AMR Seminar #60 – Short Summary of Cases:

Case 1:   F.37 with hundreds of polyps covering the stomach mucosa.

Case 2:   M.21 with rapidly growing mass in the left lower jaw.

Case 3:   F.60 with non-resolving leg ulcer.

Case 4:   M.44 with right-sided, well-circumscribed localized pleural mass 5.8 cm in diameter.

Case 5:   F.34 with 2.5 cm. soft tissue mass in her thigh.

Case 6:   F.57 with enlarged neck lymph nodes.

Case 7:   M.70 with 1.5 cm. subcutaneous lump in the lower neck.

Case 8:   M.26 with soft tissue tumor in posterior chest wall, subscapular location.

Case 9:   M.54 with slowly growing tumor in the parotid gland.

Case 10:   M.72 with elevated PSA and enlarged prostate, undergoes prostatectomy.

Case 11:   F.68 with resection of a 6 cm. pulmonary mass.

Case 12:   F.79 with left adrenal mass.

Case 13:   F.36 with a mass in the right broad ligament.

Case 14:   M.75 with second recurrence of tumor obstructing the left main bronchus.

Case 15:   M.40 with lupus nephritis and a left renal mass.

Case 16:   F.68 with recurrent soft tissue mass in her left leg.

Case 17:   F.56 with 27 cm. pedunculated mass in the esophagus.

Case 18:   M.56 with chest pain and asbestos exposure shows a density in the right side.

Case 19:   M.68 with 3.5 cm cystic mass in the head of the pancreas.

Case 20:   F.83 with solitary, painless skin nodule on left chest wall.

Case 21:   F.9 mo. old child with an enlarging and infiltrative right maxillary bone lesion.

Quiz Case #1:   M.70 with encapsulated 3.2 cm. tumor of the thyroid.

AMR SEMINAR #60
CASE 1

Contributed by: Volkan Adsay, M.D.

Clinical History: 37-year-old female with a history of colon cancer (status post partial colectomy) and "multiple inflammatory polyps" in the stomach presented with chronic anemia necessitating blood transfusions in the past few years, and was hospitalized with a chief complaint of dehydration and malnutrition. By endoscopy, the patient was found to have the entire stomach replaced by large polyps. She underwent total gastrectomy. Gross examination of the specimen revealed innumerable (hundreds of) polyps ranging 1-9 cm, covering the entire mucosal surface, most measuring in several centimeters. They had lobulated surfaces, relatively narrow stalks and a sieve like cystic changes on cut sections. After the evaluation of the stomach specimen, the colon cancer material of this patient was obtained from the outside institution and was found to be microsatellite stable and appeared to be a conventional type (intestinal type) adenocarcinoma. The patient did not have polyposis in the colon.

Diagnosis: Massive gastric juvenile/hyperplastic polyposis (SMAD4 related) with minute foci of invasive carcinoma.

Microscopic findings: There were innumerable polyps covering almost the entire surface of the stomach. Most were mushrooming from the surface epithelium while preserving the basal components of the mucosa. The polyps were measuring up to 9.0 cm, most measuring several centimeters in diameter. Most of the polyps contained benign gastric glands, mostly foveolar type, often with cystic changes. Some showed edema and congestion, while others, inflammation, which, combined with marked cystic dilatation of the glands (visible both grossly and microscopically) created a picture reminiscent of inflammatory/hyperplastic polyps. In some areas, the process resembled exaggerated form of Menetrier disease. Cystic and nodular configuration of the glands were also of the type that are seen more commonly in hamartomatous type juvenile polyps. In some areas, the process also had the features of pyloric gland adenomas. Rare glands showed intestinal metaplasia, and focal calcifications were also present. Interestingly, the lower aspects of the mucosa were largely unremarkable; the polyps appeared to be originating from the very surface of the foveolar epithelium, suggesting an intrinsic anomaly in the development of surface foveolar cells. There were no evidence of pathological changes in the submucosa or deeper aspects of the gastric wall. While most of the polyps had benign, normal-appearing epithelium, in some polyps, various degrees of dysplastic transformation characterized by enlarged nuclei located centrally or supra basally in a relatively clear cytoplasm, were noted.

More importantly, in one focus in the block (not sure if your levels of this block will still have it), this glandular dysplasia was associated with patchy minute clusters of carcinoma cells, as well as few individual carcinoma cells lying within the stroma (lamina propria) of the polyp. Molecular analysis revealed SMAD 4 germline mutation in this patient and in family members.

I believe this case is a very nice example of an emerging subset of polyposis syndromes that has been termed variably including "massive (diffuse) gastric juvenile (hyperplastic) polyposis", which is often related to SMAD4 mutation. As such, it may be closely related to that small subset (20%) of Peutz-Jeghers type Juvenile Polyposis Syndrome associated with SMAD4 mutation (rather than the BMPR1A), and can occasionally show malignant transformation as noted in this case. However, unlike JPS cases, this group shows the polyps largely restricted to the stomach. We have now 3 examples of this phenomenon which we are putting together in a report. We are considering to propose the name of massive foveolar-gland polyposis for this entity.
I would be very interested to hear from the group whether if they have seen any example of this phenomenon. I circulated this case among a few of the GI pathology gurus, and none could remember to have seen any.

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AMR SEMINAR #60
CASE 2

Contributed by: David Ben-Dor, M.D.

Clinical History: A rapidly growing mass in the left lower jaw of a 21-year-old male found in the soft tissues overlying the bone. The lesion was said to reach the surface of the bone but the clinical impression was that the bone itself was not involved. Radiology was said to show a "fracture". Previous history was remarkable for the patient having been treated with radiotherapy for retinoblastoma (the family told the clinicians that it was unilateral but no documentation is available) about 20 yrs previously.

Gross and Microscopic Findings: Two biopsies were sent, one superficial and the second deep reaching the bone, both measuring about 2 cm. and composed of grayish tissue. Histological examination was remarkable for a myxoid lesion composed of immature mesenchymal cells, in many areas showing no particular growth pattern (which I interpreted as consistent with "tissue culture" type). To be honest at first I wasn't at first overly impressed with cytologic atypia and while I found mitoses I didn't notice any atypical ones. However in other areas these cells are disposed in a reticulate or lace like pattern. There is also delicate fibrillary material some of which was basophilic in the background.

Further evaluation: to be totally honest my first impression was nodular fasciitis which could explain some of the findings (as I understood them) but not all. What I do in situations where I have some diagnostic uncertainty is to informally send photos to colleagues and get their reactions just to make sure that I'm not overlooking something major or totally misapprehending the situation. I've done this in the past with some of the members of this group and I've found their comments to be extremely helpful – they have my undying gratitude. So I took some photos and sent them to someone who rose to the occasion and made what I consider to be a brilliant diagnosis (especially given the fact that all he had were a few photos!)- osteogenic sarcoma. I was totally unprepared for this as well as dumbfounded- I never thought of OS as a myxoid lesion. Further the lesion wasn't understood to be a bone mass either clinically or radiologically . I also didn't know where the osteoid in this lesion was: there was that noodle like fibrillary material in the background but I didn't conceive of osteoid looking like that. I should add that this person took the clinical history into account and understood the connection between the history of retinoblastoma as well as previous radiotherapy (which may or may not have passed through the jaw) and OS. The case (representative slides and block along with CD containing the imaging) was sent to Dr. Pieter Slootweg in Utrecht, the Netherlands, who emailed me the following comments:

 "The slides have arrived in my office. Both show unequivocally the picture of an osteosarcoma. Pleomorphic stromal cells with elongated cytoplasmic extensions alternate with more cellular areas. Moreover, the cells form foci of irregular and coarse osteoid. The CD that you included show irregular bone destruction and a widened periodontal ligament space which radiologically is a typical feature of jaw osteosarcomas. A formal report will be send by mail in due time. Thank you for consulting me on this issue"

In his formal reply he stated the following:
The slides show a lesion that is characterized by the presence of a fibromyxoid lesion that shows a bosselated cell-rich periphery. More centrally, the tissue becomes less cellular and in the more central areas, also osteoid deposition is observed. In higher detail, the cells show atypia and mitotic activity. Moreover, they sometimes form strands that fuse to form a lattice enclosing cell-poor myxoid stromal areas. Focally, a partly ulcerated surface covered with squamous epithelium is seen. In those areas, an intense inflammatory infiltrate is observed.
The bosselated cell-rich periphery and the central osteoid cores are entirely compatible with a diagnosis of osteosarcoma.

Further Developments: The patient presented himself to the oral surgery department of one of the larger referral medical centers in the "big city" and took slides from the same biopsy examined by the consultant. The oral pathologist there was at first skeptical of the diagnosis at first, but later became convinced after I provided more

material from a separate subsequent biopsy, in which the osteoid was more obvious. The patient then underwent excision of the left mandible which showed a rather large soft tissue mass adherent to the bone, and while there was no obvious mass in the bone itself, there was a discontinuity on the surface. However radiology of the specimen showed the classical "sunburst" image of OS. A section taken from the bone in that portion of the specimen showed classical osteogenic sarcoma, osteoblastic type. Sections taken from the soft tissue component show the same type of myxoid proliferation seen in the biopsies. No chondroblastic areas were documented in either location.

Final Diagnosis: Osteogenic sarcoma of the left mandible, osteoblastic type, presenting as an extra-osseous myxoid tumor, in a patient with a history of retinoblastoma and radiation therapy in early childhood.

Comments: This case is remarkable for a number of reasons:
Etiological factors: retinoblastoma (at least the genetic form- assuming the clinical history I have is correct and the tumor was unilateral it may be sporadic) and a history of irradiation to the head and neck are well known risk factors mentioned in standard reference works (such as the AFIP fascicle on jaw tumors (series III, no. 29)) for the development of osteosarcoma of the jaw. Both of these were apparently present in this patient, a "double whammy", with the latter being given to treat the former. I am not familiar with the technical details of the treatment so I don't know for a fact to what extent the jaw may have been effectively protected. I also don't know whether these two risk factors can act in synergy or if they are additive. In any case awareness of this connection should raise the level of suspicion for osteosarcoma in biopsies of jaw tumors in patients with this history.
Clinical presentation: the tumor presented as an extra-osseous mass. There was no obvious expansile space occupying lesion in the jaw on radiology as perceived by the clinicians treating him. The surgeon who took the biopsy told me that the surface of the bone as visualized by him during the procedure looked normal. This was also borne out by gross examination of the resected surgical specimen performed at the other hospital. However specimen radiography showed the classical "sunburst" pattern characteristic for osteogenic sarcoma, and histological examination of the bone in that portion did show a malignancy producing classic osteoid (in contrast to the material seen on the biopsy I examined). On the surface of the bone a thin surface discontinuity was visualized through which the tumor escaped to the surface. (Parenthetically, for the sake of completeness, there are osteogenic sarcomas originating on the surface of the bone- the parosteal/juxtacortical and periosteal variants. The first would show a more spindly fibroblastic type appearance, unlike what was seen in the biopsies of this case, and the second is extremely rare. In any case after all is said and done this tumor originated in the bone).
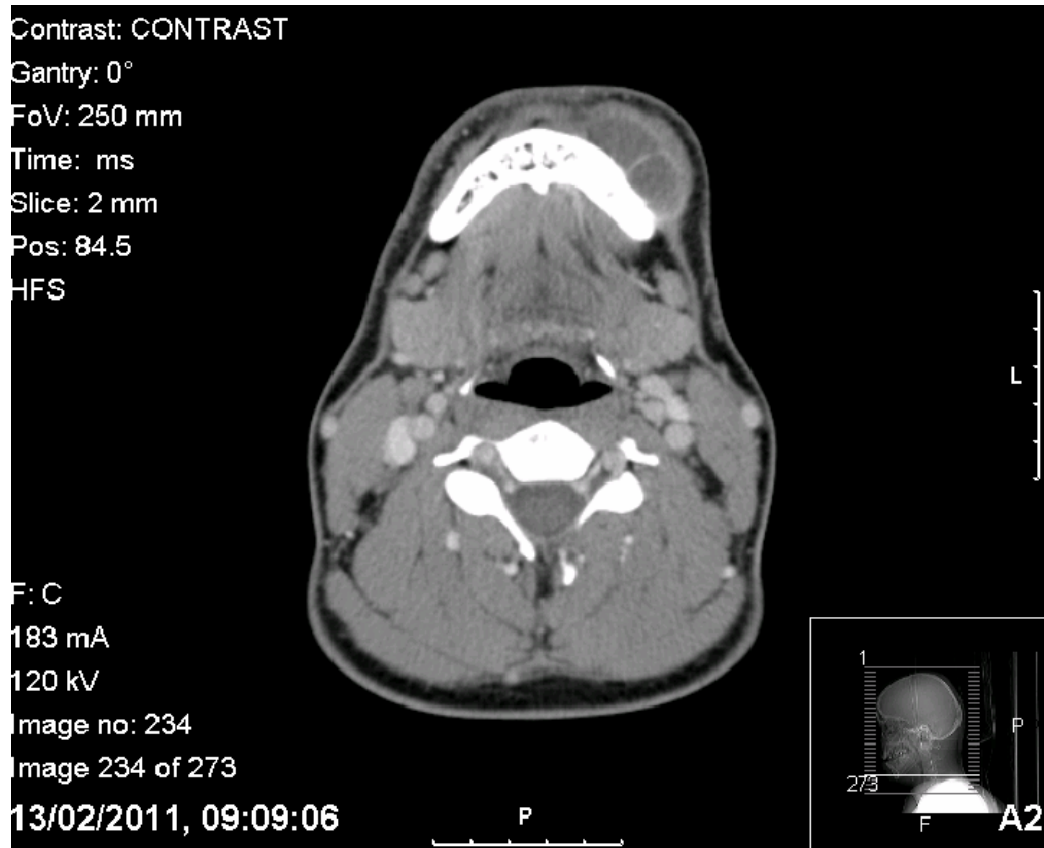Histology: the AFIP fascicle describes three main histological types of osteogenic sarcoma: osteoblastic, chondroblastic, and fibroblastic (low grade). There is no formally recognized subcategory of myxoid osteogenic sarcoma. However the AFIP fascicle does refer to the fact that "occasionally there is abundant acid mucopolysaccharide-rich ground substance, producing a myxoid histologic pattern that resembles odontogenic myxoma. Such lesions require detailed clinico-pathologic and radiologic correlation and thorough evaluation of histologic and cytologic features" (p. 186). In addition there are 1-1/2 pages of microphotographs illustrating this, some of which showing the same features as the biopsy you are seeing.

Performing a Medline search using the terms "myxoid- osteosarcoma" I didn't find any articles specifically relating to myxoid osteogenic sarcoma. However plugging in these terms into the search engine on the USCAP website I found a presentation given by Dr A. Kevin Raymond (MD Anderson Cancer Center) at the 2005 conference entitled post radiation osteosarcoma of the jaw, who made the following points concerning that tumor: " As with Mayo Clinic, the M.D. Anderson Cancer Center series has a predominance of chondroblastic osteosarcoma (45%). And while hyaline cartilage is the typical matrix of appendicular chondroblastic osteosarcoma, this does not appear to be true of jaw osteosarcoma. The vast majority of cases have cartilage matrix *that is either myxoid cartilage* (my italics) or mimics the pattern seen in periosteal osteosarcoma. In the former, the matrix is poorly formed, with infrequent lacunes and stellate neoplastic cells similar to the appearance of soft tissue (myxoid) chondrosarcoma. While in the second form, the cartilage has the appearance of zonated hyaline cartilage. It is centrally hypocellular, while being hypercellular at the periphery, and osteoid is present either in the center and/or as fine filigree lines running through and from the lobule periphery". Thus those "in the know" about jaw osteosarcomas would be prepared for this histological presentation- someone like myself may not be. It may thus be possible to conceive of this myxoid pattern as being an expression of chondroblastic differentiation. However there was no production of typical cartilage anywhere in either the biopsies or in the operative material. It's interesting that the myxoid pattern was limited to the tumor growing outside the bone and was not seen in the histology from the intra-osseous component. The similarity raised with extraskeletal myxoid chondrosarcoma is also intriguing- again the soft tissue and bone people would be better able to comment on this.

A recent article, "The Spectrum of Gnathic Osteosarcoma: Caveats for the Clinician and the Pathologist" by R. J. Padilla and V. A. Murrah (Head and Neck Pathology (2011), 5: 92-99) presents a number of cases of this entity which illustrate the pitfalls in making the correct diagnosis. While all of their cases showed an expansile bone lesion
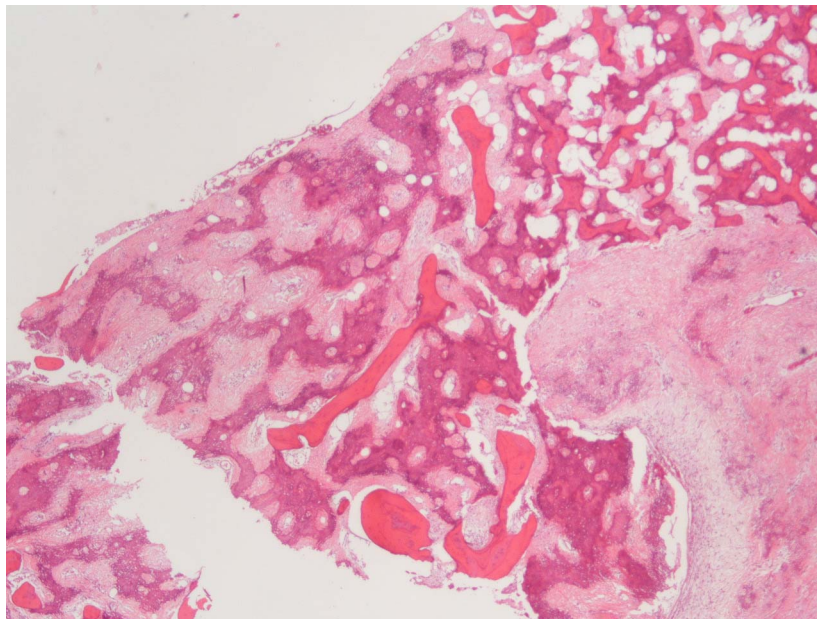
on radiology (unlike my case), none showed the classical sunburst image (which was found in the resected specimen here). The authors take pains to warn pathologists and clinicians that small superficial biopsies may be underdiagnosed as pyogenic granuloma or peripheral ossifying fibroma, and that "GO often presents with equivocal histopathological features". They recommend review of the specimen by an experienced oral pathologist. My experience with this case is in accordance with these recommendations.
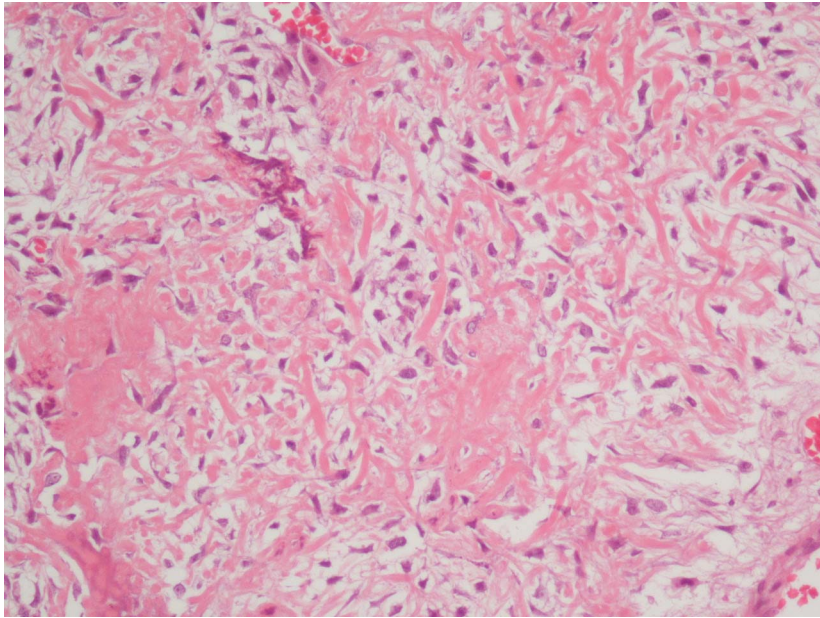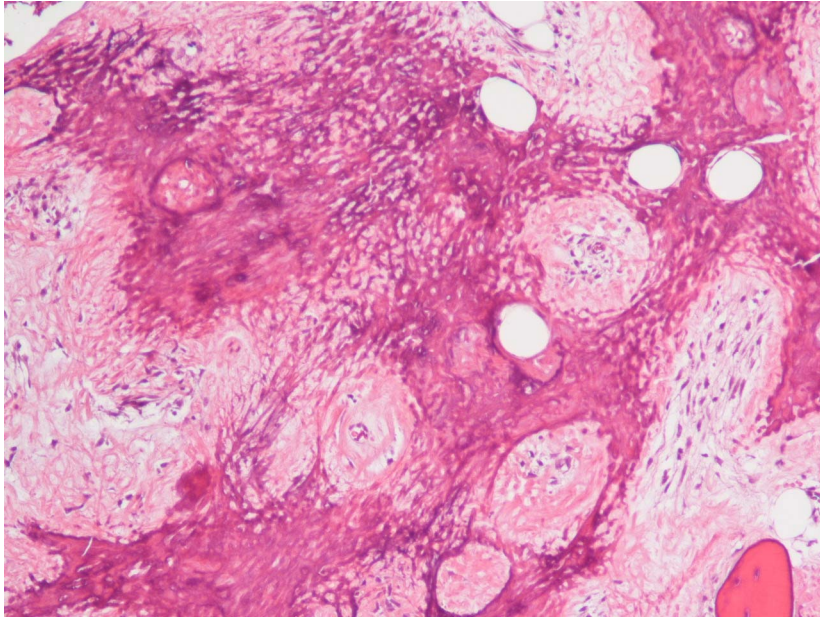
I am including for your judgment two clinical radiological images (not the radiology of the specimen which was said to be typical for osteogenic sarcoma) from the series sent to and commented on formally by the consultant.. I would be interested in comments for those with expertise in this field as to what degree the diagnosis should have been suspected

Here are some microphotographs of the intra-osseous tumor in the resection specimen (sent to me by the oral pathologist in the hospital where the patient was operated) to illustrate the more conventional appearing osteoid (in contrast to that seen in the slide from the extra-osseous tumor):

AMR SEMINAR #60
CASE 3

Contributed by: Ofer Ben-Itzhak, M.D.

CASE HISTORY AND PATHOLOGY: This skin biopsy (slide A) from a 60-year-old woman, was accompanied by the clinical information of "non-resolving ulcer in the leg" (A relatively very detailed information for our busy surgeons). The patient suffered from the ulcer for several weeks and the biopsy was performed "to rule out carcinoma". The slide shows prominent epidermal hyperplasia, suspicious of well diff. squamous cell carcinoma, but the intense inflammatory reaction-both acute and chronic-and small foci of necrosis warrant a closer inspection. Indeed, by high-magnification, few histiocytes with rare leishmania-bodies were detected (should be distinguished from karyorrhectic bodies).

To help the diagnosis of this woman's leg-ulcer, her husband was recruited. The same tray of slides contained the biopsy (slide B) of this woman's husband - a 63year-old man, also with a clinical information of "ulcer of the leg". However, in the husband's biopsy the leishmania-laden histiocytes are much more prevalent (just beneath the ulcer base and beneath the epidermis) with a lot of intracellular organisms. The focal epidermal hyperplasia at the margin of the ulcer is much less pronounced in the husband's slide.

DIAGNOSIS: Cutaneous leishmaniasis with pseudoepitheliomatous hyperplasia (or : How husbands can help their wives).

COMMENTS: Leishmania is an obligate intracellular parasite, endemic in central and south America, Mediterranean countries (including parts of south Europe and north Africa), Middle East and the Indian subcontinent. Up to 2 million people develop symptomatic disease annually. The incidence of the disease increases, probably related to increased deforestation, and global warming, and can be seen worldwide with increased travel to endemic areas. Leishmania is a zoonotic disease. The animal reservoirs (and humans) become infected when the organisms are injected from the proboscis of the female sandfly while it takes blood. The parasites enter phagocytic cells, transform to amastigotes and begin intracellular replication. The packed infected cells ultimately rupture, liberating organisms into surrounding tissue and into the circulation. Ingestion of amastigotes by the sandfly closes the life cycle of the leishmania. The amastigotes seen within macrophages are 2 to 4 microns basophilic structures with cell membrane, round to oval nucleus and a kinetoplast in the cytoplasm (best seen in Giemsa stains after alcohol fixation of aspirates, smears or touch preparations). The disease may involve the skin, mucous membranes and visceral (by different species of leishmania for each type of involvement).

Cutaneous leishmaniasis, in contrast to visceral leishmaniasis is not rare in Israel, and is acquired mainly in the hot eastern areas of the Jordan river (including Tiberius and Jericho areas) and in certain areas of the Negev desert in the south. It is caused by L. tropica and L. major, and the hosts are mainly field rodents. Several cases of L. braziliensis were reported in Israel in travelers returning from the Amazon region of Bolivia. I see few cases of cutaneous leishmaniasis almost every year, many with no clinical suspicion of the disease. The pathologic features maybe highly variable. The epidermis may be normal, ulcerated, atrophic or hyperplastic. Pseudocarcinomatous hyperplasia , as seen in the current case, is occasionally present. Foci of necrosis, from minute to large, are not rare.

The inflammatory reaction includes histiocytes, lymphocytes, plasma-cells, granulocytes and later granulomatous reaction with epithelioid cells and giant cells, sometimes with central necrosis. Thus, abscesses, pseudolymphomatous reactions and pseudotuberculous reactions may all be seen. The late granulomatous reaction signals a dramatic decline in the number of organisms, which may be difficult to find (similar to leprosy, with the transition from anergy with abundant bacteria-laden histiocytes to hypersensitivity granulomas). A high index of suspicion is needed to diagnose the disease in cases with rare organisms.
The cutaneous nodules and/or ulcers, which begin at the site of the sandfly bite, heal during several months, leaving a scar. Drug therapies are directed toward eradication of amastigotes to reduce the size of the lesions, to promote healing with minimal scarring and to prevent metastatic spread.

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AMR SEMINAR #60
CASE 4

Contributed by: Gerald Berry, M.D.

Clinical History: This 44-year-old life-long nonsmoking man had radiological imaging done following an upper respiratory tract infection. He was found to have a right-sided lung/possible chest wall mass. PET-CT revealed a posterior hypermetabolic mass with maximum SUV of 18.3. A needle biopsy was performed and then the patient went to surgery.

Macroscopic Findings: At surgery a modified lateral thoracotomy incision was made and a chest wall mass was found fixed to the 6th rib. No other pleural nodules were found. The mass and attached ribs were resected   with at least 4 cm margins circumferentially around the lesion. The circumscribed, nonencapsulated mass measured 5.8 x 4.5 x 2.6 cm and the cut surface revealed a yellow-tan firm appearance with a white-tan fibrous rim in some portions of the lesion. It did not invade the rib. (see accompanying photo)

Microscopic Findings: The epithelioid neoplasm is composed of epithelioid cells arranged in a pseudoglandular or microcystic pattern. Immunostaining showed strong reactivity for CK5/6, calretinin, CK7. CK20, BerEp4, TTF-1 were negative. Interestingly, portions of the neoplasm showed a plaque-like fibrous thickening around the periphery.

Diagnosis: Localized malignant mesothelioma, epithelioid type, pseudoglandular pattern.

Comments: I thought the group would be interested in this unusual form of epithelioid mesothelioma. Not only was the histological pattern uncommon but localized MM is also (unfortunately) the rare exception. The immunoprofile supports mesothelial differentiation and distinguishes adenocarcinoma. There are a number of references related to localized MM and I have included a couple below. Most reports are in the form of cases reports with review of the literature. I have included the first series from Crotty et al in 1994 and the largest series by the United States–Canadian Mesothelioma Reference Panel in 2005. The prognosis is better than diffuse MM but recurrence in the form of diffuse pleural spread is reported. Some have a documented association with asbestos exposure but in other cases no association can be found. Our patient is now 2 years out from surgery and disease-free.

References
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AMR SEMINAR #60
CASE 5

Contributed by: Michele Bisceglia, M.D.
(slides labeled 146698-7)

Clinical History and Diagnosis: In October 2007, a 34-year-old unmarried female underwent surgical excision of a subcutaneous lump of 2.5 cm size from her left thigh. The lesion was present for 1 year. The clinical diagnosis was that of a fibroma. Grossly this lesion was rubbery in consistency and solid on sectioning. Histologically the most characteristic features were: *i.* a tumor cell population consisting of round to polygonal clear cells with microvacuolated cytoplasm. *ii.* a well developed arborizing network of capillary-sized vessels surrounding the tumor cells (slides labelled: 146.698-7). Immunohistochemically the tumor cells were: diffusely immuno-positive with vimentin, S-100 protein, NSE, CD57, BCL-2, and CD-99; and immuno-negative with EMA, muscle specific actin, alpha-SMA, desmin, H-caldesmon, and calponin. Scattered tumor cells also showed focal dot-like immunoreactivity for neurofilaments: At the tumor periphery focal reactivity for CK/AE1-AE3 was also seen in a few cells, probably entrapped cells of uncertain type. Inhibin-alpha was not done. On the assumption that the tumor cells were the same "stromal cells" one sees in hemangioblastomas of the central nervous system and taking everything into account a diagnosis of peripheral extraneural hemangioblastoma was rendered and the suggestion was given to look for other (possible) clinical manifestations of von Hippel-Lindau syndrome in the patient and patient's family.

Follow-up: In November 2007 after realizing that Dr. Rosai had just reported in the October issue of AJSP a series of 5 cases of extraneural hemangioblastomas, I sent this case to him to see what he thought of it. Although Dr. Rosai agreed on the fact that this case could "possibly" be another example of extraneural hemangioblastoma, similar to the other ones in the published series, he was not completely convinced (I also was not completely convinced despite having already signed out the report – a doubt which I transmitted to Rosai). His personal diagnosis was that of "richly vascularised, benign mesenchymal hemangioblastoma-like tumor of soft tissue". However he agreed with the idea of a molecular investigation to see if any germline or somatic mutation was present in this patient and her tumor. A normal peripheral blood sample from this patient and tumor tissue from paraffin block was available, and an extensive molecular characterization of the *VHL* gene was performed by mutation analysis, fluorescent loss of heterozygosity (LOH) with microsatellites, and methylation analysis. No VHL genetic alteration was demonstrated by means of any of these techniques employed.

Discussion: Hemangioblastoma (or capillary hemangioblastoma) (HGB) is a discrete, solid or cystic tumor made up of variable combination of interstitial stromal cells of uncertain histogenesis and a rich network of thin-walled vessels. While capillary HGB is the most frequent manifestation of von Hippel-Lindau (VHL) disease, an autosomal dominant condition, the majority of cases (70%) are of the nonfamilial, sporadic type. VHL-associated HGB may occur in any part of the CNS (*central or neuraxial HGB*), including optic nerve and retina. Rarely, HGB may also occur outside the CNS either in association with or as unassociated with VHL disease. HGBs outside the CNS in which the association with VHL disease was not found or was not stated by the reporting authors were described in the following anatomical locations: spinal nerve roots or pia (Raghavan et al; Chazono et al; Wisoff et al), filum terminale, and cauda equine (da Costa et al) (*perineuraxial HGB*); internal organs, such as kidney (Nonaka et al; Ip et al; Miquel et al); and soft tissue (soft tissue of body cavities, such as retroperitoneum and pelvis [Fanburgh-Smith et al; Yoshida et al]; somatic soft tissues, either related to peripheral nerves [Brodkey et al; Kline and Hudson; Giannini et al] or unrelated [Michal et al; Patton et al]); skin (Boyd and Zhang); and even in bone (Panelos et al) (*peripheral HGB*).

In patients with VHL, who inherit germline inactivating mutation of the *VHL* tumor suppressor gene mapped to chromosome 3p25-26, according to the "two hit" theory of Knudson, HGB is due to a second "hit" occurring in the tissue, where the tumor arises (somatic inactivating mutation involving the second allele).

In sporadic HGB of CNS (cerebellar HGB) molecular analyses performed on microdissection studies on stromal cells have already documented allelic losses and mutations of the *VHL* tumor suppressor gene in a proportion of cases (around 50%), thus suggesting that this gene plays a role also in sporadic cerebellar hemangioblastoma tumorigenesis (Lee et al). [[[In regard to sporadic HGB of the CNS relatively recent studies of mutation analysis on DNA from peripheral blood [Olschwang et al; Catapano et al; Woodward et al] also suggested: *i.* that a subset (4-

14%) of patients with an apparently sporadic HGB of CNS has a germline *VHL* mutation, but may not be at risk for developing classical VHL disease; *ii.* in most solitary central HGB no *VHL* mutation was detected but a small group (5%) of patients who developed a second VHL-type tumor, more often a second HGB of the CNS, may be mosaic for germline mutation that cannot be detected in blood cells.]]]

It seems obvious that the *VHL* gene is presumed to be involved also in the development of sporadic HGB, either in central (neuraxial) HGB and in peripheral HGB, where somatic inactivation of both alleles in a "two-hit" manner also should occur. To the best of our knowledge, only 2 cases of sporadic extra-axial HGB have been analyzed at the molecular level, one was on multifocal, recurrent lesions, arising from different spinal nerve roots of mid cervical medullary segments in a 57 year-old male (Raghavan), and the other involved the soft tissue of the ankle in a 74 year-old woman (Michal et al). Both these previous molecular analyses performed on the HGB tumor tissues did not document genetic alterations in *VHL* gene: in one case both complete sequence analysis and LOH analysis had been performed, and the failing to document any genetic alterations led those authors to conclude that a molecular event directly involving the *VHL* gene may not be the causative factor in the tumorigenesis of extra-axial HGB (Raghavan); in another study, employing mutation analysis only, no change in the coding sequence of *VHL* gene was found (Michal et al). At the last Italian SIAPEC Congress (Bologna, Italy, 2010) and USCAP (San Antonio, TX, 2011), in collaboration with J Lamovec, Michal M, and J Fanburgh-Smith we presented such a molecular study (using mutation, microsatellite, and methylation analyses) on 6 cases of extra-neuraxial HGB (Muscarella et al), of which 1 was VHL-associated and 5 were non-VHL associated: both germline and somatic mutations (double hit) were documented in the VHL patient, one single somatic hit in 2 other cases, and two somatic hits in another patient, thus confirming the hypothesis that the *VHL* gene is involved also in the development of extra-axial HGB. However in the remaining 2 cases no mutation was found (as no mutation was found also in the cases herein presented, not included in the SIAPEC-USCAP series).

I am personally interested in everyone's opinion in regard how to consider this case. Would you regard it as an example of peripheral hemangioblastoma? If not what tumor do you believe it is?

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AMR SEMINAR #60
CASE 6

Contributed by: Michele Bisceglia, M.D. (slides labeled 179267-9)

Clinical History and Diagnosis: In May 2009 a 57-year-old male was admitted with a diagnosis of suspected lymphoma due to constitutional symptoms (such as malaise, cough, mild serotinus fever and a significant weight loss of 7 kilos) in addition to the appearance of superficial neck and supraclavian lymphadenopathy for 1 to 2 months. Lymph nodes ranged in size from 1,5-2.5 cm. Hematology and blood chemistry tests were all normal, except for a direct Coombs test which was positive. A left neck lymph node biopsy was performed and histological examination showed "classical morphological features" (which I do not describe further) of Rosai-Dorfman disease (RDD) (slide labeled: 179.267-9), which was confirmed on the basis of few but fundamental immunohistochemical stains (all intrasinusoidal histiocytes were positive for CD68/KP-1, CD68/PGM-1, and S100 protein; and were CD1-alpha negative). In addition CT scan of the thorax also showed enlarged mediastinal lymphadenopathies. Trephine bone marrow biopsy revealed normal bone marrow haematopoietic population with no evidence of RDD infiltration.

Follow-up: The patient was given 6 courses of chemotherapy with cyclophosphamide, vincristine, and prednisone, with partial clinical response. In July 2010 due to the persistence of multiple enlarged lymph nodes a second left neck lymph node was excised and histologically examined with confirmation of Rosai-Dorfman disease involvement. Mediastinal lymph node enlargement was again documented by means of a new CT scan. In August 2010 4 courses of a new protocol of chemotherapy were administered, using iphosphamide, epirubicin, and etoposide along with rituximab, aiming to cure this patient by means of bone marrow transplantation, during the phase of reconstitution of the hematopoietic system, CD34-positive peripheral blood stem cells were collected and cryopreserved. In February 2011 myeloablation was accomplished according to the FEAM regimen, including fotemustine, arabinoside-C, vepesid, and melphalan followed by autologous peripheral blood stem cells infusion. Currently 3 months after bone marrow transplant the patient is alive and well and is being followed-up.

Comments: Rosai-Dorfman disease is a polyclonal proliferative histiocytic disorder, of unknown cause, affecting mainly children or young adults. Some patients are asymptomatic at presentation, but many manifest constitutional symptoms, and around 10% also exhibit autoimmune phenomena (autoantibodies against red blood cells, neutrophils, and platelets). In around 60% of cases RDD is an exclusive nodal disease, while in 40% of cases the RDD manifests as extranodal disease either (more often) in association with nodal involvement or as exclusive extranodal localization. Nodal involvement may be limited to a single node or may involve numerous lymph nodes, usually bilaterally in the neck area but also in other anatomical locations (mediastinal, intrabdominal, inguinal). Among extranodal sites almost every organ has been described, including skin, soft tissue, central nervous system (both brain and meninges), upper respiratory tract (nasal cavity and paranasal sinuses), breast, eye and orbit, and rarely the gastrointestinal tract, including liver, and serosal membranes (mostly pleura; epicardium in 1 case with generalized dissemination). RDD is more often a self-limiting disease, undergoing spontaneous resolution, but may also have a protracted clinical course, and occasionally may also show a poor prognosis (Chen et al). RDD with a chronic course is generally treated with corticosteroids, usually with a good response. RDD has been reported also in association with other diseases or in other clinical settings: *i.* in patients with Hodgkin's and non-Hodgkin's lymphomas, either as coincidental in the same organ or simultaneously found in a different organ (Di Tommaso et al [review]; *ii.* in patients affected by autoimmune lymphoproliferative disease (ALPS) (Maric et al); *iii.* following intensive treatment for T-cell acute lymphoblastic leukemia (Allen et al, case of cervical lymph nodal RDD [review]; and Carlos Galliani, Cook's Children Medical Center, Fort Worth, TX – his personal case, an apparently pleuromediastinal and fibrosclerosing process harbouring RDD, case also shown by e-mailing images to Tom Colby, Larry Weiss and Juan Rosai, who all confirmed his initial diagnosis); and *iv.* also as coincidental with Langerhans' cell histiocytosis (Sachev et al; Wang et al; O'Malley et al; 5 cases – I think – in Rosai's personal colelction), this latter form maybe representing a monoclonal subset of the disease (O'Malley et al).

Etiologic hypotheses in regard to RDD include immune dysregulation and infectious agents, with polyoma virus (SV40) as the last pathogen, among others, being recently documented in 3 of 18 soft tissue cases (Al-Darraji et al).

Although anatomical involvement of some organs (lymph node, skin, CNS, breast) are relatively well-described, intrathoracic manifestations have only occasionally been reported. Of 21 patients of Rosai-Dorfman disease diagnosed over a period of 30 years in the Mayo Clinic records (1975-2005), only 9 were found with intrathoracic manifestations, 6 of which consisted of lymphadenopathy, with the remaining involving the lung parenchyma and appearing as cystic changes or interstitial lung diseases (Cartin-Ceba et al). In 1 case RDD presented as a solitary mediastinal mass, most likely a soft tissue mediastinal mass (Hida et al). The heart has been reported in 7 cases, in which more often the (right) atrium has been reported as the site of involvement (Ajise et al).

There have been 9 cases of Rosai-Dorfman disease submitted to our AMR seminars so far. Seven of them were from extranodal sites, including kidney (Seminar # 29, case 6 by AP Dei Tos), skin (Seminar # 35, case 18 by LM Weiss), bone (1 patella and 1 tibia: Seminar # 46, case 16 by DV Spagnolo and Seminar # 55, case 22 by Wakely, Jr, respectively), brain & meninges (Seminar # 49 – case 7 by V Eusebi), somatic soft tissue (thigh - Seminar # 55, case 6 by I Damjanov). Only two cases were of nodal involvement, 1 neck lymphadenopathy (Seminar # 4. case 6 by G Herrera) and 1 para-aortic lymphadenopathy (SHML associated with Hodgkin's disease, Seminar # 16, case 11 by DV Spagnolo). In other terms only 1 case of typical RDD was circulated in AMR seminars in 1991, when only 9 of the current 44 AMR participating members were in the club at the time. The case herein described is a classical case with classical histology in a classical nodal location, in an adult patient with classical constitutional symptoms, classical hematochemical laboratory abnormality (positive direct Coombs test), and intrathoracic manifestations, who was treated (maybe for the first time) with autologous bone marrow
transplant by means of peripheral CD34-positive blood stem cells.

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AMR SEMINAR #60
CASE 7

Contributed by: Michele Bisceglia, M.D. (slides "A" labeled 178566-9 and slides "B" labeled 180437-9)

Clinical History and Diagnosis: In April 2009 a 70-year-old Caucasian man underwent surgical excision of a subcutaneous lump of 1.5 cm in size, located on the right lateral side of the lower neck, suspected to be a lymph node metastasis of unknown origin, which was histologically examined. Histologically the tumor nodule corresponded to a nodular metastatic seeding of a basal cell carcinoma with focal squamous cell differentiation. The tumor infiltrated adipose tissue and no residual of lymph node parenchyma was visible (slide A – labeled 178.566-9). This man had a clinical history dating back to 2004 of repeated surgical excisions of 2 cutaneous metachronous basal cell carcinomas, 1 located on the nose, 1 of which locally recurred 4 times, and 1 on the left nasolabial ridge, respectively. All slides relating to the original cutaneous tumors were reviewed and all histological diagnoses confirmed, including the lack of any squamous component in any of them. The former tumor of 1 cm in size and the subsequent recurrences were of the nodular type and the second tumor of 0.2 cm was a morphea-like variant; both exhibited classical pure cytological features of basal cell carcinoma with no foci of squamous cell differentiation. After the diagnosis of *subcutaneous metastasis from (cutaneous) basal cell carcinoma* with squamous cell differentiation was rendered, on June 2009 the patient underwent ipsilateral radical neck lymph node dissection. From the surgical specimens a total of 18 lymph nodes were identified, 13 of which were massively involved by metastatic basosquamous carcinoma, with invasion into perinodal fibroadipose tissue in 3 (slide B – labeled 180.437-9).

Follow-up: This patient was then given adjuvant local external radiotherapy. Since he lives in my same hometown I called him up and spoke with him over the telephone just today 30th May 2011. His last follow-up was just few days ago (24 May) and was found ANED.

Comments: In 2004 (AMR Seminar # 44, case 3) I had the opportunity to contribute another case of a cutaneous basal cell carcinoma metastatic to bone in a 43-year old lady. Multiple systemic skeletal metastases, involving cranium, vertebral column, ribs, pelvis, and left femur, and bilateral lung metastases were well documented in that case by radiological and scintigraphic examinations. AMR members received sections from a needle biopsy from the iliac bone. That was a case of a retroauricular locally recurring tumor, which previously underwent three excisions over the last 7 years. That patient died in 5 months after metastatic disease was discovered. *Here is the comment I sent at that time (now updated and with different references).*

Basal cell carcinoma of the skin is the most frequent malignant tumor in humans (mostly in Caucasian populations), with an approximate incidence of 400,000 to 750,000 new cases per year in USA. It usually does not give rise to metastasis. However there are exceptions to this rule and this case as well as the case presented in 2004 are two of these exceptions. Based on a computerized literature search a few more than 300 of such ordinary (histologically-proven) cutaneous metastasizing cases of basal cell carcinomas have been found on record up to 2010 (Tavin et al; Ting et al; Saladi et al; Robinson et al; personal updated review). The frequency of such an occurrence is around 1:10,000 histologically examined cases (range: 1 out of 1,000-30,000 histologically examined basal cell carcinomas) (Van Domarus et al; Motegi et al). The interval time for the appearance of metastasis is dated between 1 and 25 years after the original diagnosis of the primary cutaneous tumor. The tumor has the ability to spread by both the lymphatic and hematogenous routes, with the regional lymph nodes (mostly cervical lymph nodes), lung and bones as the most frequent sites of metastatic seedlings. Several factors, including male gender, tumor size, duration, histology, lymphatic invasion, and perineurial spread have been postulated as markers of the aggressive basal cell carcinoma phenotype (Walling et al). Liver, brain and kidney as well as soft tissue (either nearby or on the route to lymph nodes) have also been rarely described as the sites of metastasis. Around 85% of basal cell carcinoma which metastasized were located in the head and neck area (Malone et al), however metastases have been recorded also with tumors from special areas, including breast [nipple-areola complex], axilla and other non-facial sites, and male and female genitals (Ferguson et al; Martorell-Calatayud et al; Berlin et al; Feakins et al; Jones et al; Ribuffo et al). Only less than 15% of cutaneous metastasizing basal cell carcinomas have been found harbouring foci of squamous cell carcinomas in the main tumor mass either in the primary or in the metastasis (van Domarus et al). Although it has been never proved that the metastatic capability of a cutaneous basal cell carcinoma is imparted to it by the associated squamous tumor component, according to some the basosquamous variant of basal cell carcinomas are considered more aggressive forms (Martin et al; Garcia et al). Only two cases of the metastasizing basal cell

carcinomas so far described occurred in the context of a nevoid basal cell carcinoma syndrome (Lamon et al). Lymph node sentinel has been successfully used in a case where lymphatic invasion was seen during examination of the primary excision specimen (Harwood et al). No effective therapy has been devised for basal cell carcinoma in metastatic phase and the experienced mean survival time from the diagnosis of (systemic) metastasis is of 10 months. Our 1st patient from 2004 with systemic metastases died in 5 months, while the current one (with regional metastases) is ANED now 2 years post surgery.

Conclusively: *i.* basal cell carcinoma is a very low grade malignancy, which needs be radically treated by surgery as most of the metastasizing cases in the literature recurred repeatedly before they metastasized; *ii.* metastasis from a cutaneous basal cell carcinoma should be considered by clinicians at least when evaluating cervical lymph node metastases of an uncertain head and neck primary.

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AMR SEMINAR #60
CASE 8

Contributed by: Thomas Colby, M.D.

Clinical History: A 26-year-old man presented with a soft tissue tumor of the posterior chest wall that clinically appeared to be underneath the inferior end of the scapula. A biopsy, which included neoplasm and overlying skin, was taken. Unfortunately the recuts for the club are from deeper in the block and relatively little tumor is left but the morphology was the same throughout.

Pathologic Findings: On H & E slides there is a cellular neoplasm with necrosis in the deep dermis and soft tissue. Some might call this a "small blue cell tumor." The cells are small to intermediate in size and some have slight spindling. Mitotic activity is abundant. PAS stains with and without diastase did not show appreciable glycogen. Our accessioner initially thought this patient was a woman and since I had not history other than "chest wall" I included ER staining in addition to a number of other stains. My initial battery of immunostains gave the following results:

AE1/AE3 – moderate to strong positivity in approximately 25% of the neoplastic cells
EMA – moderate to strong positivity in more than 50% of the neoplastic cells
Desmin – positive with dot-like pattern in some foci
Estrogen receptor– diffuse strong positivity in all of the neoplastic cells
Myogenin – negative
CD99 – negative
CD138 – negative
CD45 – negative
Synaptophysin – negative
S-100 – negative

My initial differential had included proximal epithelioid sarcoma and various small blue cell tumors. The above staining pattern raised the possibility of a desmoplastic small round cell tumor (that was not so desmoplastic) and with that consideration I got a WT-1 which was negative (with good internal control positivity in the small vessels).

At that point I realized that I was out of my depth so I enlisted the help of Andrew Folpe who documented by fluorescent ISH that the tumor was positive for SS18 (SYT) gene rearrangements in 90% of the cells. TLE-1 was diffusely positive. RT-PCR for desmoplastic small round cell tumor was negative as was FISH for EWS gene rearrangements. Cytokeratin 20 and myo-D1 were negative. His conclusion was that this was a poorly differentiated synovial sarcoma with anomalous expression of desmin (and I guess ER).

Diagnosis: Poorly differentiated synovial sarcoma with anomalous expression of desmin (and I guess ER).

Since I was running short of interesting lung cases to share with the club, I decided to make a foray into soft tissue pathology (fortunately with an experienced collaborator). I would appreciate comments from the group regarding the desmin expression and the strong positivity for ER.

Contributed by: Goran Elmberger, M.D. - (Case Elmberger Karolinska 110413)

Clinical History: A 54-year-old male with a 3 year history of a slowly growing tumor in superficial parotid gland. Consult case: probably benign – R/O very low-grade mucoepidermoid carcinoma.

Pathological Findings: Microscopy revealed a 6 mm sized well-delineated but not encapsulated nodule surrounded by normal parotid salivary gland. Parts of the lesion consists of a lobular adenosis like proliferation of small tubuloacinar structures. In other areas variably sized microcysts in a densely fibrotic and sparsely inflamed background were seen. Focally, lamellar periductal fibrosis, giant collagen rosettes and collagen spherulosis were noted. A minor focus of psedoinfiltrative ductular proliferation was seen. No atypical intraductal proliferations or invasive component could be detected. Neither could typical macrocytes or epidermoid cells be demonstrated.

Special Studies: The constituent cells were a biphasic proliferation of epithelial and myoepithelial cells where the myoepithelial cells formed a continuous abluminal layer surrounding every ductal and acinar structure. (Fig 1). The cells were S-100 positive and also showed a weak nuclear staining for ER and AR (Fig 2). Proliferation rate 2 % ki-67.

Fig 1. p63 IHC of myoepithelial cells surrounding all acinar and ductular proliferations.
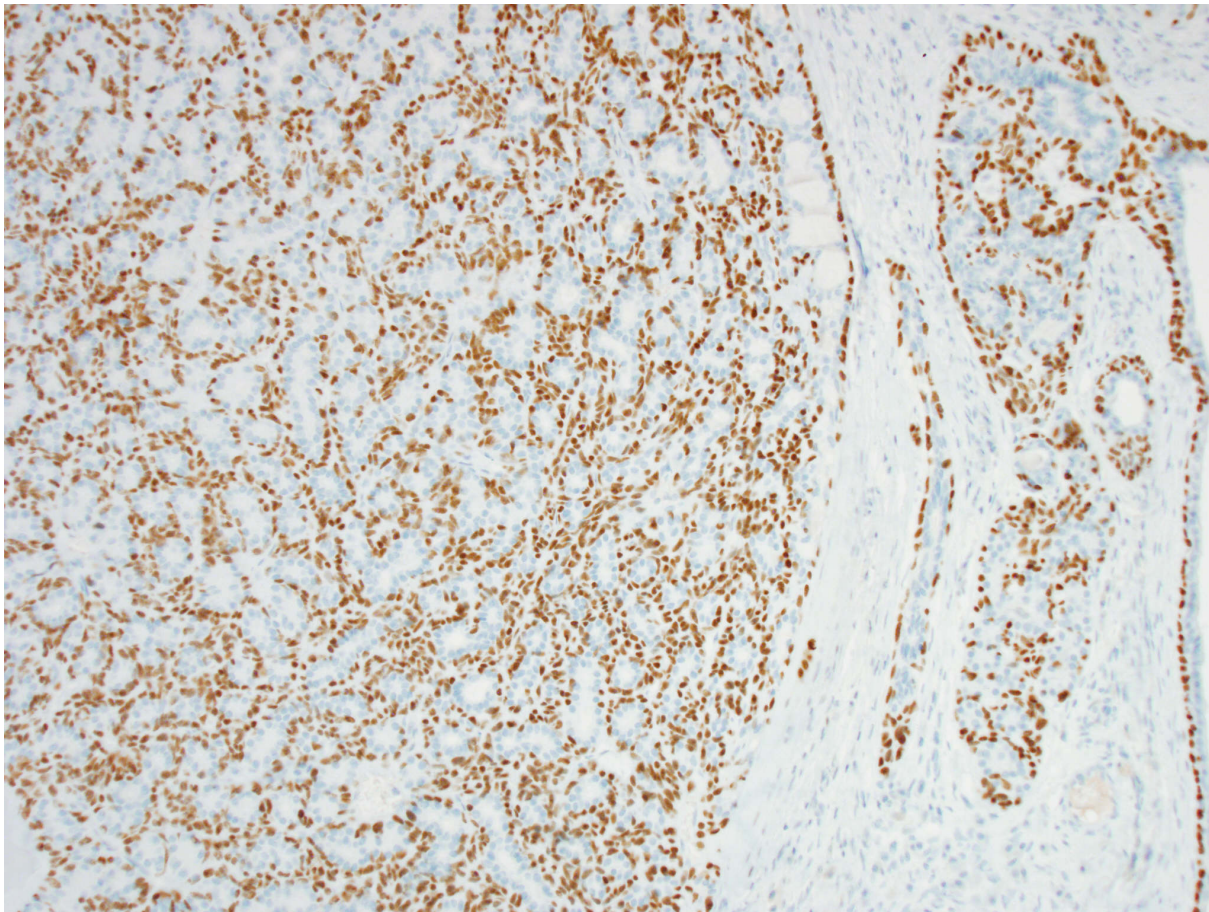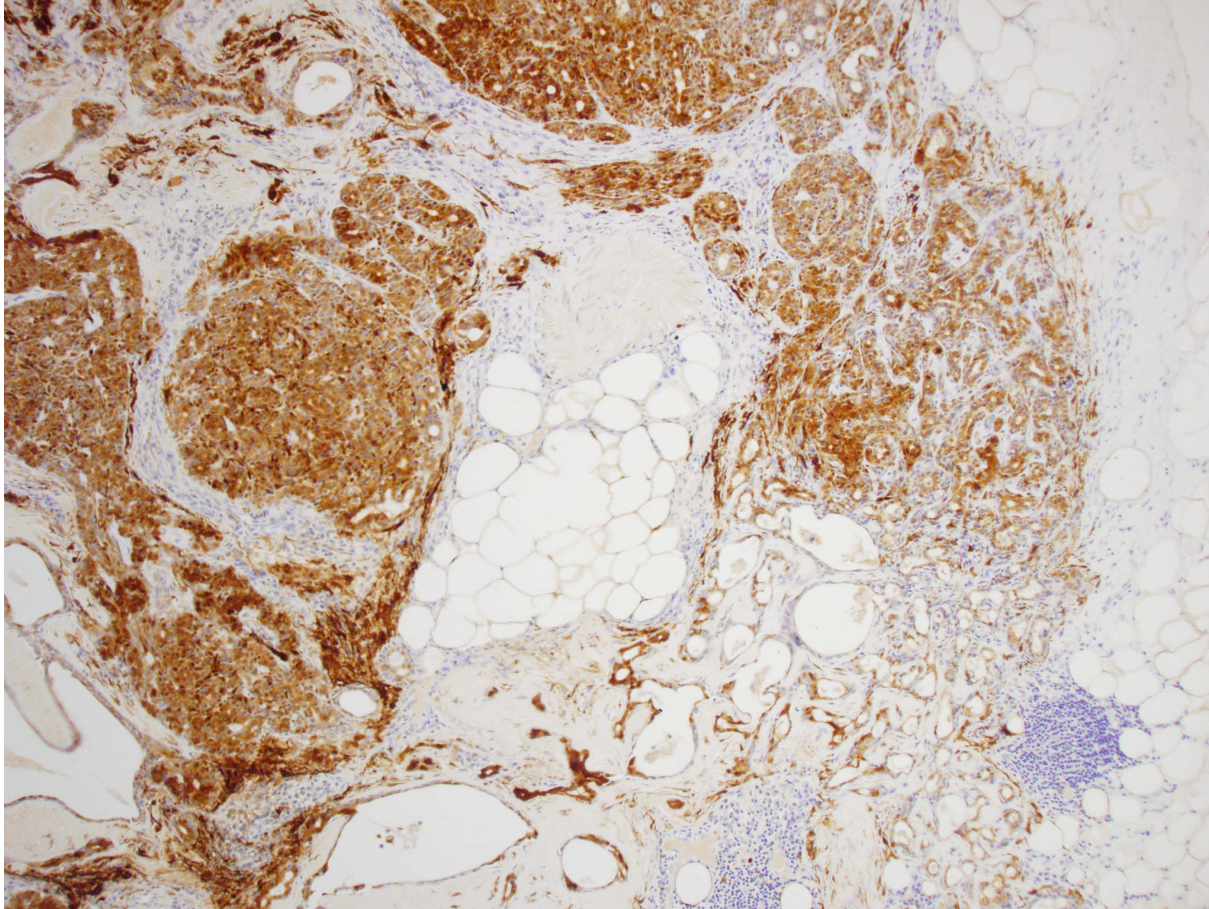
Fig 2. S-100 IHC including psedoinfitrative ductular proliferation.

FISH and RT-PCR for t(11;19) CRTC1-MAML2 were both negative.

Diagnosis: Sclerosing polycystic adenosis (SPA) of parotid gland

Follow-up: NA

Discussion: This case represents a very classical fit to the original descriptions of the entity as published by Smith et al 1996. Up to date there are 21 publications and around 50 cases in the literature. The true nature of the lesion is unknown, but it has originally been seen as a pseudoneoplastic proliferative disease similar to benign fibrocystic breast disease. Lately Skalova et al have published evidence on its monoclonal nature using the HUMARA assay. This may go well in line with a recurrence rate of 30 % and recent publications of cases associated with development of DCIS. So far I am not aware of any case with a fully developed invasive carcinoma but I suspect this could happen just as in the breast. Lately one publication claim that SPA is an EBV related disease (Swelam et al 2010) but confirmatory studies are still lacking and since I was not aware of the publication I missed the chance to test this consult case. Once being familiar with the entity I believe it is quite unique but the main differential diagnoses would in my mind be obstructive sialoadenitis, cystadenoma and low-grade mucoepidermoid carcinoma.

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AMR SEMINAR #60
CASE 10

Contributed by: Jonathan Epstein, M.D.

History: A 72-year-old man with a serum PSA level of 3.7 ng/ml was noted to have an abnormal digital rectal exam (cT2b). A 12 core needle biopsy was performed. Five cores were diagnosed as "Intraductal adenocarcinoma of the prostate", and a radical prostatectomy was performed.

Macroscopic Findings: The prostate weighed 70.5 grams with prominent BPH. No gross lesion was noted that was suspicious for carcinoma.

Microscopic Findings: The majority of the right side of the prostate was replaced by cribriform glands with round lumina lined by cuboidal epithelium. While some glands were expanded by the process, the overall configuration of the glands in terms of their size, branching, and spatial configuration with intervening stroma was consistent with an intraductal process. Some of the cribriform glands contained relatively few lumina relative to epithelium and multiple glands contained comedonecrosis. Cytologically, the nuclei were enlarged with prominent nucleoli yet not overtly pleomorphic beyond what would be seen in HGPIN. There were two minute separate foci of Gleason score 3+3=6 adenocarcinoma in the left lobe (not shown). Several of the slides show cribriform carcinoma in vessels which represent contamination from detached fragments of tumor.

Immunohistochemical Findings: Five paraffin blocks were studied with a triple cocktail of p63/high molecular weight cytokeratin/AMACR. Every cribriform gland was invested with a basal cell layer.

Diagnosis: Extensive intraductal carcinoma of the prostate (IDC-P) with separate incidental minute foci of Gleason score 3+3=6 adenocarcinoma.

Comment: As it is critical to distinguish between HGPIN and IDC-P, as the former is typically not treated with definitive therapy and recent data has questioned whether HGPIN on needle biopsy even requires immediate rebiopsy within the first year following its diagnosis, we have developed stringent criteria for its diagnosis on needle biopsy. The definition of IDC-P is: Malignant epithelial cells filling large acini and prostatic ducts, with preservation of basal cells composed of: 1) solid or dense cribriform pattern , or 2) loose cribriform or micropapillary pattern with either marked nuclear atypia (nuclear size 6 x normal) or comedonecrosis. Dense cribriform glands contain more epithelium (>70%) than lumina, whereas cribriform HGPIN demonstrates the reverse. These objective morphological criteria either architecturally or cytologically clearly exceed those seen in HGPIN. Cases which do not satisfy the strict criteria for IDC-P on needle biopsy yet appear more atypical either architecturally or cytologically than usual high grade PIN can be diagnosed as borderline between IDC-P and high grade PIN with a recommendation for repeat biopsy.

Typically, IDC-P is seen on biopsy and radical prostatectomy (RP) in the presence of Gleason score 8 or 9 infiltrating cancer. In our series of 23 RPs done for IDC-P on biopsy, more than ½ of the cases showed extra-prostatic extension; almost all the cases with organ-confined cancer were not totally submitted for histological examination.[1] Only 2(10%) cases were similar to the current case with no identifiable infiltrating cancer in the totally submitted specimens. Rarely, IDC-P may be identified on biopsy material in the absence of infiltrating carcinoma. Based on earlier studies done on RP and the two studies that we have done on RPs following IDC-P on biopsy, we recommend definitive therapy (radiation or RP) for IDC-P even though infiltrating cancer is not identified. [1-5]

Infiltrating cribriform acinar adenocarcinoma (Gleason pattern 4 or Gleason pattern 5 with comedonecrosis) closely mimics cribriform IDC-P. Most cases of IDC-P would be diagnosed as cribriform carcinoma if immunohistochemistry demonstrating basal cells had not been performed. In some cases, the contour and branching pattern of normal duct architecture distinguishes IDC-P from infiltrating carcinoma. Ultimately, the presence of a basal cell layer with immunohistochemistry rules out infiltrating acinar prostate adenocarcinoma. Despite the presence of comedonecrosis, Gleason pattern 5 adenocarcinoma is ruled out also by the identification of a basal cell layer. On

biopsy when there is both infiltrating high grade cancer and IDC-P, we diagnose these lesions as, for example, "Gleason score 4+4=8 adenocarcinoma of the prostate with associated intraductal carcinoma" and for the extent of cancer measure the entire process without separately measuring the IDC-P component. In the uncommon setting where we see lower grade cancer and IDC-P, we diagnose, for example, "Gleason score 3+3=6 adenocarcinoma of the prostate with IDC-P" and add a note stating: "Intraductal carcinoma is more frequently seen with Gleason patterns 4-5 carcinoma although these are not present on the current tissue samples." so that the clinicians do not consider the patient as only have Gleason score 6 cancer.

There is significant morphological overlap between ductal adenocarcinoma of the prostate and IDC-P. Ductal adenocarcinoma is defined by its cytology consisting of tall pseudostratified columnar epithelium usually with amphophilic cytoplasm, classically arranged in cribriform patterns with slit-like spaces and/or true papillary fronds. In contrast, IDC-P has cuboidal cells, cribriform patterns with rounded lumina, and micropapillary tufts without fibrovascular cores. Typically, basal cells are absent in ductal adenocarcinoma. However, just as acinar (usual) adenocarcinoma of the prostate can have an intraductal component (IDC-P), ductal adenocarcinoma can arise in or extend into ducts and have a preserved basal cell layer. Although we don't use the term "*Intraductal* ductal adenocarcinoma" for ductal adenocarcinoma with basal cells, it is analogous to IDC-P for acinar carcinoma. Similar to IDC-P, we recommend definitive therapy for ductal adenocarcinoma even if there is a preserved basal cell layer, as it is recognized that it is almost always associated with an invasive aggressive component.

There are two explanations for IDC-P. Prostate cancer patients with IDC-P have higher Gleason scores and larger tumor volumes and are more likely to show seminal vesicle involvement and disease progression than those without IDC-P.[5] While high grade PIN is often present in prostate glands that have not yet developed invasive carcinoma, IDC-P is almost always associated with invasive cancer. Morphologically, one can often see what appears to be partial involvement of a gland with solid nests of IDC-P suggesting intraductal spread. These findings support that IDC-P often represents an advanced stage of tumor progression with intraductal spread of tumor. However, cases such as the one presented demonstrate that IDC-P may be an in-situ process, representing a more advanced in-situ malignancy than HPGIN. Given the relative uncommon situation of IDC-P without associated invasive carcinoma, IDC-P must quickly and readily go on to invasion as opposed to HGPIN. For this reason, definitive therapy is justified for IDC-P on biopsy, even in retrospect for the uncommon case where only IDC-P is seen at RP.

I remember an astute comment made to me by Juan at one USCAP meeting drawing an analogy of IDC-P with breast pathology. He stated that HGPIN and IDC-P are analogous to low and high grade DCIS of the breast, respectively. I am in total agreement conceptually. Not that Juan was recommending a change in terminology, but I would not use term "low grade DCIS" to denote HPGIN. The word "carcinoma" in low grade DCIS would cause many men to be overtreated or undergo repeat biopsy for a lesion that when unifocal poses no increased risk of subsequent carcinoma over 2-3 years, and regardless of the extent should not be treated by RP in the absence of infiltrating cancer.

References:

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AMR SEMINAR #60
CASE 11

Contributed by: Giovanni Falconieri, M.D., Udine, Italy
(Case contributed by Maurizio Mirra, M.D., General Hospital, Lodi, Italy)

Clinical History: The patient is a 68-year-old lady who has recently undergone lobectomy for a 6 cm pulmonary opacity discovered incidentally during the work up of some minor clinical problems

Pathologic Findings: The mass is expansile rather than infiltrating, and is basically composed of spindle to epithelioid cells with a moderate amount of clear or slightly granular cytoplasm. Nuclei are oval to spindle, with fine chromatin, inconspicuous nucleoli, lacking mitotic activity. I have not noticed significant atypia.
Minor features were scattered islands of mature adipose tissue and patchy lymphoid aggregates.
All the stains tried have been negative (ker, EMA, S100, Melan-A, HMB45, desm, CD34, bcl2, CD99, plus many others). PAS and PAS-D are negative as well.

My initial thought was a "stromal tumor" with adipocytic component, I guess benign, yet I was not able to offer better interpretations

The case was sent out to Suster for his diagnostic opinion which I am summarizing as follows:

… Very strange lesion but the only thing similar to this I have seen before is sugar tumor. I've just reviewed the stains I ordered on this case. They are all negative, including PAS-D for intracellular glycogen. Morphologically it looks like a clear cell sugar tumor. Although S100 and HBM45 positivity can be very spotty and weak in PECOmas, you should be expected to see at least some positivity - but this tumor is completely clean and negative. Moreover, the lack of intracellular glycogen is also another factor that speaks against that diagnosis. I'm afraid I don't have a diagnosis to offer in this case other than a generic and descriptive "clear cell tumor of unknown etiology ….

Dr. Suster also recommended to circulate this amongst the club members. Hence, any further suggestion shall be very welcome!

AMR SEMINAR #60
CASE 12

Contributed by: Franco Fedelli, M.D.

Clinical History: A 79-year-old-female presented with a left adrenal mass.

Macroscopic Findings: There was a 11x 9,5x 6 cm tumor that weighed 450 g. Cut surface was brownish with diffuse necrotic appearance. No follow-up is available.

Microscopic Findings: The microscopic appearance was that of an invasive cellular proliferation obscuring the normal appearance of the adrenal cortex. Extensive foci of necrosis and hemorrhage were observed. The tumor cells were arranged in solid sheets or nests and frequently lined vascular spaces. The morphology of the tumor cells lining the vascular spaces was epithelioid with round vesicular nuclei with prominent centrally placed eosinophilic nucleoli. The cytoplasm was eosinophilic. Mitotic activity and pleomorphism were readily found. The tumor cells showed rare intracytoplasmic lumina, often contained red blood cells. Inflammatory cells were present in the surrounding connective tissue. Residual adrenal cortical tissue could be identified at the periphery of the neoplastic proliferation.

Immunohistochemical Findings: The tumor cells were intensely positive for CD31, FVIII-Rag, CK Cam5.2, WT1, Vimentin. Cd34 and CK7 were focal and weak positive. Negative for CK20, P63, 34   12, S-100 protein, Chromogranin, Synaptophysin, Desmin, HMB-45 and D2-40 and FLI-1

Diagnosis: Epithelioid angiosarcoma of the adrenal gland

Comments: Primary adrenal gland soft tissue sarcomas are rare. To the best of mine knowledge less than twenty-five cases of epithelioid angiosarcomas of the adrenal gland are described in the literature. Nine of these were described by Bruce Wenig in 1994 (1). The average age is 60 Y.O. Epithelioid variant of angiosarcoma occurs principally in the skin, thyroid and deep soft tissues. For unknown reasons adrenal angiosarcomas share an epithelioid cell appearance. Immunohistochemical studies play a major role in establishing the vascular nature of this tumor.

This case as well as the cases reported in Wenig's papers was intensely positive for keratin. On the other hand the same immunoreactivity has not been observed in a study of eighteen cases as reported by Carlos Bacchi in 2010 (2). The identification of epithelial markers, may confuse epithelioid angiosarcoma with adrenal cortical carcinoma or metastatic carcinoma. The absence of S-100 protein and HMB-45 excludes metastatic malignant melanoma.

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AMR SEMINAR #60
CASE 13

Contributed by: Masaharu Fukunaga, M.D.   (S10-3313)

History: A 36-year-old, gravida 1, para 1, female presented with abdominal discomfort. CT, MRI and physical examination revealed a mass with calcification in the pelvic cavity. At laparotomy, a mass was found in the right broad ligament. The uterus and bilateral ovaries and tubes showed no abnormality. She underwent excision of the broad ligament mass and right salpingo-oophorectomy. The patient is alive with no evidence of disease at 4 months after surgery.

Macroscopic Features: A yellowish, white solid mass measuring 6.5x6.0x5.0cm. No hemorrhage or necrosis was seen.

Immunohistochemical Studies: CAM5.2, vimentin, calretinin, CD10: (++), EMA, CEA, ER, PGR, D2-40, inhibin – alpha: (1).

Diagnosis: Wolffian tumor of the broad ligament (female adnexal tumor of probable Wolffian origin).

Comments: Several members had submitted this type of tumor. The present case shows clinically and histologically typical features. The tumors are unilateral and usually found in the leaves of the broad ligament, occasionally in the fallopian tube or ovary. Histologically, it is solid with scattered cysts or dilated glands. The solid areas consist of sheets of cells or hollow tubules. The stoma is fibrous with basal lamina-like changes. The differential diagnoses include sex-cord stromal tumor and adenocarcinoma. The behavior of the tumor is unpredictable, with a potential to develop delayed local recurrence or distant metastasis after many years. All tumors should be considered to have a malignant potential and the follow-up should be prolonged.

References:

1. Kariminejad MH, Scully RE. Female adnexal tumor of probable Wolffian origin: a distinctive pathologic entity. Cancer 31; 671-677, 1973.

2. Young, RH, Scully RE. Ovarian tumors of probable Wolffian origin: a report of 11 cases. Am J Surg. Pathol 7; 125-136, 1983.

AMR SEMINAR #60
CASE 14

Contributed by: Thomas Krausz, M.D.

Clinical History: 75-year-old male with second recurrence of tumor obstructing the left main bronchus in 2011. Previous bronchoscopic resections of intrabronchial tumor in years 2001 and 2002.

Pathological findings: Anastomosing islands of biphenotypic tumor cells with focal acinar formation infiltrating the bronchial submucosa. The morphologic features are consistent with a "salivary gland type" tumor exhibiting both epithelial and myoepithelial differentiation. Rare tumor cells contain targetoid intracytoplasmic mucin. Mitotic figure is difficult to find. Immunohistochemical findings are consistent with epithelial and myoepithelial differentiation: smaller myoepithelial cells are positive for p63, S100, cytokeratin 5/6, weakly positive for cytokeratin 7 but negative for keratin Cam5.2; luminal cells are positive for cytokeratin Cam5.2, cytokeratin 7, and also positive for cytokeratin 5/6. The tumor islands are separated by prominent stromal spindle cells which are immunoreactive for SMA but negative for keratins.

Diagnosis: Salivary gland type tumor, most consistent with low-grade epithelial-myoepithelial carcinoma (low grade adenomyoepithelioma)

Comments: This tumor was first resected bronchoscopically in 2001 and resection of recurrence was performed in 2002. The completeness of the resections could not be determined on the fragmented specimens. The patient presented this year (2011) again with bronchial obstruction and bronchoscopic resection was performed (representative fragments were submitted for AMR seminar). The histologic features of the current specimen are similar to those seen in the previous excisions. The WHO classification of bronchial salivary gland type tumors is still debatable. I found it difficult to classify this tumor precisely as dual epithelial-myoepithelial differentiation is common in both benign and malignant salivary gland type tumors. The intracytoplasmic mucin in some of the tumor cells is also a bit puzzling in this context. I favor the diagnosis of low grade epithelial/myoepithelial carcinoma (low grade adenomyoepithelioma), but I would like to know from members whether they would regard this tumor as benign or malignant, and which diagnostic category they favor.

AMR SEMINAR #60
CASE 15

Contributed by :   Alberto M. Marchevsky, M.D.
(Case contributed by Daniel Luthringer, M.D., Cedars-Sinai Hospital, Los Angeles, CA)

Clinical History: 40-year-old man with end-stage renal disease secondary to lupus nephritis. He was diagnosed with systemic lupus in 1998 that was treated with immunosuppressive medications, but gradually became dialysis dependent in April 2008. Recent imaging studies of the kidney showed a left renal mass. He underwent left radical nephrectomy, adrenalectomy and retroperitoneal lymph node dissection in May 2011.

Pathology Findings: End-stage kidney involved by numerous vascular tumors scattered throughout the renal parenchyma. They range in size from 1 mm to 2.8 cm, and focally involve the perinephric fat and a retroperitoneal lymph node. The neoplasms are composed of endothelial cells which are generally flattened, without cytologic atypia or mitotic activity. They form small vascular channels with an overall lobular architecture. Focal extramedullary hematopoiesis is present. Immunohistochemical studies for CD4, CD5 and CD8 to explore for possible splenic differentiation were negative.

Diagnosis: Anastomosing hemangiomas of the kidney.

Comments: Anastomosing hemangioma of the genitourinary tract is a rare neoplasm that often exhibits "spleen-like" anastomosing growth features. It can be mistaken for angiosarcoma due the appearance of anastomosing cells and local invasion. Limited follow-up in the small number of reported cases supports that the lesion is benign. They need to be distinguished from other vascular lesions of the kidney, including arteriovenous malformations, identical to those in other locations, capillary hemangioma and angiosarcoma. The latter exhibit cytologic atypia and mitotic activity, features absent in our case.

References:

-    Brown JG, Folpe AL, Rao P, et al. Primary vascular tumors and tumor-like lesions of the kidney: A clinicopathologic analysis of 25 cases. Am J Surg Pathol 2010:34:942-949.
-    Montgomery E, Epstein JI. Anastomosing hemangioma of the genitourinary tract. A lesion mimicking angiosarcoma. Am J Surg Pathol 2009;33:1364-1369.

AMR SEMINAR #60
CASE 16

Contributed by : Thomas Mentzel, M.D., Germany

Clinical History: Initially, we received fragments of a recurring myxoid soft tissue neoplasm arising on the left lower leg of a 69-year-old female patient (the H&E slides were cut from two different blocks).

Pathological Findings: Histologically, an infiltrating fibroblastic neoplasm of low cellularity is seen. The neoplastic cells contain relatively uniform spindled nuclei and are set in a prominent myxoid stroma containing numerous elongated vessels.

Initial Diagnosis: Recurring myxoid fibroblastic neoplasm.

Comments: Given the clinical informations listed above the differential diagnosis is between recurring myxoma of soft tissues and low-grade myxofibrosarcoma. Despite the information that the neoplasm recurred, the diagnosis of an infiltrating, recurring myxoma was given tentatively. After many phone calls it turned out that the patient had developed multiple myxomas as well as "low grade myxofibrosarcomas" during the last eleven years on the lower extremities. In addition, the radiologists found changes comparable with fibrous dysplasia. With these additional informations we performed molecular studies and found a mutation of the *GNAS1* Gene in codon 201, and the final diagnosis was **multiple myxomas in Mazabraud syndrome**. Mazabraud syndrome represents a rare spontaneous disorder first described in 1967, that occurrs more frequently in female adults and is characterized by polyostotic fibrous dysplasia associated with multiple myxomas of soft tissues. A clinical overlap with McCune-Albright syndrome has been reported and discussed in the literature. The presence of *GNAS1* mutations in a considerable number of cases of intramuscular myxoma, that were present in the included case as well, is very interesting, given the fact that the same changes are found in fibrous dysplasia.

References:

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AMR SEMINAR #60
CASE 17

Contributed by: Elizabeth Montgomery, M.D.

History: This was a cervical esophageal pedunculated mass that resulted in dysphagia and was resected from a 56-year-old woman. The lesion had been seen at endoscopy as a pedunculated mass 27 cm from the incisors (cervical esophagus) with overlying unremarkable squamous mucosa and was assumed clinically to be a giant fibrovascular polyp but imaging had not disclosed an adipose tissue component. It was technically impossible to perform a polypectomy and thus a partial esophagectomy was performed.

Diagnosis: Solitary fibrous tumor with areas of giant cells (giant cell angiofibroma/giant cell rich solitary fibrous tumor).

Comments: The lesion features spindled cells, haphazard collagen, a "hemangiopericytoma"-type vascular pattern, and scattered giant cells (I hope they are on everyone's slides). We did not perform immunolabeling as the histologic features were so typical but would have expected the lesion to be immunoreactive for CD34 but not for actin, desmin, or S100 protein. This entity is not a novel one to this group but the location was really fun since we would expect either a leiomyoma or giant fibrovascular polyp based on the history. The patient has been free of recurrence/metastases for about 2.5 years (the lesion was resected in Fall 2008).

References:
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AMR SEMINAR #60
CASE 18

Contributed by: Cesar Moran, M.D.

Clinical History: A 56-year-old man presented with chest pain and cough of several weeks duration. Past history revealed that the patient may have been exposed to asbestos. Chest radiographic imaging showed the presence of a density in the right side. A prior biopsy done elsewhere was reported a "fibrous tissue." Because of the clinical history and imaging the possibility of mesothelioma was raised. A wider excision of the lesion was performed.
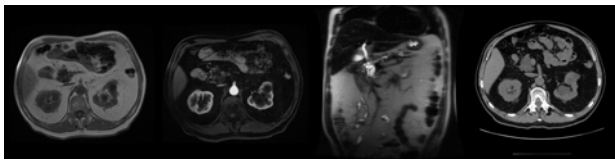
Diagnosis: Elastofibroma

AMR SEMINAR #60
CASE 19

Contributed by: Santiago Ramon y Cajal, M.D.

History: 68-year-old male patient in his usual state of health, who while being studied for hypertension, was found to have an incidental mass in the head of the pancreas on a CT scan. His past medical history was only significant for type 2 DM. The abdominal CT scan showed a polycystic mass of 3.5 cm in the head of the pancreas communicating with the main pancreatic duct. Differential diagnosis was mucinous cystadenoma of the pancreas or intra-ductal papillary mucinous tumor (IPMT).

A partial pancreato-duodenectomy was performed.

Pathology: Macroscopically, sections of the pancreas showed markedly dilated pancreatic ducts with a maximum diameter of 2.5 cm. Microscopic pathology showed cystic ducts lined by adenomatous epithelium.
The surrounding pancreas was extensively involved by chronic pancreatitis with significant loss of normal architecture. Therefore invasion is extremely challenging to rule out. In this case I could not convince myself about invasion in any of the sections. IHC for muc1, muc2 and p53 are non-contributory.

Diagnosis: Intra-ductal papillary mucinous tumor with low grade dysplasia.

Comment: I wanted to share this case which can be very challenging and in which we still rely so much on the old fashioned "good eye".   As a follow-up, one year post treatment, pt is well, no recurrence has been found.

References:
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AMR SEMINAR #60
CASE 20

Contributed by: Dominic Spagnolo, M.D. ,PathWest Laboratory Medicine, Nedlands, Western Australia (Accession Q11B5939K).

Case History: 83-year-old female with 3 months' history of rapidly growing, solitary, painless, velvety skin nodule left chest wall. Clinically well without fever, sweats or weight loss. No medications. No significant past history. Skin biopsy performed (slide provided).

At review one month later found to have four further small pink papules 5–15 mm in size. These increased in number to 12 over one week, all limited to the trunk. There was no lymphadenopathy or hepatosplenomegaly. Peripheral blood examination was normal. Bone marrow had some increase in monocytoid cells but no myelodysplastic features, no increase in blasts or evidence of leukemic infiltration (outside review). Marrow cytogenetics showed a duplicate ring 1q chromosome of uncertain significance. Commenced on etoposide 50mg daily. The skin lesions resolved completely within 2 weeks. No change at last follow-up approx. 3 months after presentation.

Pathological features: A diffuse infiltrate of mononuclear cells fills and expands the dermis and is separated from epidermis by a narrow grenz zone. There is infiltration into subcutaneous fat both along expanded septa and interstitially within lobules. There is no epitheliotropism, angiocentricity or angioinvasion. The infiltrate is composed of medium sized and large cells (2 - >4x size of small lymphocytes) arranged dyscohesively. "Squaring off" of intercellular borders is evident. The cells have rounded, ovoid or reniform nuclei with stippled chromatin and one or more generally small nucleoli though macronucleoli are evident in some of the larger cells. The cytoplasm is moderately abundant and amphophilic to lightly basophilic with a suggestion of fine basophilic stippling in some cells at high power. On close scrutiny, only in very rare cells can fine eosinophilic granules be discerned in the cytoplasm. There are no mature granulocytes. Mitotic figures abound and there are scattered apoptotic cells throughout the infiltrate. Very few small mature lymphocytes may be found widely dispersed in the infiltrate.

Immunohistochemistry: As I was also presenting the case in another forum, an over-inclusive panel of immunostaining was performed from the perspective of an "undifferentiated" hematolymphoid infiltrate of skin. The malignant cells stain as follows:
Positive: CD4, CD56 (both strong, diffuse), myeloperoxidase (heterogeneous, <50%), CD68 (KP1 clone; strong, diffuse), CD68 (PGM1 clone; fewer than KP1), CD163 (heterogeneous), CD15, CD43 (patchy), CD23, BCL2 (weak), MIB1 ~70%;
Negative: CD45RA, CD123, TCL1, CD303 (BDCA-2), CD2AP, BCL11A, CD3, CD2, CD5, CD7, CD8, CD57, TIA1, perforin, granzyme B, TdT, CD1a, CD99, CD34, CD117, ALK1, EMA, CD30, CD1A, langerin (CD203), S100, CD20, PAX5, CD138, CD10, cyclin D1, MUM-1, CD21, CD61, EBER.
Interphase FISH: No evidence of any of the following: *RUNX1-RUNX1T1* fusion associated with t(8;21)(q22;q22); *CBFB* inv(16)(p13.1q22); *PML-RARA* fusion of t(15;17)(q22;q12); *MLL* (11q23) abnormalities; trisomy 8.

Diagnosis: Cutaneous myeloid sarcoma ("aleukemic" myeloid leukemia cutis), consistent with acute myelomonocytic leukemia (AMML).

Discussion: At the risk of annoying at least some friends and colleagues, I have submitted a hematolymphoid case. The diagnosis of myeloid leukemia cutis (MLC) in this case is not particularly problematic. The morphology and immunophenotype (MPO+, CD68+, CD163+, CD15+, other lineage markers negative) is definitive, though the strong and diffuse CD4 and C56 coexpression present a pitfall if it is not realized that these antigens may be expressed in MLC. The CD23 (low affinity Fc-epsilon receptor II for IgE) positivity is unusual but may occur in a minority of AML cases.

The classification of myeloid neoplasms is according to the latest WHO classification (2008) of acute myeloid leukemia (AML) and related precursor neoplasms. The incidence of specific subtypes in the skin according to this latest scheme is not clear as there are few published data and early publications based on previous classifications (FAB) do not translate accurately into the latest WHO classification. Nevertheless, the overall prevalence of cutaneous involvement in patients with myeloid neoplasms is estimated at about 3%, occurring most frequently in

AMML and acute monoblastic/monocytic leukemia (AMoL) where as many as 50% of patients develop skin lesions. In the case presented, in the absence of fresh tissue for cytochemical and flow cytometry assessment the precise classification remains uncertain but the overall features are consistent with AMML. In any event, when confronted with such an infiltrate, urgent haematological opinion is indicated to determine the status of the blood and bone marrow and to enable precise classification of the process.

Extramedullary myeloid sarcoma (MS): In a recent review of 92 cases of adult MS of any site (Pileri 2007), there was a slight male predominance, the median age was 55.8 yrs and the most frequent sites of involvement were skin (28%), lymph nodes (16%), testis (6.5%), intestine (6.5%), bone (3%) and CNS (3%). 27% presented with *de novo* MS, 35% had simultaneous AML, idiopathic myelofibrosis or myelodysplastic syndrome (MDS) and 38% had a previous history of AML, myeloproliferative disorder (MPD), mastocytosis or MDS. Notably, 40% of *de novo* cases had been submitted in consultation with alternative unrelated diagnoses. Most cases were of the "blastic" variant (now probably including the categories of AML with minimal differentiation or without maturation), followed by monoblastic and myelomonocytic categories. CD68(KP1) was the most frequently expressed marker, followed by MPO, CD117, CD99 and CD68(PG-M1). 89.5% died of disease at median F/U of 150 months. Patient outcome was not affected by age, sex, site, *de novo* disease or coexistence with AML, MDS or other MPD, morphology, immunophenotype or cytogenetic features. Patients treated aggressively as for AML and including allogeneic or autologous marrow transplantation, seemed to have a better outcome than those receiving less aggressive therapy.

Myeloid leukemia cutis: Patients with acute (or less commonly, chronic) myeloid leukemias may develop cutaneous leukemic infiltrates, typically in the setting of known AMLs, particularly those showing monocytic differentiation. Chronic MPD or MDS cases with cutaneous involvement indicate blastic transformation to AML as there are no cutaneous phases of the chronic disorders *per se*. AML presenting *ab initio* in the skin is much less common and may occur in the absence of blood and marrow disease (aleukemic leukemia cutis) or it may occur simultaneously. Typically, there are multiple violaceous plaques or nodules, either localised or generalised. More rare, as in this case, is presentation as a solitary nodule. Other uncommon presentations mimic specific dermatoses such as viral or drug eruptions or leukemic vasculitis. In most patients with a cutaneous presentation evolution to frank leukemia occurs usually within a year of presentation and the prognosis is poor.

The largest series of MLC was recently published as a French multi-institutional retrospective study of 173 cases (Bénet 2011) classified according to the earlier FAB classification. Males predominated (M:F = 1.4:1) and the median age was 62 yrs. The lesions were solitary in 23%, multiple in 77% and there was no site predilection. *De novo* presentation occurred in 7.5%, in 27% there was concurrence with a known myeloid disorder, in 61% the skin became involved subsequent to the diagnosis of a myeloid disorder and in 5% the chronology was not known. 65.3% of the cases (113) were AML and those showing monocytic predominance were overrepresented in skin compared with peripheral blood; 56% were FAB 4 or 5 (FAB4-AMML 13%, FAB 5-AMoL 43%), 21% were FAB 0-2. Medium sized cells predominated in most cases but nearly 20% had mixed medium and large cells. Mitoses typically were few. AMLs with monocytic differentiation (FAB 4,5) were significantly more likely to have a greater tumour cell density and to be composed of larger cells than FAB 1,2 cases. Antigen expression in the 173 MLC cases was as follows: CD68 (97%), CD163 (52%), CD14 (35%), CD4 (61%) – these were considered as monocytic markers; MPO (63%), CD33 (93%), CD117 (30%) – considered to be myeloid markers; and CD56 (19%), CD123 (9%), CD303(BDCA-2) (3%) – considered to be plasmacytoid dendritic cell (PDC) markers.

In this series, *de novo* cases of MLC were more likely to have these characteristics:
- AML-FAB 4 or 5 (ie. with monocytic features)
- multiple rather than solitary nodules
- diffuse pattern of infiltration
- high tumour density
- large cell morphology, high mitotic index and apoptosis
- intense CD4 and CD56 expression, and widespread CD68 positivity.

It is worth making some points concerning tissue immunophenotyping in MLC. Approximately 50% of all MLC cases may be MPO negative therefore a negative result does not exclude MLC. While MPO and CD33 are often considered as markers of myeloid/granulocytic differentiation, they lack specificity as they are frequently positive in cases showing monocytic differentiation. CD68 (KP1) shows high sensitivity for MLC across all categories but has low specificity in distinguishing between the subtypes. Note that CD68 (PGM-1 clone) has relatively greater specificity for the monocytic lineage. CD4 is reported in ~40% of AML-FAB 1,2 cases (and in up to 60% of all AML cases). Thus, none of these markers can be taken to be specific for distinguishing between myeloid (granulocytic) and monocytic differentiation. CD56 is positive in ~20-50% of all cases of MLC and is more often positive in AML-FAB 4,5 than AML-FAB 1,2 cases. There is a strong correlation between CD56 and CD4 expression. In the series of

Bénet *et al*, 85% of CD56+ cases were also CD4+ (most were AML), though 2 cases were later reclassified as blastic plasmacytoid dendritic cell neoplasms (BPDCN).

The stem cell marker CD34 is rarely positive in MLC (~5%) and CD117 is also uncommonly positive (~30%). There is frequent discordance between antigen expression by tissue IHC in cutaneous infiltrates compared with the concurrent marrow infiltrates (flow cytometry), particularly for these antigens. Thus, these markers cannot be used to indicate the presence of blasts in skin. To a lesser extent, discordance may be found for other markers including CD56 and MPO.

The PDC markers CD123 and CD303 are rarely expressed in AML-FAB 1,2 and are more likely to be positive in acute or chronic myelomonocytic cases.

Cytogenetics: Data pertaining to MLC are few. Numerical abnormalities of chromosome 8 (trisomy mainly), a myeloid-associated but nonspecific aberration, appear to be significantly more common in AML patients with, than without cutaneous involvement, typically in AML-FAB 4,5.

Differential diagnosis: There are several differentials to be considered in this case, particularly in the context of an infiltrate which is strongly CD56+ and CD4+.
1. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
2. Lymphoblastic leukemia/lymphoma (precursor)
3. Non-Hodgkin lymphoma (mature; T or B)
4. Anaplastic myeloma
5. Mast cell sarcoma
6. Histiocytic/dendritic neoplasms
7. Non-hematolymphoid neoplasms, e.g. Merkel cell carcinoma; metastases.

CD56+ cutaneous hematologic lesions: A multicentre study was recently conducted by the Cutaneous Lymphoma Task Force of the EORTC to define prognostic features and to establish diagnostic and therapeutic guidelines in 34 patients with CD56+ hematologic neoplasms presenting in the skin (Assaf 2007).

Based on clinical, histological, immunophenotypic and molecular features, the cases were classified as follows:
1. Blastic plasmacytoid dendritic cell neoplasms *(20)*
2. AML, CD56+ *(4)*
3. Extranodal NK/T-cell lymphoma, nasal type *(5)*
4. "Classical" primary cutaneous T-NHL, CD56+ *(5)*.
Of the AML cases (AMML) all were CD56, CD33, CD4, CD68 and MPO positive. The PDC markers CD123 and TCL-1 were positive in 1 of 2 cases, and in 2 of 3 cases studied, respectively.

With the exception of the last category, all other cases had a very poor prognosis (93% died of disease, median survival of 11 months). Patients with T-NHL, nos, were all alive at last follow-up (median 62 months). While the study emphasizes the importance of the correct categorization of CD56+ hematological infiltrates of skin in respect of prognostication, it should be noted that the cases of T-NHL studied (lymphomatoid papulosis, mycosis fungoides, subcutaneous panniculitis-like T-cell lymphoma) self-select for relatively indolent behavior as this group did not include other aggressive forms of cutaneous T-NHL (e.g. gamma-delta T-NHL). Within the AML group, it has been previously recognized that CD56 expression may be associated with a more aggressive course and reduced survival compared with CD56 negative cases, and to have a greater propensity for extramedullary involvement at presentation, particularly involving skin and lymph nodes.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN):
Given the CD4+ CD56+ phenotype, the main consideration is that of a BPDCN which shares very similar clinicopathological features with MLC and which has far greater morphological and immunophenotypic heterogeneity than originally thought. Typically the cells of BPDCN are of medium size and the nuclear chromatin has a more blastoid quality but by morphology alone it is not be possible to make a distinction from MLC. Until recently the diagnosis depended on finding the CD4+ CD56+ phenotype (+/- CD45RA, CD68) in the absence of other lineage-specific markers. But none of these is specific for BPDCN and there is considerable overlap with myeloid neoplasms, particularly chronic forms. However, there are now *relatively* more specific markers for this entity (Marafioti 2008) (paraffin-reactive, commercially available) - CD123, TCL1, CD303 (BDCA2), CD2AP, BCL11A, IRF8 - though it should be remembered that none of these has 100% specificity for BPDCN. While the myeloid marker CD33 may be expressed in these cases, myeloperoxidase is always negative, whilst CD7 may be positive in both AML and BPDCN.

Some cases of BPDCN may evolve into, or be associated with various myeloid proliferations. In up to 20% of CMML cases there are tumoral accumulations of mature PDC and at least in some there are shared identical clonal cytogenetic aberrations. This underscores the relationship between these lineages.

Lymphoblastic leukemia/lymphoma (LBL) :
Precursor LBL shows relatively frequent cutaneous involvement though precise data are few. Whilst in most cases there is known underlying LBL, in rare cases, even after thorough staging the skin is the sole site of involvement at presentation (more often in B-LBL than T-LBL) though evolution to frank leukemia typically ensues within weeks to months. The morphology can mimic BPDCN and MLC, but immunophenotyping should readily resolve the diagnosis (mixed lineage leukemias notwithstanding). The precursor markers TdT, CD10, CD34 and CD99 are typically though variably expressed, in addition to B- or T-lineage markers. Note that TdT is not infrequently positive in BPDCN and may also be expressed in AML.

Other considerations:
Primary or secondary cutaneous NHL (mature) should be readily resolved on the basis of the clinical features, morphology and an appropriate immunohistochemistry panel. In particular, NHL cases with high grade "blastoid" features might be confused with leukemia cutis (blastoid forms of mantle cell or follicular lymphoma, Burkitt lymphoma, DLBCL either conventional or showing features borderline with other aggressive lymphomas). Note that some MLC cases may express CD30 (potential for misdiagnosis of null-ALCL). Similarly, various histiocytic/dendritic neoplasms (Langerhans cell histiocytosis, histiocytic sarcoma, indeterminate dendritic cell neoplasm, follicular dendritic cell tumour, interdigitating dendritic cell sarcoma) can be distinguished clinicopathologically and by including in the IHC panel, appropriate discriminating antibodies (S100, CD21/23/35, CD1A, Langerin/CD203, CD163). Exceptionally rare is dot-like keratin positivity which may lead to confusion with metastatic carcinoma.

SUMMARY: The case illustrates the uncommon presentation as a solitary cutaneous nodule of aleukemic MLC (most likely AMML) strongly expressing CD4 and CD56 and thus necessitating distinction from other mimics, particulary BPDCN.

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AMR SEMINAR #60
CASE 21

Contributed by: Eduardo Zambrano, M.D.

Clinical History: 9-month-old baby girl from South America presented with an enlarging and infiltrative right maxillary bone lesion. A clinical photograph and CT images are available at the AMR website. The mass was excised and recurred 5 months later. No other lesions were apparent. Clinical history was otherwise unremarkable.

Immunohistochemistry: Immunohistochemical stains showed SMA and HHF35 expression (available at AMR website) and focal bcl-2, while desmin, EMA, CD34, CD99 and S100 were negative. Beta-catenin was predominantly expressed in a cytoplasmic distribution, but occasional nuclei were also positive.

Diagnosis: Low-grade myofibroblastic neoplasm.

Discussion: I interpreted this lesion as a low-grade myofibroblastic neoplasm. The lesion is certainly locally destructive and has recurred shortly after initial excision. I am not sure how to further classify it, but I raised the possibility of a desmoid-type infantile fibromatosis. Other aggressive myofibroblastic tumors of infancy, in particular infantile fibrosarcoma and myofibroma/myofibromatosis, seem less likely to me given its morphologic features. Any concurring or dissenting thoughts will be greatly appreciated.

AMR SEMINAR #60
QUIZ CASE 1

Contributed by: Manuel Sobrinho Simoes, M.D., IPATIMUP, Portugal

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