from the tumor (including the "malignant" areas), and perform additional stains, such as bcl-2, CD99, CD31, keratin, EMA, to name a few, before a more committed opinion can be rendered.

Paul Wakely: Santiago, this looks like an angiosarcoma to me. I would make sure the CD31 stain is negative.

Lawrence Weiss: I have a hard time calling this a malignant solitary fibrous tumor. I would perform a wide battery of immunos to "fish" for a diagnosis. I wonder about an epithelioid vascular tumor, so I would include a CD31.

CASE NO. 15— CONTRIBUTED BY: DR. JOSHUA SICKEL

Phil Allen: Neuroendocrine carcinoma of the cervix associated with overlying in-situ squamous cell carcinoma (cervical intraepithelial neoplasia). I think the atypia in the squamous epithelium and the koilocytes are too prominent to ignore. Seven of Ishida's 10 cases were associated with cervical adenocarcinoma or squamous cell carcinoma or cervical intraepithelial neoplasia (Int J Gynecol Pathol, Oct 2004, 23(4) p366-72).

David Ben-Dor: This case reminds me of a biopsy I saw which was taken from a vaginal mass in a similarly aged woman. The histology was essentially that of a blue cell tumor with abundant crush artifact. I tried the usual panel of immunohistochemical stains (including cytokeratins) and came up with nothing. I sent it to Allen Gown who had the foresight to perform synaptophysin which was positive. Despite the keratin negativity we decided it was small cell carcinoma. How often small cell carcinomas turn out to be cytokeratin negative is a different story- I understand that cytokeratin isn't necessarily a prerequisite for diagnosing small cell carcinoma in a small bronchoscopic biopsy.

Gerald Berry: The first case of small cell neuroendocrine carcinoma that I encountered was in a Pap smear!

Michele Bisceglia: Small cell neuroendocrine carcinoma of uterine cervix. Nice case. Thank you, Josh. I wonder if this case was CK22+ (as it is written in the case description) or it is CK20+. One month ago I have seen a case at autopsy of small cell carcinoma (without neuroendocrine differentiation) of the cervix with disseminated metastases in abdominal, mediastinal and neck lymph nodes and bilateral massive subpleural and intraparenchymal interstitial involvement which caused the patient be admitted under an acute pulmonary failure syndrome and with the clinical diagnosis of acute interstitial pneumonia. Along this line I would recall the nice paper (a review) our colleague and friend Kum Cooper published in Adv Anat Pathol in September 2002 (Grayson W, Cooper K.A reappraisal of "basaloid carcinoma" of the cervix, and the differential diagnosis of basaloid cervical neoplasms. Adv Anat Pathol. 2002 Sep;9(5):290-300).

Ira Bleiweiss: Agree. Nice Case

Tom Colby: Agree with diagnosis. Beautiful case.

Kum Cooper: Agreed. These tumors are uniformly positive for integrated HPV 18 (a type that is usually associated with aggressive carcinomas of the cervix!).

Ivan Damjanov: SCNE carcinoma. Agree!

Vincenzo Eusebi: Nice case of small cell neuroendocrine carcinoma with squamous cell differentiation.

Giovanni Falconieri: I agree, small cell carcinoma of the uterine cervix. Thanks for this educational slide.

Cyril Fisher: Small cell carcinoma of cervix, rare and excellent example.

Christopher Fletcher: A very beautiful teaching case – many thanks!

Andrew Folpe: Nice case- thanks. There does seem to be some focal squamous differentiation.

Jeronimo Forteza-Vila: I agree with this diagnosis.

Allen Gown: Since there is not a cytokeratin 22, I'm wondering if you meant cytokeratin 20.

Thomas Krausz: Agree with diagnosis.

Thomas Mentzel: A nice example of neuroendocrine carcinoma arising at an unusual anatomic site.

Markku Miettinen: Agree on small cell neuroendocrine carcinoma of the uterine cervix, with in situ and invasive squamous components.

Elvio Silva: I agree with the diagnosis, but in this case, as in several small cell carcinomas of the cervix there are some areas with larger cells with more cytoplasm, which are most probably also neuroendocrine. In the cervix, probably large cell neuroendocrine and small cell carcinoma should not be separated because both are very aggressive. CD 56 is the best stain for the small cell, chromogranin for the large cell, and synaptophysin is good for both.

Dominic Spagnolo: Nice example of cervical mixed neuroendocrine/squamous carcinoma – thank you.

James Strauchen: Small cell neuroendocrine carcinoma of the uterine cervix. Thank you!

Lawrence Weiss: Great case. CK22 or CK20?

CASE NO. 16 — CONTRIBUTED BY: DR. DOMINIC SPAGNOLO

Phil Allen: Rosai-Dorfman disease, patella, in a 26-year-old female with alleged treated Hodgkin's disease, location not specified. Way back in the early seventies, I misdiagnosed the first case of Rosai Dorfman disease I had seen as some kind of Hodgkin's disease. Can the slides from Colombia be reviewed?

David Ben-Dor: Diagnostic difficulty is in the eye of the beholder! Was the provided clinical descriptor (Hodgkin's disease) supposed to be a hint as to the diagnosis?- I wasn't aware of the connection between it and Rosai Dorfman disease. Without this knowledge the polymorphous inflammatory infiltrate could lead to vain and fruitless attempts to identify R-S cells. Unfortunately my slide was faded- I will have the technician restain it. I have no personal experience with this condition; truthfully how often does it show up?

Gerald Berry: Dr. Dorfman was not available to review the case but Roger Warnke agreed with the diagnosis of Rosai-Dorfman disease. He didn't remember seeing it in this location.

Michele Bisceglia: Rosai-Dorfman disease involving the patella. Nice and difficult case, Dominic. Never seen it in bone.

Tom Colby: Agree with diagnosis.

Kum Cooper: Thanks Dom. No, I have not seen this in the patella before (although I have seen lesions in other bony sites!). Yes the association with HD has been well known.

Ivan Damjanov: I could not make the diagnosis on my slide but would not argue with you.

Vincenzo Eusebi: Nice case of Rosai Dorfman disease.

Giovanni Falconieri: Great case, Dom. Despite the location I agree with RDD, the hallmark is there! Thanks for this exotic case.

Cyril Fisher: Rosai-Dorfman disease in a totally unexpected location!

Christopher Fletcher: Very convincing Rosai-Dorfman disease – I have not personally encountered isolated skeletal involvement in the past and certainly the patella would seem to be a very rare location.

Andrew Folpe: Agree with Rosai-Dorfman disease. Very unusual in bone.

Jeronimo Forteza-Vila: I agree with this diagnosis.

Thomas Krausz: Agree with diagnosis. I have seen several examples in soft tissue but only a couple in bone before.

Thomas Mentzel: A fascinating case of Rosai-Dorfman disease involving bone structures.

Markku Miettinen: Rosai-Dorfma , nice needle biopsy specimen. I have seen one example of nodal Rosai-Dorfman in a person with peripheral T-cell lymphoma.

Elizabeth Montgomery: What a neat case. What glorious emperipolesis! I don't think I have seen RDD in the patella. Years ago, we reported a soft tissue series and I don't think we even had any near the knee!

Joshua Sichel: Beautiful case!

Dominic Spagnolo: My case. Apologies if others' slides show the same atrocious staining as my copy – the hematoxylin seems to have faded – ab initio the staining was fine.

James Strauchen: Classic Rosai-Dorfman! I have seen one or two cases involving bone, including one in the calcaneus! Occurrence following lymphoma is well recognized.

Saul Suster: Agree – nice case of Rosai-Dorfman disease. Have seen cases in bone but never in the patella. I think you need to ask the folks in Colombia to send you the slides from the "Hodgkin's disease" for you to review!

Lawrence Weiss: Great case. Agree. Never seen one in the patella.

CASE NO. 17 — CONTRIBUTED BY: DR. BRUCE WENIG

Phil Allen: Poorly differentiated malignancy with foamy tumor cells, parotid, ?carcinoma, ?sarcoma. I am unable to be any more precise than the AFIP. I don't recognize it as a described sarcoma or carcinoma.

David Ben-Dor: For whatever it's worth the round cells look histiocytoid, bringing up the old saw "MFH". There must be a few tumors which justify the term.

Gerald Berry: Unfortunately I could not get beyond undifferentiated malignant neoplasm.

Michele Bisceglia: Undifferentiated malignant tumor in parotid with extensive angioinvasion. Do not know, Bruce. Very difficult. Would agree on all the opinions expressed so far.

Ira Bleiweiss: I'm stumped.

John Chan: Undifferentiated malignant neoplasm. Given the CD68 positivity, the possibility of histiocytic sarcoma may be considered as well (although not the most typical morphology). Perhaps staining for the new histiocytic marker CD163 as well as CD4 may help.

Tom Colby: I rather like the idea of some sort of peculiar sarcomatoid carcinoma.

Kum Cooper: Sorry Bruce, I leave this to the STT gurus!

Ivan Damjanov: MFH.

Vincenzo Eusebi: Very nasty looking tumor.

Giovanni Falconieri: Quite challenging. Any option sounds good. Despite negativity for epithelial markers I am still inclined to consider lesions like this as pleomorphic sarcomatoid carcinoma, keratin negative.

Cyril Fisher: Undifferentiated pleomorphic neoplasm!

Christopher Fletcher: Malignant epithelioid and spindle cell neoplasm. I do not think that the appearances fit well with any specific type of sarcoma and I would be concerned that this more likely represents either metastatic melanoma or else some type of sarcomatoid carcinoma, albeit with an aberrant immunophenotype. I do not believe that it would be possible to make a definitive diagnosis in a case such as this in the context of the unsupportive immunostains.

Andrew Folpe: Undifferentiated malignant neoplasm, positive for 4 of the 5 least specific IHC markers in existence (NSE is the other). I forgot who referred to CD10 as the "vimentin of the new millenium" but I liked that line a lot. Sorry- I can't do any better than that.

Jeronimo Forteza-Vila: Thank you for this interesting case. I think the sebaceous differentiation is so evident.

Allen Gown: Bruce, if you can't figure this one out neither can I! Unfortunately none of the markers that are positive in this tumor (CD10, CD68, CD99) are lineage specific and thus there are no positive IHC results to help light the way to a diagnosis.

Thomas Krausz: I have seen a histologically somewhat similar tumor which presented originally as a soft tissue mass of the foot and subsequently also in the tibia. We could not classify and called it high-grade sarcoma with epithelioid features, NOS. Our case was focally also EMA and CD10 positive. There was no tumor in the kidney, clinically/imaging.

Thomas Mentzel: Unfortunately, I've got a very pale slide, and I cannot make any sensible comment.

Markku Miettinen: Agree on unusual high-grade sarcomatoid neoplasm; undifferentiated sarcoma (MFH); rule out sarcomatoid carcinoma. Being embedded in salivary gland, cannot rule out the latter possibility (more keratins, CK18, CK5/6); even metastatic sarcomatoid Ca [kidney??, other] could be possible; I could not see evidence for sebaceous differentiation, however. Undifferentiated sarcoma (MFH) is purely histologically perhaps a more likely possibility. Metastatic origin has to be ruled out. Has this patient possibly received radiation to neck area [for hemangioma, other condition]?

Elizabeth Montgomery: This is tough. It seems to be in a node on my slide; despite the lack of keratins I'd be worried about getting burned [again] by metastatic RCC or a bizarre local primary spindled carcinoma before sticking my neck out and calling this a pleomorphic sarcoma.

Joshua Sickel: Undifferentiated sarcomatoid neoplasm. Did this case set a personal record for most IPOX stains ordered? Very frustrating case

Dominic Spagnolo: I don't know what this is – I thought melanoma despite the bubbly cytoplasm (balloon cells), but that seems unlikely on the evidence you give. I have to leave it at undifferentiated malignant neoplasm, ? sarcoma ??histiocytic sarcoma. ??CD163 available

James Strauchen: Sarcoma versus sarcomatoid carcinoma. Morphologically I favored carcinoma, but the immunohistochemistry goes more with MFH!

Saul Suster: Sorry, undifferentiated malignant neoplasm is the best I can do! By H&E it looks to me like a metastasis of malignant melanoma. We have had the unpleasant situation before of confronting metastases of melanoma (in well documented cases with a prior

history in which this diagnosis was the only clinically sensible option) that were completely negative for all melanoma-associated markers tested! Could this be one of those?

Lawrence Weiss: Pleomorphic sarcoma is as good a diagnosis as any for me.

QUIZ CASE NO. 1 — CONTRIBUTED BY: DR. SAUL SUSTER

Phil Allen: Probable atypical granular cell tumor. I would recommend wide local excision.

David Ben-Dor: The cells look like a malignant variant of those seen in reticulohistiocytoma.

Gerald Berry: I favor clear cell sarcoma despite the negative HMB45 and the age.

Michele Bisceglia: Would favor "epithelioid malignant peripheral nerve sheath tumor".

Tom Colby: Epithelioid MPNST.

Ivan Damjanov: Melanoma, rhabdoid.

Giovanni Falconieri: Malignant granular cell tumor vs rhabdoid melanoma.

Christopher Fletcher: This is a tough case – with all the eosinophilic cytoplasm and S-100 protein positivity, one would first think of a melanocytic lesion, but your negative results for HMB45 and Melan-A seem to make that less likely. I note the presence of readily identified mitotic figures and I wonder, perhaps, if the lesion was not as slowly growing as the patient has suggested.

Andrew Folpe: Atypical granular cell tumor.

Jeronimo Forteza-Vila: Attending with the immunohistochemistry I think a good diagnosis could be malignant granular cell tumor.

Thomas Mentzel: Histologically, a plump invasive cellular neoplasm is seen. The neoplasm is composed of enlarged cells with abundant eosinophilic cytoplasm and enlarged and atypical nuclei. Some nuclei contain prominent nucleoli and mitoses are identified. Given the mentioned expression of S-100 protein, malignant melanoma with rhabdoid features (metastatic ?) would be on the top of my differential diagnosis.

Markku Miettinen: Malignant granular cell tumor (?)

Elizabeth Montgomery: Based on the IHC you report after getting rid of biotin I thought of malignant granular cell tumor [though noted the neg CD68 but understand that only about two thirds of malignant GCT have CD68].

Joshua Sickel: Epithelioid malignant peripheral nerve sheath tumor.

James Strauchen: ? Unusual epithelioid or rhabdoid peripheral nerve sheath tumor.

Lawrence Weiss: Crystal storing histiocytosis secondary to immunoglobulin.

Dominic Spagnolo: Interdigitating dendritic cell tumor??

Saul Suster (my case): I favored a diagnosis of neurotropic melanoma with rhabdoid features. Unfortunately, sections containing overlying epidermis were not available for review, so the presence or absence of a junctional component could not be established. The alternate possibilities of malignant peripheral nerve sheath tumor and malignant granular cell tumor were also considered. The superficial (dermal) location would be extremely unusual for a MPNST; also, I have never seen such striking and extensive "rhabdoid" features in such tumors, and the strong and diffuse positivity for S-100 protein we obtained in this case would be out of character for a malignant NST. Malignant granular cell tumor was another possibility, but the sharp, pushing borders of this lesion would also be unusual for that condition – even small granular cell tumors of the skin are characterized by the diffusely infiltrative borders with granular tumor cells infiltrating subcutaneous fat and surrounding collagen fibers. Also, the striking fascicular organization of this tumor resembling nerve or smooth muscle fibers is not a feature associated with granular cell tumors. This case reminds me of a few previous examples of neurotropic melanoma that were diagnosed by the late Arkadi N. Rywlin at Mount Sinai Hospital in Miami, which displayed a similar "rhabdoid" morphology and showed an identical architectural pattern of growth. Of course, absence of HMB45 and Melan-A positivity is a known attribute of these tumors, and therefore does not argue against this diagnosis. The cases seen by Dr. Rywlin at Mount Sinai were shared with Dr. Richard Reed from Tulane University, the person who originally described neurotropic melanoma, and he concurred with Dr. Rywlin's diagnoses. I do admit, however, that this diagnosis may be subject to question and others may have valid reasons to disagree with this interpretation!