AMR Seminar # 46 – Short Summary of Cases

Case 1: 65-year-old woman with bilateral nodular enlargement of parotid suspicious for lymphoma

Case 2: 11-month-old boy with heart failure of unknown etiology

Case 3: 13-year-old girl with nodular lesion from parotid region

Case 4: 51-year-old woman with a breast mass

Case 5: 32-year-old man with nasal septum perforation

Case 6: 49-year-old woman with lesions in left lung on routine exam

Case 7: 60-year-old man with history of nodular melanoma develops a soft tissue mass in the chest wall

Case 8: 39-year-old man with invasive melanoma of the calf presents with enlarged inguinal node

Case 9: 60-year-old man with history of elevated skin lesion on toe

Case 10: 92-year-old male with skin lesion on right temple

Case 11: 49-year-old female presented with abdominal pain; imaging revealed a retroperitoneal mass, 8.0 cm maximum diameter

Case 12: 62-year-old male with nodular lesion on back of right foot

Case 13: 30-year-old woman with severe hypertension undergoing evaluation for infertility
Is found to have a renal tumor

Case 14: 37-year-old woman with a large mass in the pleura

Case 15: 73-year-old woman with a 4 cm tumor involving the uterine cervix

Case 16: 26-year-old female with history of Hodgkin disease in 2003, apparently in remission, is seen for a cystic lesion in the patella

Case 17: 49-year-old male with enlarging right parotid gland area mass

Quiz Case 1: 49 year old woman with skin tumor on left shoulder, primarily involving the subcutis

AMR SEMINAR #46
CASE 1

Contributed by: David Ben-Dor, MD

Clinical Summary: 65-year-old woman with bilateral nodular enlargement of the parotid, clinically suspicious for follicular lymphoma.

Pathology findings: An incisional biopsy of one of the glands was performed by the oral surgery department and was identified as "intraparotid lymph nodes". Two tan colored fragments were sent, one submitted for flow cytometry and the other for histology. Microscopically a uniform proliferation of clear cells in an organoid pattern was found. These structures were separated by thin connective tissue septae containing delicate capillaries. The cells looked cytologically monotonous with small regular nuclei. No lymphoid parenchyma was identified.

Further workup: My initial diagnosis was metastatic renal cell carcinoma pending further clinical evaluation. As it happens I stopped by the oral surgery clinic when the patient happened to be there and I was confronted by a spry lady who looked to be in good general shape and who told me that she had been aware of the parotid enlargement for a number of years (seven to be exact). In fact she had consulted at first for an unrelated problem. She also did not relate any urinary tract problems or other symptomatology which might be related to a renal neoplasm. This information put a damper on my enthusiasm for a metastatic tumor. However not having a better alternative diagnostic hypothesis (the assumption being that a primary salivary gland neoplasm was ruled out by the absence of a singular mass lesion in the parotid) I consulted with John Chan via email. His initial thoughts went along the same lines as mine, but upon further prompting by me regarding the duration of the finding and following receipt of the results of further clinical evaluation which did not reveal evidence for a renal tumor, he came up with the (in my view) brilliant suggestion of diffuse clear cell cell oncocytic hyperplasia. Upon receipt of the block I sent him, he performed immunohistochemical testing which was negative for CD10, and he had the further inspiration to test for basal/myoepithelial cells with high molecular weight keratin and p63, both of which showed scattered positive cells. This ruled out the possibility of metastatic renal cell carcinoma. An oncocytic process was further supported by focal positivity with mitochondria marker. I also sent a block to Allen Gown, who in addition to corroborating the previous findings, found positivity for GCDFP and also performed staining for gp200 renal tubular protein, with negative results, the first supporting a salivary gland tumor and both ruling out a possible renal tumor metastasis.

Diagnosis: parotid clear cell oncocytosis, presumably diffuse bilateral.

Discussion: On more careful directed examination of the slide, I found a few cells which were not clear but instead showed eosinophilic granular cytoplasm. Furthermore in the midst of the clear cell proliferation I found a lone salivary duct which could not be part of an extrinsic neoplasm.

I found this case to be most intriguing. Aside from the intrinsic interest of the uncommon condition illustrated by this case, its challenging nature also resides in the unorthodox biopsy procedure used. As far as I know in the case of a salivary gland mass FNA may be performed but diagnosis is based on conventional pathologic examination following surgical removal of the gland. I never had to deal with an incisional biopsy specimen from a salivary gland previously and I would be interested in knowing if any of you have dealt with this sort of specimen. The approach was justified by the clinician's working assumption that this was lymphoma and that the removed tissue represented intraparotid lymph nodes. Once that assumption was refuted I was still left with the task of explaining the pathological findings without the luxury of having the entire gland to examine. The absence of a defined mass made the possibility of pathology intrinsic to the salivary gland seemingly less inviting at the onset.

Figuring this case out requires dealing with several issues. First, the differential diagnosis of clear cell proliferations. This feature can be seen in the context of several entities: acinic cell carcinoma, epithelial- myoepithelial cell carcinoma, mucoepidermoid carcinoma, clear cell carcinoma (hyalinizing and NOS), and sebaceous neoplasms. One can I believe summarily deal with these possibilities based on the presentation as diffuse bilateral parotid enlargement in the absence of a clinically defined discrete mass (or masses). Also, the biopsy I received showed a quite uniform and orderly proliferation without demonstrating the hallmark diagnostic features of any of these other entities; however one can raise the objection that the sample obtained by the biopsy was limited. As far as acinic cell carcinoma specifically is concerned, clear cells are rare and the nuclei would be situated at one end of the cell as opposed to the central placement in oncocytic lesions (in reviewing this case many of the nuclei but not all are central).

The pathology of oncocytic lesions was nicely reviewed by Brandwein and Huvos in 1990 and in the third series fascicle of the AFIP series. Oncocytic metaplasia is a common age related phenomenon which can result in the formation of multiple micronodules (oncocytosis), one or more tumor nodules (nodular oncocytosis), or a discrete tumor mass (oncocytoma). These processes are interrelated and can coexist. When widespread the normal parenchyma may be replaced nearly in its entirety by oncocytes (diffuse oncocytosis). Pertinent to this case, while clear cells can be interspersed amongst eosinophilic oncocytes in oncocytic lesions in general, in the experience of these authors, they are particularly abundant in diffuse bilateral lesions which also tend to recur. This is in keeping with the current case. Though in an earlier paper Ellis described a group of nodular clear cell oncocytic tumors which were not bilateral, he mentions that in most cases the masses were accompanied by clear cell oncocytosis in the surrounding parenchyma.

P63 is a relatively recent marker whose utility in the diagnosis of salivary gland tumors has been recently explored. As reviewed by Bilal et al., in normal salivary glands this marker identifies myoepithelial cells at the periphery of the acini and basal cells in ducts. Positivity for this marker in salivary gland tumors reflects the degree of participation of these cell types and in fact, as shown by the authors, is seen to varying extents in many types of neoplasms, both benign and malignant. Oncocytomas show nuclear positivity only in smaller cells seen at the periphery of the oncocytic cell clusters. In the review by Savera and Zarbo on myoepithelial differentiation in salivary gland tumors, it is specifically mentioned that it is absent from oncocytomas; however this may refer to myoepithelial differentiation being not intrinsic to the nature of the tumor and not necessarily precluding its presence (possibly as a residua of the normal structures whose luminal cells were replaced by oncocytes via metaplasia).

As myoepithelial cells are found in malignant as well as benign salivary tumors their identification cannot serve to discriminate between the two, unlike the situation regarding breast or prostate lesions. As mentioned John Chan found cells positive for p63 and high molecular weight keratin both in this case and, similar to the findings in the articles cited above, also in a different case of

oncocytoma. Thus oncocytoma cannot be differentiated from diffuse oncocytosis or nodular oncocytic hyperplasia using this marker. If the various types of oncocytic proliferations are in fact different manifestations of oncocytic metaplasia occurring in pre-existing structures, this would be expected.

Acknowledgments: I would like to thank again John Chan for his perspicacity and habitual selflessness in helping me with this case and for thinking of the diagnostic solution, and to Allen Gown who performed the immunohistochemical studies helping to rule out a possible renal cell carcinoma.

References:

1. Chapter 4 in Armed Forces Institute of Pathology, Tumors of the Salivary Glands, Third Series, Fascicle 7
2. Brandwein M and Huvos A, Oncocytic tumors of the major salivary glands, Am J Surg Path 1991; 15(6): 514-528
3. Bilal H, Handra-Luca A, Bertrand JC, and Fouret PJ, p63 is expressed in basal and myoepithelial cells of human normal and tumor salivary gland tissues, J Histochem Cytochem, 2003; 51(2): 133-139
4. Ellis G.L, "Clear cell" oncocytoma of the parotid gland, Hum Pathol, 1988; 19: 862-867
5. Savera AT and Zarbo RJ, Defining the role of myoepithelium in salivary gland neoplasia, Adv Anat Pathol 2004; 11:69-85

AMR SEMINAR #46
CASE 2

Contributed by: Gerald Berry, MD

History: This 11-month old infant boy presented with heart failure of unknown etiology. The work-up revealed that there were no structural heart defects. The clinical diagnosis was ventricular noncompaction. He developed intractable arrhythmias prior to transplantation.

Pathological Findings: The native heart (less the majority of the atria) weighed 71 gm (Normal 40 gm). Biventricular dilatation (left >>> right) was noted. Axial slices using a short axis orientation through the ventricles revealed nodular yellow-tan subendocardial lesions measuring less than 5 mm (see accompanying photograph). The subendocardial nodules were composed of sharply delineated unencapsulated collections of pale eosinophilic cuboidal and polygonal cells with granular cytoplasm and round nuclei. These lesions were present predominantly in the left ventricular free wall and to a lesser degree in the IVS and RV free wall. Desmin staining showed intense membrane staining and muscle specific actin and S100 were negative. Formalin fixed material was submitted for EM and showed numerous mitochondria and cytoplasmic vacuoles with occasional perimembranous leptomeric fibrils.

Diagnosis: Histiocytoid cardiomyopathy

Comment: The case is unusual but illustrates (along with my last submission of desmin cardiomyopathy) that not all cases of nonstructural pediatric heart failure are post-viral dilated cardiomyopathy. Histiocytoid CMP usually presents in children under the age of 2 with refractory arrhythmias such as tachycardia or sudden death. The origin of these cells is unclear as some think that they are Purkinje-like and others purpose an oncocytic origin. A unifying concept is that the lesion is hamartomatous.

References

Malhotra V, Verrans VJ, Virmani R. Infantile histiocytoid cardiomyopathy: 3 cases and literature review. Am Heart J 1994:128:1009-1021.

Gelb A, Van Meter S, Billingham ME, Berry GJ, Rouse R. Infantile histiocytoid cardiomyopathy--myocardial or conduction system hamartoma: what is the cell type involved? Human Pathol 1993: 1226-1231.

AMR SEMINAR #46
CASE 3

Contributed by: Michele Bisceglia, MD

It is since last year when I first observed the metastatic lymph node of the case here presented that I wanted to circulate it in the club. Then, I was recently prompted to do so, when Carlos Bacchi contributed his similar case in the last seminar. While hoping that members will be not bored in looking at a second case, at the same time I wonder whether it is not worth inviting Carlos to put together both cases and consider to publish them altogether (Adv Anat Pathol is the best choice, if Phil Allen will accept them as selected cases). The following case description has been made having in mind this possibility. Finally I would like to let everyone know that this same case will be presented at the 2nd International AMR Symposium in Czech Republic in next June, 2005. Please note that only those AMR members who will be participating in the AMR Czech Symposium are going to get from Michal Michal a glass slide from the original primary skin lesion of the scalp of this patient (sorry I did not have enough material of the original scalp lesion to get 45 slides for all the member in the club. Michal Michal has also got one slide from the first local recurrence of this case: please read the history). Of course I look forward to hearing the members' opinions regarding the interpretation of this case and am interested very much in these. I apologize in advance with Saul Suster for the space in excess that this case description will need to be circulated: I am confident he will be merciful and let this manuscript be published entirely.

CLINICAL HISTORY

In June 2004, a nodular lesion (which the circulated slides are from) 3.5 cm in diameter was removed from the right parotid region of a 13- year old girl. The lesion had first appeared 2 months previously. However the past medical history of this young patient was remarkable for several previous surgical excisions of cutaneous or subcutaneous lesions in the head and neck area. In 1993, at the age of 2, a likely congenital skin lesion 2.5 cm in size was excised from her right temple and diagnosed as *"benign fibrous histiocytoma with cellular features"*. The lesion came in fragments and seemed to be located in the dermis, but no overlying epidermis was seen. As a matter of fact, while extension into the subcutis could not be excluded, the only piece of subcutaneous tissue recognizable as such was uninvolved. Anyway, a comment was added to the diagnostic report, emphasizing the possibility of a local recurrence. In 1996, the lesion locally recurred at the same anatomic site and examined in another hospital where it was diagnosed as *"benign cutaneous fibrous histiocytoma with aneurysmal features"*. In order to trace back the pathologic itinerary taken by this lesion, I requested slides of the recurrence and received one block of tissue, containing half of the tumor, and which appeared similar to the primary tumor, although less cellular (more akin to conventional benign fibrous histiocytoma), implying that the aneurysmal features described by the reporting pathologist was only focal. In this specimen, which included the overlying epidermis, the tumor was totally encased by the dermis. In 2001, at the age of 10, a right laterocervical tumefaction arose, which was interpreted as reactive lymphadenopathy and which did not resolve under antibiotic medication. The neck mass (size: 3.5x2.5x1.5) was excised in a third separate institution and diagnosed as a *"subcutaneous recurrence of aneurysmal fibrous histiocytoma"*. I had access to all slides (as well as to an adequate paraffin block) of this third surgical lesion specimen, which could be better interpreted as a *"lymph node metastasis of aneurysmal fibrous histiocytoma with extension into the perinodal fat tissues"(as a remote second option* –it was reported- *this lesion could be also interpreted as a subcutaneous metastasis with involvement of two superficial neck lymph nodes, which were almost completely replaced by tumor).*

PATHOLOGY

Gross features: The gross appearance of the lesion was that of a well-circumscribed and encapsulated oval tumor mass, 3.5 cm in its greatest diameter, which on cut section had a brownish bloody spongy-like appearance . The entire mass was sampled and totally embedded in paraffin.

Microscopic findings: The specimen is definitely a (neck) lymph node, in the absence of any surrounding parotid gland tissue. The most striking histological features are represented by aneurysmal changes, with several cystic non-endothelial-lined blood-filled cavities, which were crossed by transverse and variously thickened cellular septa, alternating with small solid tumor areas. The blood-filled spaces also contain many floating mononucleated as well as several reactive multinucleated histiocytic giant cells, partly hemosiderin laden. Generally the transverse septa are mainly composed of mononucleated histiocyte-like cells mixed with inflammatory cells, numerous non-descript multinucleated hemosiderin-laden giant cells, foam cells, osteoclast-like cells, and a few fibroblasts. Sparse cholesterol clefts and granulomas are also visible in the septal tissue. On close inspection the solid tumor areas partly display the same morphology and cell composition as the tissue septa , being speckled by small interstitial dissecting hemorrhages (heralding clefts and lakes), and partly appearing in the form of scattered tissue foci, comprised of more spindly cells with collagen deposition in the intercellular matrix. Mitotic figures are easily visible at high power, both in the septa and in the solid foci (2-3 M:10 HPF). Very rare abnormal mitoses were seen. Necrosi was not documented. Remnants of normal lymphnodal tissue are left both at the periphery, in a subcapsular location, and in the inner zones.

Immunohistochemistry: Tumor cells in the septal tissue were focally positive for CD68/KP-1 and Factor XIIIa. CD34, desmin, alpha-smooth muscle actin, S-100 protein, EMA and cytokeratin were negative. Immunohistochemical staining for HHV-8 was also negative.

DIAGNOSIS

Massive lymph node metastasis of aneurysmal fibrous histiocytoma (primary in the skin: see above). So-called (benign) metastasizing cutaneous fibrous histiocytoma.

Two more small lymph nodes, which were additionally present in the surgical excisional material, were also examined and found free of disease.

DIFFERENTIAL DIAGNOSES

The differential diagnosis included here:

A. Primary deep form of aneurysmal fibrous histiocytoma: key points are the location in the lymph node (no such type of tumor has been described as a primary in lymph node), the possibility of transformation from one form of fibrous histiocytoma of the skin to another, and the clinical history.

B. Intranodal hemorrhagic cell tumor with "amianthoid" fibers: key points are the cell morphology which was not spindly but rather polymorphic with a predominance of "histiocyte-like" cells and the absence of amianthoid fibres.

C. Intranodal vascular tumor. C1: angiosarcoma $\rightarrow$ key points are the lack of endothelial differentiation, the expression of fibrohistiocytic markers; additionally, angiosarcoma in lymph node is almost always secondary, with no primary vascular tumor with a similar morphology arising in the lymph node having been described so far. C2: intranodal kaposiform hemangioendothelioma $\rightarrow$ key points are the absence of lobular architecture, the absence of fibrin microthrombi in the peripheral capillaries, the absence of infiltrative margins, and the immunohistochemical results; additionally, no case of this tumor has been observed as a primary in a lymph node so far. C3: capillary hemangioma of the infantile hemangioendothelioma type $\rightarrow$ key points are the absence of capillary structures and the lack of expression of endothelial markers.

D. Intranodal Kaposi's sarcoma: while this condition is a well recognized possibility in childhood, key points are the absence of slit-like spaces, the absence of hyaline bodies, and the negative results of immunohistochemical testing for HHV-8.
E. Aneurysmal variant of pleomorphic atypical fibroxanthoma, either as a unique primary deeply located form (not yet described) or as a secondary lymph node involvement: key points are the patient's age, the absence of any skin involvement, and the absence of true atypicality, anaplasia, or pleomorphism of the tumor cells.
F. Aneurysmal bone cyst of soft tissue: key points are the absence of the peripheral bone rim usually seen in this entity; additionally, the case herein presented is situated in a lymph node.
G. Giant cell tumor of the skin or soft tissue with secondary aneurysmal cystic changes (both as primary and metastatic): key points are the prominence of cystic changes, the absence of metaplastic bone or any foci of osteoid formation, and the presence of foci of conventional fibrous histiocytoma; since this lesion is in a lymph node, the absence of any other bone location as clinically evaluated could exclude the possibility of a metastasis from an underlying bone tumor.
H. Telangiectatic osteosarcoma (both as a soft tissue primary and metastasis): the absence of cytologic anaplasia, the absence of osteoid formation, the good circumscription of the lesion herein presented.
I. Leiomyosarcoma with osteoclast-like giant cells: key points are the absence of any fascicular arrangements of spindle tumor cells; the prominence of cystic bloody cavities, the lack of expression of smooth muscle markers (mostly desmin).
L. Angiomatoid fibrous histiocytoma of soft tissue (formerly called malignant fibrous histiocytoma, angiomatoid type): this was the most challenging differential diagnosis, in that several features are shared in common between this entity and the lesion under discussion. Key points are the prominent multinucleation, cholesterol clefts, the true nodal location (instead of chronic inflallatory peripheral infiltrates), and mostly important the focal evidence of conventional fibrous histiocytoma.

FOLLOW-UP
About 3 months following diagnosis (in September 2004), a total ipsilateral neck lymph node dissection was performed, with removal of 21 nodes from anatomic-surgical levels I-IV. Level IIB was the site of a residual 1-cm sized tumor nodule with aneurysmal features, which may represent either a lymph node totally replaced by tumor or a direct seeding into perinodal soft tissue. Level IV was the site of soft tissues involvement in form of interstitial permeation. Focal perimysial infiltration of skeletal muscle was also observed.
In April 2005, at a 10-month clinical follow-up the patient is alive and free of disease. The primary site on the scalp has been free of tumor since 1996, when the only true local recurrence was excised.

DISCUSSION
Benign fibrous histiocytoma of the skin, usually synonymic with dermatofibroma, is definitely the most common mesenchymal tumor of the skin. Probably it represents the tumor with the largest spectrum of variants and subtypes (1,2). Most often it is completely located in the dermis, although a deep penetrating variant has been recognized (3). Subcutaneous and deep variants are also on record (4). Benign fibrous histiocytoma almost always pursues a benign course, even though it rarely may locally recur (recurrence rate, <1-2%) (1). A higher rate of recurrence is universally accepted for special variants, such as the cellular (5), the aneurysmal (6), and the atypical (pseudosarcomatous) (7,8,9). The subcutaneous and deep type also show a higher rate of recurrence in comparison to the conventional cutaneous type (4). For sake of clarity we wish to specify here that the term atypical fibrous histiocytoma in this context has also been used alternatively by some other authors to designate both cellular and subcutaneous/deep (benign) fibrous histiocytomas together (10), without reference to cytologic pleomorphism and aberration.

Metastases from benign cutaneous fibrous histiocytoma were unheard of until 1996, when the first report of two cases was published of such an occurrence by Colome-Grimmer and Evans (11), which also prompted TV Colby to bring to light two other similar cases described as "*multiple cystic fibrohistiocytic tumors of the lung*" with mural "*cellular proliferation .... identical to that in benign cutaneous fibrous histiocytomas*" (12,13). Actually with regard to one of the cases, the correct interpretation of metastatic dermatofibroma subsquently became apparent after publication when it was revealed that the patient had a past medical history of repeated excisions of benign cutaneous fibrous histiocytomas (13).

To date a total of only 9 cases of metastasizing benign cutaneous fibrous histiocytoma have been reported in the literature (14-16). Another dubious case is on record, in which it was difficult to determine whether the lymph node involvement resulted from direct infiltration from recurrent tumor in the perinodal soft tissue or represents lymphatic metastasis. To these few cases can be added the case under discussion along with another one recently contributed to the AMR club by Carlos Bacchi from Brazil (17) , for a grand total of 11. Actually one more possible case is mentioned in the literature (6), concerning a metastatic nodule in the lung with the microscopic appearance of cellular dermatofibroma in a patient with a past medical history of excision of dermatofibrosarcoma protuberans in the shoulder (the slides of the latter were not reviewed by the author, but this case is excluded from the statistics herein detailed.

The patients' age ranged from 18 to 65 years, with 10 cases out of 11 between 18 and 45 years (in one case the age was 65). The only pediatric case is the present case. The male to female sex ratio is 8:2 (sex not stated in one case). The anatomic location of the primary tumor was the thigh in three cases (11,14), the back (12,15) and neck in two cases each (11,14), and the scalp (present case) and knee (17) each in one case. The primary site remained unknown in one case (12) and in the last case it was not specified (either the back or neck or thigh) (16). The size of the lesions in the six cases in which the information is made available ranged from 1.3 cm (case 1 in Guillou et al's series [14] and Bacchi's case [17]) to 5 cm (De Hertog et al's case[15]). Metastases occurred in ipsilateral regional lymph nodes (6,14,17, and present case) or in the lung (11,12,15). In one case both lymph node and lung metastases were noted (case 2 of Colome-Grimmer and Evans [11]) and in another case disseminated metastatic deposits were documented in the skin, regional lymph nodes, abdominal organs (colon) and lungs (one of the two metastasizing cases –case 26 of a series of 59 described by Kaddu et al [16]: case 28 - which was also included in the same series and which also gave rise to (lung) metastasis- in our review is quoted as De Hertog et al's case, who first published it with details [15], and qualified it as of cellular form). Multiple lymph node metastases from the same regional site were documented in 4 cases (case 2 of Colome Grimmer and Evans [11], case 1 and 3 of Guillou et al [13], and the present case). Lung metastases were always multiple and located in multiple lobes, both unilaterally and bilaterally (11,12).

Metastases usually occurred following one to multiple local recurrences within a time interval of a few to several years (2-7 years in the published cases [11-16]; 4 years in Bacchi's case [17], and 9 years in the present case). In two cases metastases occurred in absence of local recurrence (case 2 of the series of Guillou et al [14] , and the case of De Hertog et al [15]), presenting in one after a four months' interval (14) and after a two-years interval in the other (15).

The microscopical features of the primaries of these cases of metastasizing "benign" cutaneous fibrous histiocytomas were those of the cellular variant in five (Colome-Grimmer and Evans cases [11], case 2 and 3 of Guillou et al [14], De Hertog et al's case [15]), and those of a combined aneurysmal/atypical (pseudosarcomatous) variant in one case (case 1 of Guillou et al [14]) and those of a pure atypical (pseudosarcomatous) variant in another one (16). Primary tumors were always located in the dermis with only focal invasion of subcutis (14,15).

The histological features of metastases were usually similar to those of the primary tumors. In the case herein presented -as above stated- the histological features were those of the cellular subtype in the primary. which transformed into aneurysmal in the recurrence and in the metastasis. Changes from conventional type to aneurysmal type in the recurrence was already documented as it on record in the dubious case (6), in which the tumor subtype -while being of

conventional type in the primary- was aneurysmal in the recurrence. Even the reverse phenomenon of transformation of an aneurysmal case into the conventional form is also on record in a non-metastasizing case (6). However, conventional features also were partly retained in the case herein presented and this was seen in the interstitial perinodal soft tissue. In Bacchi's case (17) the histology was conventional in the primary and cellular in the nodal metastasis. Thus it seems that the cellular, aneurysmal and atypical (pseudosarcomatous) are the main histological variants at risk of giving rise to metastasis, even though in the first two reported cases of Joseph and Colby (12,13) the histology of the secondary lesions in the lung (12) was described as "identical to that of benign cutaneous fibrous histiocytomas", but the histology of the primaries was not specified.

Mitotic activity in the primary tumors of the cases in which (9 out of 11) the information is available was variable ranging from 3-5 to 10-15 mitoses per 10 HPF. Occasional increase of the mitotic index is on record only in recurrences (case 2 of Colome-Grimmer [11]. No significant increase of mitotic activity has been noted from primary to metastasis (in one case –case 3 of Guillou et al [14]- it was noticed the contrary). Necrosis was not documented in metastases, not even in those 3 cellular cases in which it was already observed in the primaries (14, and present case).

The differential diagnosis of primary tumors as well as of their local recurrences has been treated elsewhere in the original publications of the variants of (benign) cutaneous fibrous histiocytoma more often involved with such unusual biological behaviour, which we have already quoted here, but the reader can easily consult good standard textbooks of dermatopathology and surgical pathology. The differential diagnosis of a lymph node metastasis showing aneurysmal features has been previously discussed in the case presentation section. As to the differential diagnosis concerning lymph node or lung metastasis from an atypical (pseudosarcomatous) fibrous histiocytoma, the reader is again referred to seminal papers which primarily described this tumor type (refs already quoted). Finally all the conditions entering the differential diagnosis in a case of lung metastasis exhibiting cellular fibrous histiocytoma features with an architectural cystic pattern are listed and discussed in the original paper by Joseph and Colby (12), which one should refer to.

In the majority of cases the clinical course was indolent with patients alive with evidence of lymph node (14) or lung metastases (case 2 of Joseph and Colby [12]; and ref. 13) after 13 and 20 years, respectively. In two cases (15,16) the clinical outcome was aggressive, with the former showing clinical disease progression under chemotherapy and the latter exhibiting disseminated spread of disease with death 96 months after excision of the skin primary.

Thus (benign) metastasizing fibrous histiocytoma of the skin is a recently well-established tumor condition, which broadens the group of tumors that can show metastatic behaviour even though there was no way to predict this from the appearances of the original lesion (these could be named "clinically-based retrospectively diagnostic" low grade malignant tumors), the most renowned examples being first the so-called benign metastasizing leiomyoma of the uterus (18) and second the metastasizing benign mixed tumors of the salivary glands (19), without mentioning the issue of metastasizing (benign) Spitz nevus, and others.

The recognition of such an occurrence would be the starting-point for a hot debate, concerning the best name to give the metastatic lesion in general in this context as well as how these primary tumors are to be called and considered. At this regard I wish to quote -by partly paraphrasing Rosai's sentence on his view with regards to the analogous issue on benign metastasizing leiomyoma of the uterus (20)- and say "a*s to whether such a very rare occurrence should be called [metastasizing benign cutaneous fibrous histiocytomas or low grade fibrohistiocytic sarcomas of the skin] depends on whether one wishes to designate tumors according to their morphology (in which case it would be [a benign fibrous histiocytoma]) or their behaviour (in which case it would be [a fibrohistiocytic sarcoma])* (20).

The current WHO (21) classification of soft tissue tumors runs as follows *"... it is recommended to divide soft tissue tumors into the following four categories: benign, intermediate (locally aggressive), intermediate (rarely metastatizing) and malignant"*. Concerning the category of

benign tumors one can read the following statements *"most benign soft tissue tumours do not recur locally. Those that do recur do so in a non-destructive fashion and are almost always readily cured by complete local excision. Exceedingly rarely (almost certainly >1/50,000 cases, and probably much less than that) a morhologically benign lesion may give rise to distant metastases. This is entirely unpredictable on the basis of conventional histological examination and, to date, has been best documented in cutaneous benign fibrous histiocytoma."*

Analogously it was written three decades previously elsewhere with regards to metastasizing mixed tumor that *"... there is scarcely a tumor so benign that metastasis has never been reported; such isolated instances must be overlooked if the useful practical distinction between benign and malignant tumors is to be retained. Also in such cases, the situation is more analogous to transplantation than metastasis, because the progressive course to death which characterizes malignancy is not a part of the picture"* (22).

The so-called benign metastasizing leiomyoma of the uterus and metastasizing benign mixed tumor of salivary glands are very low grade malignant tumors (metastasis appearing many years after the occurrence of the primaries, up to more than 20 in the former [18] and up to 52 in the latter [19]) as it seems also the case for this new entity of benign metastasizing cutaneous fibrous histiocytoma.

Since we do not have up to the moment any means to predict the biological behaviour of these tumors, it seems unavoidable (if not logical) to continue to call the primary benign until the contrary is proven or until no evidence of metastasis is found. In fact again quoting Rosai *"we simply have to accept the fact that tumors do not need to have the conventional morphologic attributes of malignancy to be able to metastasize"* (20).

Notwithstanding, although it would appear logical to reverse the diagnosis of benign to malignant at the appearance of metastasis (as it is occasionally the case when -based on available morphological criteria- the correct diagnosis is overlooked or misinterpreted), it is desirable that the word "benign" be dropped in the diagnostic report of the metastatic event for clinical usage and publications and that the term dermatofibroma (implying benignancy) as well be supplanted by the unspecified one of fibrous histiocytoma in order to avoid conflicts.

Although there was (and probably still is) some controversy about whether benign cutaneous fibrous histiocytoma (dermatofibroma) is a reactive or neoplastic process (23,24), the evidence of clonality (25) and the metastasizing potential in combination (even though the latter is in essence exceedingly minimal) point not only strongly to the neoplastic nature of this proliferative mesenchymal lesion in general, but sadly allows the recognition retrospectively of the possibility of malignant behaviour in a subset of lesions previously diagnosed as benign.

Consequently it is recommended that benign fibrous histiocytoma be completely excised with clear margins, especially in case of recurrence. Surgery is the therapeutic means of choice. Regional lymph node metastasis is best treated by total lymph node dissection of the entire anatomical site, since multiple nodes are commonly affected in rare .cases. Systemic metastasis (usually to the lung) also is best treated by means of surgery when feasible (11,12). Chemotherapy and radiotherapy has also been employed (11,15,16), but the experience experience is very limited.

REFERENCES

1. Calonje E and Fletcher CDM. *Cutaneous fibrohistiocytic tumors: an update*. Adv Anat Pathol 1994;1:2-15.
2. M. Bisceglia, C. Fisher, S. Suster, D.V. Kazakov, K. Cooper, M. Michal. *Tumoral, quasitumoral and pseudotumoral lesions of the superficial and somatic soft tissue: new entities and new variants of old entities recorded during the last 25 years. Part II: The review and a list*. Pathologica 2004; 96:52-94.
3. Kamino H, Jacobson H. *Dermatofibroma extending into the subcutaneous tissue*. Am J Surg Pathol 1990;14:1156-1164.
4. Fletcher CDM. *Benign fibrous histiocytoma of subcutaneous and deep soft tissue: a clinicopathologic analysis of 21 cases*. Am J Surg Pathol 1990;14:801-809.

5. Calonje E, Mentzel T, and Fletcher CDM. *Cellular benign fibrous histiocytoma. Clinicopathologic analysis of 74 cases of a distinctive variant of cutaneous fibrous histiocytoma with frequent recurence*. Am J Surg Pathol 1994;18:668-676.
6. Calonje E, Fletcher CD. *Aneurysmal benign cutaneous fibrous histiocytoma: clinico-pathologic ananlysis of a tumor frequently misdiagnosed as a vascular lesion*. Histopathology 1995;26:323-331.
7. Fukamizu H, Oku T, Inoue K, Matsumoto K, Okayama H, Tagami H. *Atypical ("pseudosarcomatous") cutaneous histiocytoma*. J Cutan Pathol 1983;10:327-333.
8. Leyva WH, Santa Cruz DJ. *Atypical cutaneous fibrous histiocytoma*. Am J Dermatopathol 1986;8:467-471.
9. Beham A, Fletcher CDM. Atypical *"pseudosarcomatous" variant of cutaneous benign fibrous histiocytoma: report of eight cases*. Histopathology 1990;17:167-169.
10. Marrogi AJ, Dehner LP, Coffin CM, Wick MR. *Atypical fibrous histiocytoma of the skin and subcutis in childhood and adolescence*. J Cutan Pathol 1992;19:268-277.
11. Colome-Grimmer MI, Evans HL. *Metastasizing cellular dermatofibroma. A report of two cases*. Am J Surg Pathol 1996;20:1361-1367.
12. Joseph M, Colby TV, Swensen SJ, Mikus JP, Gaensler EA. *Multiple cystic fibrohistiocytic tumors of the lung: report of two cases*. Mayo Clin Proc 1990;65:192-197.
13. Colby TV. *Metastasizing dermatofibroma*. Am J Surg Pathol 1997;21:976.
14. Guillou L, Gebhard S, Salmeron M, Coindre JM. *Metastasizing fibrous histiocytoma of the skin: a clinicopathologic and immunohistochemical analysis of three cases*. Mod Pathol 2000;13:654-660.
15. De Hertogh G, Bergmans G, Molderez C, Sciot R. *Cutaneous cellular fibrous histiocytoma metastasizing to the lungs*. Histopathology 2002;41:82-88.
16. Kaddu S, McMenamin ME, and Fletcher CDM. *Atypical fibrous histiocytoma of the skin. Clinicopathologic analysis of 59 cases with evidence of infrequent metastasis*. Am J Surg Pathol 2002;26:35-46.
17. Bacchi C. *AMR Slide Seminar N.45, Case 2*. January 2005: p-6-7.
18. Kayser K, Zink S, Schenider T, Dienemann H, André S, Kaltner H, et al. *Benign metastasizing leiomyoma of the uteurs: documenation of clinical, immunohistochemicla and lectin-histochemical data of ten cases*. Vircows Arch 2000;437:284-292.
19. Wenig B, Hitchcock CL, Ellis GL, and Gnepp DR. *Metastasizing mixed tumors of salivary glands. A clinicopathologic and flow cytometric analysis*. Am J Surg Pathol 1992;16:845-858.
20. Rosai J. Rosai and Ackerman's Surgical Pathology. Ninth edition. St. Louis, Mosby, 2004.
21. Fletcher CDM, Unni KK, Mertens F. *World Health Organization Classification of Tumors. Tumors of soft tissue and bone*. Lyon: IARC Pres, 2003
22. Thackray AC, Lucas RB. *Tumors of the Major Salivary Glands. Atlas of Tumor Pathology.* Second Series: Fascicle 10. AFIP, Washington D.C., 1974
23. Zelger BG, Zelger B. *Dermatofibroma (fibrous histiocytoma): an inflammatory or neoplastic disorder?* Histopathology 2001;38:379-381.
24. Calonje E. *Dermatofibroma (fibrous histiocytoma): an inflammatory or neoplastic disorder?* Histopathology 2001;39:213.
25. Vanni R, Fletcher CDM, Sciot R, et al. *Cytogenetic evidence of clonality in cutaneous benign fibrous histiocytomas: a report of the CHAMP Study Group*. Histopathology 2000; 37:212-217.

AMR SEMINAR #46
CASE 4

Contributed by: Ira Bleiweiss, MD

History: 51-year-old woman with a suspicious right breast lump discovered mammographically (see attached photo). She underwent lumpectomy.

Diagnosis: Invasive adenosquamous carcinoma (low grade metaplastic carcinoma).

Comment: This case was sent to me by Dr. Bella Maly at Hadassah Medical Center in Jerusalem. The mammogram is certainly scary looking with a large, very dense stellate tumor that should be an invasive carcinoma. The slides, however, are surprising in that there are areas that look like radial scar, but other foci of small glands directly invade adipose tissue. The invasive pattern is like invasive lobular, but the cytology is not. Focally, hopefully in all of your slides, the tumor shows squamous differentiation which is the key to the diagnosis. A P-63 stain was performed (see attached pictures) to rule in or out invasion (depending on your perspective) which turned out to be blazingly positive in all the cells - glandular and squamous. Dr. Rosen described this entity some years ago, and, seeing about 1000 breast cancers a year as I do, I must say that I'd begun to doubt the existence of this entity.....until now. Dr. Rosen was correct as classifying this as a metaplastic carcinoma. Recently P-63 has been shown to be positive in the more typical high grade metaplastic carcinomas, implying myoepithelial derivation. Thus the positivity here as well. This is a very rare tumor, and patients with it typically do well. Thus I recommended re-excision to achieve negative margins and sentinel node biopsy, the results of which I don't know.

Reference: Rosen PP, Ernsberger D, Low-grade adenosquamous carcinoma. A variant of metaplastic mammary carcinoma. Am J Surg Pathol 1987;11(5):351-8.

AMR SEMINAR #46
CASE 5

Contributed by: John Chan, MD (Case number: 04AH16733)

History: A 32-year-old man presented with nasal septum perforation. The clinical diagnosis was Wegener granulomatosis versus lymphoma. A biopsy of the nasal septum was performed.

Diagnosis: Cocaine-induced osteocartilaginous necrosis and mucosal ulceration/inflammation

Comment: The biopsy from the nasal septum shows ulceration and inflammation. The septal cartilage shows necrosis and inflammatory cell infiltration. Definite features of Wegener granulomatosis and NK/T cell lymphoma are lacking. Given the young age of the patient, the clinical presentation with nasal septum perforation, and the presence of cartilage necrosis, the possibility of cocaine abuse was raised. Indeed, on specific questioning, the patient admitted to drug abuse including use of cocaine.

The pathologic features of cocaine abuse are rather non-specific, but this diagnosis should be suspected in the appropriate clinical setting, especially when the biopsy fails to yield more specific diagnoses (such as Wegener granulomatosis or lymphoma). Cocaine induces vascular damage and vascular construction and thus can lead to necrosis of various tissues (including cartilage). In a mucosal site, the tissue necrosis leads to ulceration and superimposed inflammation/infection.

Cocaine abuse should always be suspected for unexplained infarction/hemorrhage occurring in young patients. I have previously seen a brain biopsy from a lawyer (CT scan of brain showed rapidly progressive, extensive and large lesions, most prominent in the frontal lobes): there was prominent hemorrhage, necrosis and chronic inflammatory cell infiltration. The lymphoid infiltrate was so striking that the possibility of lymphoma was raised by some pathologists. Eventually it turned out that the lawyer had taken a huge intranasal dose of cocaine some time before the presentation. So don't be fooled by the patient's occupation.

AMR SEMINAR #46
CASE 6

Contributed by: Thomas V. Colby, MD

History: A 49-year-old healthy woman was found to have lesions in the left lung on routine exam. CT scan demonstrated a 3.0 cm diameter mass in the apex of the left lower near the hilum and two lesions in the upper lobe, 1.2 and 1.1 cm in diameter. PET scan demonstrated several foci of uptake in the left lung. CT-guided biopsy of the largest mass was performed and a generic diagnosis of "tumor of mesenchymal origin with a wide differential diagnosis" was made. The patient underwent wedge resection of all the lesions. Wedge resection of the upper lobe nodule showed a 1.5 cm diameter moderately differentiated papillary adenocarcinoma without pleural or vascular invasion. Margins of resection of the wedge were negative. The two other wedge resections showed two separate foci of tumor, 2.0 cm and 1.3 cm in diameter, as well as at least two separate microscopic foci with identical histology. One of these nodules is on the slides sent to the AMR society.

Diagnosis: Metastatic (benign) meningioma. The tumor is positive for EMA, and negative for smooth muscle actin, MNF116, CD34, desmin, cytokeratin, chromogranin, and ER. It is diffusely positive for EMA and vimentin. Ki-67 shows occasional scattered positive cells. PR is positive in approximately one-third of the cells.

Radiologic follow-up confirmed the presence of a large asymptomatic intracranial lesion characteristic of meningioma.

Comment: The histology and the immunohistochemistry are straightforward in this case. These cases may be diagnostic challenges because of the unusual site of presentation. I include this case for the group as another case in the theme of "benign" tumors that may metastasize to the lung.

Primary meningiomas of the lung are uncommon but relatively well described and histologically are identical to meningiomas in the CNS. Most are considered benign. Whether or not they arise from minute pulmonary meningothelial-like nodules (MPMN) is a matter or debate and some suggest that might be the case. In a recent paper by Ionescu et al. it was shown that isolated MPMN lacked mutational damage consistent with a reactive origin, whereas in cases with multiple MPMNs there was increased LOH suggesting a transition between a reactive and a neoplastic proliferation. These authors suggested that MPMNs were different from meningiomas based on their major molecular genetic features.

The fact that reported primary meningiomas of the lung tend to be solitary masses and that an association with multiple MPMNs is only rarely described also suggests these may be separate lesions. MPMNs rarely get larger than 0.3 cm in size and are rarely visible radiologically. If one encounters larger lesions in the setting of multiple nodules radiologically the possibility of metastatic meningioma from the CNS would need to be considered.

While the relationship between MPMN and primary pulmonary meningiomas remains to be fully clarified, it is important to separate metastatic meningioma from MPMN and primary meningiomas. There are also histologic clues in identifying metastatic meningioma. Of the four or five cases that I have seen, all are multiple and all have shown lymphangitic involvement away

from the larger nodules and indeed in the case presented the microscopic nodules that were identified showed lymphangitic involvement (see Figure on website). MPMN are nearly always associated with a pulmonary vein and not associated with airways. Metastatic meningioma with lymphangitic involvement, as shown in the Figure on the website, may show involvement along bronchovascular bundles. This pattern of involvement would virtually exclude MPMN.

References

Celli P, Palma L, Domenicucci M, Scarpinati M. Histologically benign recurrent meningioma metastasizing to the parotid gland: case report and review of the literature. Neurosurgery. 1992 Dec;31(6):1113-6; discussion 1116. Review.

Cerda-Nicolas M, Lopez-Gines C, Perez-Bacete M, Roldan P, Talamantes F, Barbera J. Histologically benign metastatic meningioma: morphological and cytogenetic study. Case report. J Neurosurg. 2003 Jan;98(1):194-8.

Falleni M, Roz E, Dessy E, Del Curto B, Braidotti P, Gianelli U, Pietra GG. Primary intrathoracic meningioma: histopathological, immunohistochemical and ultrastructural study of two cases. Virchows Arch. 2001 Aug;439(2):196-200.

Flynn SD, Yousem SA. Pulmonary meningiomas: a report of two cases. Hum Pathol. 1991 May;22(5):469-74.

Gaffey MJ, Mills SE, Askin FB. Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol. 1988 Mar;12(3):167-75.

Ionescu DN, Sasatomi E, Aldeeb D, Omalu BI, Finkelstein SD, Swalsky PA, Yousem SA. Pulmonary meningothelial-like nodules: a genotypic comparison with meningiomas. Am J Surg Pathol. 2004 Feb;28(2):207-14.

Kaleem Z, Fitzpatrick MM, Ritter JH. Primary pulmonary meningioma. Report of a case and review of the literature. Arch Pathol Lab Med. 1997 Jun;121(6):631-6. Review.

Kaminski JM, Movsas B, King E, Yang C, Kronz JD, Alli PM, Williams J, Brem H. Metastatic meningioma to the lung with multiple pleural metastases. Am J Clin Oncol. 2001 Dec;24(6):579-82.

Knoop M, Sola S, Hebecker R, Mann S, Bauer HG, Schmidt W. Rare pulmonary manifestation of an intracranial meningothelial meningioma. Dtsch Med Wochenschr. 2004 Sep 3;129(36):1854-7. German.

Kodama K, Doi O, Higashiyama M, Horai T, Tateishi R, Nakagawa H. Primary and metastatic pulmonary meningioma. Cancer. 1991 Mar 1;67(5):1412-7.

Kuroki M, Nakata H, Masuda T, Hashiguchi N, Tamura S, Nabeshima K, Matsuzaki Y, Onitsuka T. Minute pulmonary meningothelial-like nodules: high-resolution computed tomography and pathologic correlations. J Thorac Imaging. 2002 Jul;17(3):227-9.

Lockett L, Chiang V, Scully N. Primary pulmonary meningioma: report of a case and review of the literature. Am J Surg Pathol. 1997 Apr;21(4):453-60. Review.

Miller DC, Ojemann RG, Proppe KH, McGinnis BD, Grillo HC. Benign metastasizing meningioma. Case report. J Neurosurg. 1985 May;62(5):763-6.

Murrah CP, Ferguson ER, Jennelle RL, Guthrie BL, Holman WL. Resection of multiple pulmonary metastases from a recurrent intracranial meningioma. Ann Thorac Surg. 1996 Jun;61(6):1823-4.

Ng TH, Wong MP, Chan KW. Benign metastasizing meningioma. Clin Neurol Neurosurg. 1990;92(2):152-4.

Niho S, Yokose T, Nishiwaki Y, Mukai K. Immunohistochemical and clonal analysis of minute pulmonary meningothelial-like nodules. Hum Pathol. 1999 Apr;30(4):425-9.

Pramesh CS, Saklani AP, Pantvaidya GH, Heroor AA, Naresh KN, Sharma S, Deshpande RK. Benign metastasizing meningioma. Jpn J Clin Oncol. 2003 Feb;33(2):86-8.

Sellami D, Gotway MB, Hanks DK, Webb WR. Minute pulmonary meningothelial-like nodules: thin-section CT appearance. J Comput Assist Tomogr. 2001 Mar-Apr;25(2):311-3.

Som PM, Sacher M, Strenger SW, Biller HF, Malis LI. "Benign" metastasizing meningiomas. AJNR Am J Neuroradiol. 1987 Jan-Feb;8(1):127-30.

Spinelli M, Claren R, Colombi R, Sironi M. Primary pulmonary meningioma may arise from meningothelial-like nodules. Adv Clin Path. 2000 Jan;4(1):35-9.
Strimlan CV, Golembiewski RS, Celko DA, Fino GJ. Primary pulmonary meningioma. Surg Neurol. 1988 May;29(5):410-3. 1:
Suster S, Moran CA. Unusual manifestations of metastatic tumors to the lungs. Semin Diagn Pathol. 1995 May;12(2):193-206. Review.

AMR SEMINAR #46
CASE 7

Contributed by: Giovanni Falconieri, MD

History: This is a 60 year-old man with history of nodular melanoma (pT3) of the back 3 years before who notices a swelling lump in the anterior aspect of the chest wall. The resected mass measures 4 x 3 cm and has a soft, vaguely fascicular cut surface growing within the subcutaneous tissue. Microscopically, there are numerous spindle and epithelioid malignant cells strongly +ve for S100 protein (both nuclear and cytoplasmic staining) and negative for all other markers including keratins, desmin, actins, HMB45, melan-A. Vimentin is positive as well. Multinucleated cells are unevenly scattered within the background and show only complementary immunopositivity for CD68.

Diagnosis: Recurrent melanoma associated with (focal) osteoclast-like multinucleated giant cell reaction.

Comment: Osteoclast-like reaction associated to melanoma is apparently an underreported subject. Has anybody seen something like this? And more: would you offer alternative microscopic interpretation, regardless of the melanoma history?

References

Denton KJ et al. Histopathology 1992; 20: 179-181
Daroca PJ et al Hum Pathol 1990; 21: 978-80

AMR SEMINAR #46
CASE 8

Contributed by: Andrew L. Folpe, MD

History: A 38-year old-man with a history of a superficially invasive left calf melanoma presented with an enlarged inguinal lymph node, clinically felt to represent metastatic disease. A darkly pigmented 3 cm lymph node was excised.

Microscopic description: Sections showed a lymph node that was near-totally replaced by a cellular spindle cell proliferation. The neoplastic cells were arrayed about a thick-walled vasculature, and grew in long fascicles. Abundant pigment, showing microscopic features of hemosiderin, rather than melanin, was present, as was variable stromal hyalinization and focal calcification. A distinctive feature was presence of numerous mats of brightly eosinophilic collagen, so-called "amianthoid fibers". The neoplastic cells were normochromatic and for the most part mitotically inactive.

Immunohistochemical results: The tumor was strongly smooth muscle actin-positive and S100 protein-negative.

Diagnosis: Intranodal palisaded myofibroblastoma.

Discussion: This is (I think) a really nice example of this very rare benign lesion, also known as "intranodal hemorrhagic spindle cell tumor with "amianthoid" fibers [1, 2]. Roughly 20 cases of this distinctive benign tumor of lymph nodes have been reported since the simultaneous description of this entity by Suster and Rosai, and Weiss and colleagues. Although the referring pathologist was concerned about a metastatic melanoma, the unique histology of this tumor, as well as the absence of melanin pigment and nuclear atypism point rather strongly away from this possibility. Actually, these tumors most closely resemble a schwannoma, and these were in fact coded as unusual "intranodal schwannomas" by Sharon Weiss, prior to the advent of actin immunohistochemistry.

References:

1. Suster, S. and J. Rosai, *Intranodal hemorrhagic spindle-cell tumor with "amianthoid" fibers. Report of six cases of a distinctive mesenchymal neoplasm of the inguinal region that simulates Kaposi's sarcoma.* American Journal of Surgical Pathology, 1989. **13**(5): p. 347-57.
2. Weiss, S.W., D.R. Gnepp, and G.L. Bratthauer, *Palisaded myofibroblastoma. A benign mesenchymal tumor of lymph node.* American Journal of Surgical Pathology, 1989. **13**(5): p. 341-6.

AMR SEMINAR #46
CASE 9

Contributed by: Masaharu Fukunaga, MD (04-K-1468□#12)

History: A 60-year-old man presented in October 1989 with a several month history of an elevated skin lesion measuring 1 cm in base of the second toe of the sole of the left foot. Biospy, a wide excision and a skin graft were performed. The tumor recurred in September 2003 and the patient underwent an amputation of the distal half of the left foot in February 2004. Physical examinations and a computed tomography scan revealed no other primary site and showed no metastatic lesions. No lymphoadenopathy was found. The patient has been well without disease for 10 months after the amputation. The distributed slide is taken from the recurrent tumor.

Pathology: The recurrent tumor measuring 7.5 X 6 X 3cm was macroscopically characterized by a lobular growth with poorly circumscribed margins. The lesion was situated in the dermis, subcutis and skeletal muscles of the base of the second toe and the overlying epidermis showed erosion (**photo 1**). Microscopically, the tumor consisted of predominantly lobulated chondroid tissue with atypical cells. The cellularity was higher in the periphery of the lobules. The tumor cells had hyperchromatic vesicular nuclei with prominent nucleoli and amphophilic cytoplasm and lacunar formations were prominent. There were no melanin pigments in the tumor cells and Fontana Masson stain was negative. Cellular atypia was moderate to severe and the mitotic activity was 15 per 10 high-power fields. The stroma was chondroid with focal ossification and hyalinization. Small nests and trabecular arrangements of epithelioid cell with vesicular nuclei and prominent nucleoli were also observed. The epidermis exhibited erosion.

Immunohistochemistry: vimentin, S-100, alpha-smooth muscle actin, EMA, GFAP, HMB45: (+). MNF116, CAM5.2, HHF35, Melan A, calponin: (-).

The wide excision of **the primary tumor** revealed nests of tumor cells and single tumor cells in the epidermis and papillary dermis. The tumor cells had hyperchromatic oval or spindle-shaped nuclei with prominent nucleoli and pale to pale eosinophilic cytoplasm (**photo 2**). They were positive for Fontana-Masson stain. Cellular atypia was moderate and the mitotic activity was 11 per 10 high power fields. The lesion measuring 10X 8mm was diagnosed as malignant melanoma, Clark level II. There were 10mm free margins.

Diagnosis: Osteogenic melanoma

Comments: Osteogenic melanoma or malignant melanoma with osteocartilaginous differentiation is a very rare variant of malignant melanoma. Since the first description of bone formation in a recurrent melanoma by Urmacher (11) in 1984, only 19 cases have been reported (1-12). Ten cases of the previously reported ones have occurred in acral lentiginous malignant melanomas (1, 3-6, 12).

The present case was clinically and pathologically a typical osteogenic melanoma. The chondroblastic osteosarcoma-like lesion was found at the second recurrence 16 years after the excision of the initial cutaneous malignant melanoma of the left sole. It is very interesting that no convention melanoma was found in the amputation materials of the recurrence. Histologically, the recurrent tumor resembled extraskeletal osteosarcoma, chondroblastic type. Particular features of the current tumor included the presence of epithelioid cells, a lobular pattern, the absence of melanin and the positive immunostaining of HMB45.

The differential diagnoses include extraskeletal osteosarcoma, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, bizarre parosteal osteocartilaginous proliferation and malignant myoepithelioma (malignant mixed tumor). Although the present case was histologically very similar to extraskeletal osteosarcoma, its possibility can be ruled out because of the history of the malignant melanoma in the region and the positive immunostaining for HMB45. Since extraskeletal myxoid chondrosarcoma lacks true "cartilaginous" differentiation, it can be excluded. Mesenchymal chondrosarcoma can be excluded because the present tumor lacked solid proliferations of small undifferentiated round cells with hemangiopericytomatous vascular vessels and interspersed islands of cartilage. Bizarre parosteal osteocartilaginous proliferation shows a zonal maturation form fibroblastic areas through woven bone or chondro-osteoid matrix, and finally to mature lamellar bone (14). The maturation could not been observed in this tumor. The current tumor was light-microscopically and immunohistochemically very similar to malignant myoepithelioma with chondrosarcomatous features (15-17) and in fact my light microscopic impression without history was malignant myoepithelioma. The positivity for vimentin, S-100 protein, alpha-smooth muscle actin, pan keratin, EMA and GFAP was compatible with myoepithelioma, but the negativity for calponin and the positivity for HMB were unusual for it (15-17). The primary lesion of the classic cutaneous malignant melanoma was against malignant myoepithelioma.

It is also clinically important to distinguish osteogenic melanoma from osteosarcoma. The optical surgical treatment for malignant melanoma, unlike for osteosarcoma, should include a wide margin of skin and regional lymph node dissection. It is often recommended in clinically suspicious cases (1). Osteosarcoma rarely metastasizes to regional lymph nodes. While osteosarcoma can often be successfully treated with chemotherapy, malignant melanoma is less sensitive (1).

The histogenesis of osteogenic melanoma has been controversial. One theory is that osteo-cartilaginous formation represents a reparative response to injury, as there are reports of patients who had prior surgical trauma to nonosteogenic lesions (3, 5, 7). Another theory is that the invading melanoma cells could have induced a pseudosarcomatous proliferation of the adjacent connective tissue stroma with subsequent ossification (17). The theories of reactive osteogenesis can be ruled out because osteogenic melanomas show malignant appearance of the osteogenic cells in direct contact with osteoid or cartilaginous matrix and the positive staining for S-100 protein and HMB45 (1). The presence of osteogenesis in metastatic lesions was against the reactive process (1, 3, 8). The present case supports the theory of mesenchymal metaplasia by melanoma cells themselves (1, 3). From et al. (18) observed direct intracellular production of collagen fibers by desmoplastic melanoma cells with electron microscopy, indicating the capability of mesenchymal differentiation by melanoma cells. Nine cases of the previously reported cases have occurred in acral lentiginous malignant melanomas (1, 3-6, 12). The present patient, who had two wide excisions, was the third example arising in the sole of the foot (1, 6). The surgical procedures could somewhat induce the transformation of melanoma cells into osteocartilaginous cells as described previously (3, 7, 11).

Because of the paucity of reported cases of osteogenic melanoma, its prognosis and pathogenesis of the osteocartilaginous elements remains unclear. Several previous cases, as pointed by Lucas et al. (1), have behaved as conventional melanoma. As in conventional cutaneous melanomas, staging based on depth of invasion and evaluating regional lymph node status seems to be important to date.

References

1. Lucas DR, et al. Osteogenic melanoma. A rare variant of malignant melanoma. Am J Surg Pathol 1991; 17:400-9.

2. Banerjee SS ,et al.J. Diagnostic lessons of mucosal melanoma with osteocartilaginous differentiation. Histopathology 1998; 33:255-60.
3. Brisigotti M, et al. Malignant melanoma with osteocartilaginous differentiation. Surg Pathol 1989; 2:73-8.
4. Toda S, et al. Osteogenic melanoma: stromal metaplasia in association with subungual melanoma. Histopathology 1997:31:293-5.
5. Pellegrini AE, et al.. Malignant melanoma with osteoid formation. Am J Dermatopathol 1990; 12:607-11.
6. Nakagawa H, et al. Osteosarcomatous changes in malignant melanoma: immunohistochemical and ultrastructural studies of a case. Am J Dermatopathol 1990; 12:162-8.
7. Gunwald MH, et al.. Metastatic malignant melanoma with cartilaginous metaplasia. Dermatologica 1985; 170:249-52.
8. Hoorweg JJ, et al. Osteoid and bone formation in a nasal mucosal melanoma and its metastasis. Histopathology 1997; 31:465-8.
9. Weidner N, et al. Neurosarcomatous malignant melanoma arising in a neuroid giant congenital melanocytic nevus. Arch Dermatol 1985; 121:1302-6.
10. Wahlstrom T, et al. Malignant skin tumors of neural crest origin. Cancer 1976; 38:2022-6.
11. Urmacher C. Unusual stromal patterns in truly recurrent and satellite metastatic lesions of malignant melanoma. Am J Dermatopathol 1984; 6:331-5.
12. Moreno A, et al. Osteoid and bone formation in desmoplastic malignant melanoma. J Cutan Pathol 1986; 13:128-34.
13. Clark WH Jr., et al. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res 1969; 29: 705-26.
14. Nora FE, et al. Bizarre parosteal osteocartilaginous proliferations of the hands and feet. Am J Surg Pathol 1983; 7:245-50.
15. Hornick JL, et al. Myoepithelial tumors of soft tissue. A clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. Am J Surg Pathol 2003; 27:1183-96.
16. Mentzel T, et al. Cutaneous myoepithelial neoplasms: clinicopathologic and immunohistochemical study of 20 cases suggesting a continuous spectrum ranging from benign mixed tumor of the skin to cutaneous myoepithelioma and myoepithelial carcinoma. J Cutan Pathol 2003; 30:294-302.
17. Hornick JL, et al. Cutaneous myoepithelioma: a clinicopathological study of 14 cases. Hum Pathol 2004; 35:14-24.
18. From L, et al. Origin of the desmoplasia in desmoplastic melanoma. Hum Pathol 1983; 14:1072-80.

AMR SEMINAR #46
CASE 10

Contributed by: Allen M. Gown, MD

History: This 92 year old male presented to his dermatologist with a lesion on his right temple, which was shaved. No other clinical history noted.

Microscopic: Sections show a deeply infiltrative tumor within the dermis with spindled and epithelioid appearance, with the tumor arranged as small islands and cords. Mitotic figures are easily identified. There is a peripheral inflammatory reaction of lymphocytes and histiocytes, and the overlying epidermis is atrophic and flattened; there is focal ulceration.

Immunophenotype: The tumor shows strong, uniform expression of S100 protein as well as p75-NTR (nerve growth factor receptor), and is negative for expression of cytokeratins (using the pankeratin antibody, OSCAR, as well as the cocktail AE1/AE3). The tumor is also negative for expression of desmin, muscle actins, CD34, gp100 (HMB-45), MART-1, microphthalmia transcription factor, tyrosinase, and p63.

Diagnosis: Spindle cell melanoma vs. epithelioid malignant peripheral nerve sheath tumor

Comment: Histologically I favored the diagnosis of an epithelioid malignant peripheral nerve sheath tumor , although I don't know how to rule out the alternative diagnosis of predominantly spindle cell melanoma. The negative melanoma marker studies can be used to support the diagnosis of MPNST, but it is clear that spindle cell melanomas can lack expression of these markers. Could it be that these tumors are really one and the same?

AMR SEMINAR #46
CASE 11

Contributed by: Thomas Krausz, MD

History: 49 year old female with retroperitoneal tumor, 8 cm in maximum diameter. The tumor was discovered on scanning following the patient's complaint of abdominal pain. It was near but not adherent to the kidney.

Diagnosis: Angiomyolipoma.

Comment: One of the reasons for submitting this case is that I was so impressed with my colleague who received this case for frozen section and bluntly called it "lipoma". Subsequently, the paraffin sections were shown to me, causing me differential diagnostic problem. Of course, in the retroperitoneum the first thing one needs to do is exclude liposarcoma especially in a case like this when there are many microvacuolated cells in addition to mature fat cells, indistinguishable from lipoblasts. However, there are no bizarre stromal cells as one would expect to see in a well-differentiated lipoma-like liposarcoma. On H&E, I also considered the possibility of lipoma-like variant of hibernoma in view of the microvacuolated cells and intersitial cells with granular cytoplasm. At this point I decided to look at the gross specimen and found an ovoid, symmetrical, thinly encapsulated, deep yellow tumor mass with some tan reticulation and I thought the H&E impression of hibernoma would match with the gross. Of course, one also should not ignore the large irregularly shaped blood vessels with peculiar perivascular sclerosis and consider the possibility of angiomyolipoma which is poor in myogenic cells. At the end, the immunohistochemistry put everything in order and showed scattered SMA, HMB45, melan A, and Mitf positive cells with increased number adjacent to blood vessels. Interestingly, several of the micro- and macrovacuolated lipogenic cells were also positive by the melanocytic markers.

AMR SEMINAR #46
CASE 12

Contributed by: Thomas Mentzel

History: A 62-year-old male patient developed a nodular lesion on the back of his right foot. Clinically, a lipoma was suspected.

Pathological Findings: Histologically, an intravascular mesenchymal neoplasm is seen. The lesion contains numerous thin-walled vessels (in the periphery bilated, branching, haemangiopericytoma-like vessels are present) surrounded concentrically by cytologically bland myoid tumour cells. Neoplastic cells contain an ill-defined, eosinophilic cytoplasm and plump spindled or round nuclei; increased atypia or increased proliferative activity are not present. Immunohistochemically, neoplastic cells stain positively for alpha-smooth muscle actin and h-caldesmon, whereas desmin was positive in very few cells only.

Diagnosis: Intravascular myopericytoma.

Comments: Myopericytoma represents a distinct myoid neoplasm in the spectrum of perivascular neoplasms. These neoplasms tend to arise in dermal and superficial soft tissues of adult patients, and the extremities are frequently involved. Rarely multiple lesions are present. Most cases of myopericytoma behave in a benign fashion, however, rare cases of mainly deep seated malignant myopericytomas have been reported recently. Histologically, myopericytomas are characterized by the presence of numerous thin-walled blood vessels and composed of ovoid, plump spindled and/or round myoid tumour cells showing at least focally a characteristic perivascular, concentric growth. Most recently a broad morphological spectrum of these neoplasms has been shown in a large series, and intravascular myopericytoma represents a rare subset. Immunohistochemically, neoplastic cells in cases of myopericytoma stain positively for actins and h-caldesmon, whereas desmin is usually negative or only focally expressed. Despite overlapping features to angioleiomyoma, cutaneous myofibroma/myofibromatosis and glomus tumour, these neoplasms usually lack the characteristic concentric perivascular growth of neoplastic cells seen in myopericytoma. In addition angioleiomyoma usually contains thick-walled vessels especially in the periphery and is composed predominantly of elongated spindled cells staining positively for desmin. Cases of cutaneous myofibroma/myofibromatosis are characterized by a biphasic growth pattern and tumour cells are usually negative for h-caldesmon. Glomus tumour (glomangioma) may closely resemble myopericytoma, and immunohistochemical staining are not of help in the distinction of both entities. However, spindle-shaped tumour cells are usually not seen in glomus tumour/glomangioma and tumour cells in glomus tumour tend to be slightly separated from the vascular structures, whereas a typical spinning off of neoplastic cells from the vessel walls is seen in myopericytoma.

Literature:

Granter SR, Badizadegan K, Fletcher CDM. Myofibromatosis in adults, glomangiopericytoma, and myopericytoma. A spectrum of tumors showing a perivascular myoid differentiation. Am J Surg Pathol 1998; 22: 513-525

Kutzner H, Requena L, Hügel H, Rütten A. Adult myofibroma: an acquired neoplasm of vascular (myopericytic) character. Dermatopathology Practical and Conceptual 1996; 2: 190-195

McMenamin ME, Fletcher CDM. Malignant myopericytoma: expanding the spectrum of tumours with myopericytic differentiation. Histopathology 2002; 41: 450-460

McMenamin ME, Calonje E. Intravascular myopericytoma. J Cutan Pathol 2002; 29: 557-561

Mentzel T, Dei Tos AP, Sapi Z, Resnik K, Kutzner H. Myopericytoma of skin and soft tissues: clinicopathologic and immunohistochemical study of 52 cases. Mod Pathol 2005; 18: 86A

AMR SEMINAR #46
CASE 13

Contributed by: Elizabeth Montgomery, MD

History:
This renal tumor was found in a 30-year-old woman with severe hypertension who was undergoing an evaluation for infertility. On resection, it was about 2 cm.

Microscopic findings:
The tumor consists of a well-circumscribed nodule of composed of uniform bland cells with oval nuclei with fine chromatin and lightly eosinophilic cytoplasm. The cells are arranged haphazardly and in small nests. The tumor has a prominent vascular pattern consisting of both thin walled vessels and thick walled hyalinized vessels. Focally, the tumor contains a vascular pattern reminiscent of a hemangiopericytoma. Throughout the lesion are benign appearing tubules containing dense eosinophilic colloid material. In light of the history of hypertension in this young woman, we considered juxtaglomerular cell tumor and did not perform immunohistochemistry but went straight to electron microscopy (see below) to confirm the impression. Happily, the patient's hypertension resolved immediately following her kidney resection. This is a recent case, so we do not yet know the status of her infertility workup and whether she has been able to conceive following excision of her tumor!

Diagnosis:
Juxtaglomerular cell tumor.

Comment:
Juxtaglomerular cell tumor is a rare renal neoplasm arising from the juxtaglomerular apparatus. Approximately 70 cases have been reported in the English literature. This tumor has been considered benign and resection has so almost always been curative. Recently a metastatic juxtaglomerular cell tumor was reported (Am J Surg Pathol 2004; 28: 1098-1102). The metastatic tumor was a 15-cm mass of the right kidney of a 46-year-old man. It invaded the renal vein, and was treated by radical nephrectomy in 1995. The diagnosis at that time was renal cell carcinoma. The patient was well for 6 years and then developed bilateral lung masses, which were resected. Microscopically, the tumors from the kidney and the lungs were similar, consisting of solid sheets of uniformly round-to-polygonal cells intermixed with abundant delicate vasculature. Both renal and pulmonary tumors were positive for vimentin, renin, and only focally to CD34. Electron microscopic studies performed on the paraffin-embedded renal tumor and formalin-fixed lung tumor revealed the typical rhomboid crystals of proto-renin.

Ultrastructural findings:
Note the proto-renin crystals in the ultrastructural images attached.

AMR SEMINAR #46
CASE 14

Contributed by: Ramon y Cajal, MD

History: a 37-year-old woman with a large mass in pleura.

Pathology: The tumor measured 37 x 17 x 15 cm and weighed over 2,600 gms. It was attached to the pleura. The tumor demonstrated firm consistency and myxoid areas with several well defined nodules. Microscopy showed features consistent with solitary fibrous tumor, but CD34, S100, smooth muscle actin were negative. There were more worrying cell populations in some areas, with high mitotic activity, high cell density and focal necrosis.

Diagnosis: Consistent with malignant solitary fibrous tumor.

Comment: I am enclosing a slide where both classical solitary fibrous tumor and areas of malignant transformation are evident. Although it is difficult to make a diagnosis of malignancy in these tumors, there were areas that looked like fibrosarcoma. Malignant transformation of solitary fibrous tumors can occur in about 5% of tumors. As a result of this unusual transformation and because the tumor was CD34 negative, I would very much appreciate your comments.

AMR SEMINAR #46
CASE 15

Contributed by: Josh Sickel, MD

History: 73-year-old woman with a 4 cm tumor involving the uterine cervix. Radical hysterectomy is performed. Pelvic dissection reveals several grossly involved lymph nodes.

Pathology: Cervical tissue is replaced by a deeply infiltrative, poorly differentiated carcinoma composed of small cells with high N:C ratio, evenly distributed chromatin, small nucleoli and nuclear molding. Mitotic activity is high and there is focal necrosis. Angiolymphatic invasion is present. Immunostains show the following profile: CK22 (+, dot-like pattern), synaptophysin (+), chromogranin (-). A minor component of squamous cell carcinoma is noted superficially.

Diagnosis: Small cell neuroendocrine carcinoma of uterine cervix.

Comment: Classic example of a rare tumor for your slide collection. This clinically aggressive neoplasm accounts for < 5% of all cervical malignancies. Age at presentation varies widely (25-87 yrs old), with a median age of 42. Composite tumors, with either focal squamous or glandular differentiation, are common. In-situ hybridization studies are typically positive for HPV-18.

References:

1) Int J Gynecol Cancer 15(2):295-300, 2005.
2) Int J Gynecol Pathol 23(4):366-72, 2004.

AMR SEMINAR #46
Case 16

Contributed by: Dominic Spagnolo, PathCentre, Nedlands, Western Australia
(accession 04B21403E)

History: 26-year-old female with past history of treated Hodgkin disease in Colombia in 2003, apparently in remission. Presented with 3 month history of right anterior knee pain. Imaging showed a well defined, expansile, 16mm lytic lesion in the medial patella, breaching the cortex inferomedially, and with extensive perilesional edema. Chondroblastoma was the favored radiological diagnosis (see digital images of radiological studies). No other known osseous lesions, or lymphadenopathy. A core biopsy was performed.

Pathology: There is no normal anatomical bone seen. There is a mixed infiltrate of plasma cells, lymphocytes, neutrophils, occasional eosinophils, and numbers of large histiocytic cells. The latter have voluminous eosinophilic cytoplasm, round vesicular nuclei and central eosinophilic nucleoli. There is prominent emperipolesis, chiefly of lymphocytes, but also of other leucocytes. These cells are strongly S-100 protein positive.

Diagnosis*:* Rosai-Dorfman disease involving the patella.

Comment: The case is submitted not because of any diagnostic difficulty, but rather because of the unusual site of involvement. The pathology reports from Colombia certainly indicated the presence of Hodgkin disease. There was no mention of concomitant Rosai-Dorfman-like changes in the nodes.

Extranodal involvement in Rosai-Dorfman disease occurs in about 25% of cases, typically in association with the characteristic lymphadenopathy. Disease may be purely extranodal, and virtually all organ systems have been described as sites of involvement, including the skeletal system. Isolated osseous involvement is quite rare, and I have not found any instance of patellar involvement. Has anyone encountered this in the patella before?

The occurrence of Rosai-Dorfman disease-like changes in nodes harboring Hodgkin disease has been recognized for some time (Histopathology 1991; 19:221-224 Falk S et al). There are also reports of its occurrence in extranodal sites in some patients with treated Hodgkin lymphoma (Ann Hematol 1997; 74:41-44 Lossos I et al; Arch Pathol Lab Med 2003;127:1527-1528).

AMR SEMINAR #46
CASE 17

Contributed by: Bruce Wenig, MD

Clinical History: 49 year old male presented with an enlarging right parotid gland area mass. A parotidectomy and neck dissection were performed. The patient has no significant past history, in particular there is no past history of any malignancy and no evidence of a separate concurrent neoplasm of any other site.

Histology: Invasive undifferentiated pleomorphic and spindle-shaped cellular proliferation with focal fascicular to storiform growth patterns. Increased mitotic activity with atypical mitoses are present. Angioinvasion and neurotropism were identified although not necessarily on the submitted slide.
Histochemical stains:

- negative for epithelial mucin;
- PAS positive;
- AFB negative.

Immunohistochemical staining:

- positive for vimentin, CD10, CD68, and CD99;
- negative for cyokeratins (AE1/AE3, CAM5.2, CK903), EMA, RCC, S100, HMB-45, melanA, CD31, CD34, Fli-1, SMA, Hep 1, desmin, TTF-1, caldesmon, calponin, CD3, CD20, CD30, CD45, CD56, myoglobin, myf-4, p63, SMMS-1, Alk1, CD21, CD23, CD35, and inhibin.

Electron Microscopy:

- lysosomes, phospholipid lamellar inclusions, and occasional small intermediate junctions.

Diagnosis: Undifferentiated malignant tumor in parotid with extensive angioinvasion.
Patient requested case to be sent to the AFIP for consultation. AFIP diagnosis included opinions from separate departments:
1) First Department: Intermediate to high grade sarcoma consistent with MFH;
2) Second Department: Unusual intermediate to high-grade pleomorphic sarcomatous neoplasm of uncertain origin; the possibility of a sarcomatoid carcinoma with sebaceous cell differentiation was considered.

Any assistance in elucidating the nature of this tumor would be appreciated.

AMR SEMINAR #46
Quiz CASE 1

Contributed by: Saul Suster, M.D.
Case contributed by Dr. Carlos Ortiz-Hidalgo, A-B-C Medical Center, Mexico City, Mexico, D.F.

Clinical history: A 43 year old woman with no significant past medical history was seen for the development of a slow-growing subcutaneous skin lesion 8 cm. in greatest diameter on her left shoulder. The consulting pathologist indicated that the initial battery of stains was positive for CD35, CD21, CD68, CAM 5.2, CK7, CK20, and negative for S-100, SMA, desmin, and EMA; however he added that the positive stains looked suspicious for endogenous biotin activity. A battery of stain was repeated in our laboratory with quenching for endogenous biotin activity and showed strong nuclear and cytoplasmic positivity for S-100 protein and vimentin, and negative results for cytokeratin AE1/AE3, CK7, CK20, CD21, CD35, CD68, desmin, SMA, Melan-A, HMB45 and EMA.