AMR Seminar #50 Short Summary of Cases

Case 1: A mass on the right calf of a 77 year old male was removed.

Case 2: A 29 year old man was seen for pleural masses following treatment for Hodgkin's lymphoma at age 10, mesenteric fibromatosis at age 14 and a soft-tissue axillary mass at age 20 (slides are from the current pleural mass and from the previous axillary mass).

Case 3: A 76-year old woman presented with a short history of new onset neck mass.

Case 4: A 47-year old lady was investigated for a systemic arterial hypertension. At ETG-scan she was found harbouring a small left kidney as well as a sacciform aneurysm of the homolateral renal artery.

Case 5: A 64-year-old ex-smoker presented with chest pain and dyspnea and was found to have a pneumothorax. A giant bulla was noted in the right upper lobe.

Case 6: A 77 year-old female was found to have a tumor in the left kidney, focally calcified by image studies.

Case 7: A 51-year-old man was found to have an incidental 3.8cm solid mass in the right upper quadrant of the abdomen on an abdominal ultrasound. A subsequent CT scan revealed a 3x4cm homogeneous mass thought to arise from the posterior aspect of the 2nd portion of the duodenum, as well as a 1.4x3 cm mass in the lumen of the 3rd portion of the duodenum.

Case 8: A 73 year old woman presented with a pigmented skin lesion on the capilitium.

Case 9: A 50 year old man was seen for vague abdominal discomfort. A gastric biopsy showed minute raised granular areas in the antral mucosa.

Case 10: A 40-year-old woman was evaluated for abdominal pain and pruritus. An ultrasound scan of the liver revealed a lobulated, inhomogeneous mass.

Case 11: A 32-year-old, gravida 0, para 0, Japanese woman showed on MRI a 5-cm subserosal mass in the uterine fundus. Intraoperatively, a rubbery solid uterine mass attached to the left broad ligament was found and locally excised.

Case 12: An infant presented with a bulging blue-purple congenital scalp mass that was resected on the first day of life. The resected 7.8 x 2.6 cm. specimen was partly covered by skin.

Case 13: A 73 year old male patient developed a 2.3 x 1.2 x 1.2 cm. dermal nodule on his chest wall. A cylindroma has been excised at that site twelve years previously.

Case 14: A 93 year old man with diarrhea underwent flexible sigmoidoscopy with biopsy of an "unremarkable" segment of sigmoid colon. There were no biopsies or manipulation of the right colon. By the next day, the patient had perforated in the ascending colon, which necessitated surgical intervention.

Case 15: A 47 year old man was evaluated for symptoms of dysuria and hematuria. Radiographic examination revealed a right kidney mass. A right partial nephrectomy was performed.

Case 16: A 67 year old woman had a 7x6 cm. mass of the parietal and visceral diaphragmatic pleura and a 2.5 cm. pleural tumor at the right lower lobe removed.

Case 17: A 53 year old woman presented with a 4 cm distal pancreatic mass and surgical resection was performed. Histologic sections revealed moderate to poorly differentiated adenocarcinoma. We subsequently discovered that six months prior to her admission, she had surgery at another hospital for bilateral ovarian tumors.

Case 18: This skin lesion was taken from a 74 year old female in 1999. It was a roughly 12 mm diameter nodule present at the end of a scar on the abdominal wall, said to be the site of a previous lymph node biopsy.

AMR SEMINAR #50
CASE 1

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

History: This specimen was sent as a mass on the right calf of a 77 year old male, with the suggested clinical diagnosis of squamous cell carcinoma. No other specific clinical history was offered.

Pathologic findings: Gross examination demonstrated a 2 cm. nodule. Histological examination shows nests of primitive undifferentiated malignant cells with a high mitotic rate. The nests show varying degrees of discohesion resulting in the formation of irregularly shaped and sized spaces, some containing amorphous material. There is no palisading. Focally bowenoid dysplastic changes are seen in the neighboring epidermis (*note: this is seen only in some of the slides prepared for the seminar: my apologies. I'm including photos of this finding for those who receive the slides which don't demonstrate this*). Immunohistochemical staining showed the following results for the tumor: pan-keratins: diffuse membranous staining; CK20, p63, CK5/6- all negative; CK7- diffuse strong positivity; hmwk- diffuse positivity; Ber-Ep4-positive; EMA-focally positive; and TTF-1, S100- negative. The neighboring dysplastic foci were positive for CK7 and also p63.

Diagnosis: High grade undifferentiated adnexal carcinoma.

Discussion: My initial working diagnosis was Merkel cell carcinoma with a differential diagnosis of basaloid squamous cell carcinoma. The immunohistochemical results do not confirm these diagnoses; the question is whether they categorically refute them. However with regard to the first possibility- Dr Mark Wick in his study of Merkel cell tumors in comparison with other skin tumors which would enter into the histological differential diagnosis (Appl Immunohistochem Mol Morphol 2000: 8(1), 37-41), found a group of cases which were CK20 negative but positive for CD99 (I did not have staining for CD 99 performed). So CK20 negativity alone does not get us home free with regard to this possibility. While CK7 is reported to be negative in Merkel cell tumors according to a classical study coauthored by Lawrence Weiss (Chu et al, Mod Pathol 13 (9) 2000: 960-972), in another report (Jensen et al, Appl. Immunohistochem. Mol. Morphol. 2000: 310-315) it was positive in 6 of 23 cases. Thus I admit that the CK7+/CK20- phenotype while unlikely is not necessarily impossible in a Merkel cell tumor. However at least in our hands here the chromogranin staining was not what I would expect for a Merkel cell tumor.

I think that the negativity for p63 rules out consideration of a tumor related to squamous carcinoma or a hypothetical congener of basal cell carcinoma- as a test I tried staining two BCC's from the files and they stained uniformly for p63. In normal skin, CK7 is strongly positive in the secretory portion of eccrine sweat glands. I also found positivity in sebaceous glands and focally in the sheaths of hair follicles. Out of curiosity I tried CK7 on a random case of basal cell carcinoma and in fact in our hands it stained positively- this may result from an affinity of BCC to adnexal tumors. The sweat glands were also positive for hmwk.

A study was published a few years ago applying various antibodies to the problem of differentiating cutaneous adnexal tumors from metastatic tumors (Qureshi et al, J Cutan Pathol 31(2) 2004: 145-152). While CK7 was positive in both groups, in the former it tended to be focal in a specific pattern while in the latter it was diffuse. One could then suggest the possibility of a metastatic tumor. This would be hard to rule out categorically; as often happens with biopsy material a diagnosis is made based on the sketchy information the provider of the specimen (in this case the plastic surgeon) is able or willing to give; the patient then is referred to the oncologist who takes a decent history and reveals information that may cast the findings in a different light. For this patient (whose biopsy was taken a few weeks ago) I don't have as yet any supplementary data. One aspect which would support this being a primary tumor is the bowenoid dysplasia focally found at the periphery of the lesion; interestingly while still maintaining the immunophenotype of the native squamous epithelium (p63 positive) this tissue is acquiring the CK7 positivity seen in the tumor and not seen elsewhere in the non neoplastic epithelium. The negativity for staining with TTF-1 does not support the possibility of a small cell carcinoma metastatic from somewhere (though of course one could ask if it rules it out completely).

I accept that some would prefer to interpret the irregular spaces in the tumor as abortive gland formation rather than as a non-specific phenomenon related to discohesion; in the former situation the diagnosis of poorly differentiated adenocarcinoma becomes incumbent. Actually these spaces remind me of the "follicles" seen in the small cell hypercalcemia related carcinomas of the ovary seen characteristically in young women.

Usually adnexal tumors are noted for their arcane nature, in that they usually demonstrate very intricate patterns of differentiation at times making their exact diagnoses difficult. The highly undifferentiated nature of this tumor places it at the opposite end of the spectrum. In fact there is a published entity called small cell sweat gland carcinoma in childhood (Busam et al, Am J Surg Path 1997, 22(2): 215-220). To be applicable to this case the acceptable age limits of this tumor to the extent known would have to be stretched; additionally according to the photos included in the article, while the cytology of the individual cells in this entity seems similar enough to that of this case, overall it shows a greater amount of organoid features and architectural differentiation. I also found a very recent reference entitled "Eccrine porocarcinoma of the ear mimicking basaloid squamous cell carcinoma" (Kienzner et al, Otolaryng Head Neck Surg 2006, 135 (1): 158-160). However according to the photos in the article the constituent cells show definite squamoid features which are totally absent from this case; immunohistochemical findings were not reported.

Dr Wick in the paper cited above included in his study a group of tumors he called basaloid eccrine carcinomas, which he says have a potential for recurrence and metastasis less than that of Merkel cell tumors. In the most recently issued fourth series AFIP fascicle on non-melanocytic skin tumors (#4) edited by Drs. Wick and Patterson, under the rubric of "Eccrine carcinomas that histologically simulate metastatic tumors", subheading "Ductal eccrine adenocarcinoma" it is stated that some examples of this subtype have a "peculiarity.... to be composed of compact, almost basaloid cells", which may lead to the mistaken diagnosis of basal cell carcinoma. The illustration (fig 4-72) with the legend "small cell basaloid eccrine ductal adenocarcinoma" is very reminiscent of the case I am presenting. I haven't succeeded in finding any mention of this tumor described as an entity in the literature outside of the references Mark Wick himself has made to it in the context of other discussions. Given the confusion that this tumor is capable of creating it might be worthwhile to separately publish these cases as a specific entity.

Dr Wick's statement in the new fascicle concerning the utility of EMA staining as an indicator of sweat gland origin in poorly differentiated skin tumors in which the differential includes basal cell carcinoma I think is applicable to this case. In fact EMA was positive, which goes along with this tumor being a poorly differentiated sweat gland neoplasm.

Acknowledgements: I would like to thank our colleagues from the seminar group, Drs Bisceglia, Mentzel, and Wick for taking the trouble of responding to my email queries with helpful advice based on their unique experience with this type of problem. Additional thanks to Thomas Mentzel for reviewing the slides and for performing immunohistochemical stains, and to Mark Wick for sharing with me the relevant material from the new fascicle (which I haven't managed yet to buy).

AMR SEMINAR #50
CASE 2

Contributed by: Ofer Ben-Itzhak, MD

History: A 29 year old man was seen for pleural masses following treatment for Hodgkin's lymphoma at age 10, mesenteric fibromatosis at age 14 and a soft-tissue axillary mass at age 20 (slides are from the current pleural mass and from the previous axillary mass). The patient presented at the age of 10 with fever, weight loss and a huge retroperitoneal and pelvic mass and anterior mediastinal mass. A biopsy of the mass revealed Hodgkin's lymphoma, nodular sclerosis (stage IIIB). He was treated with total nodal irradiation of 4000 rad ("mantle" and "inverted Y" fields) and chemotherapy with subsequent complete remission. Four years later (age 14) he presented with abdominal pain and abdominal mass suspected of recurrent lymphoma. An 11 cm mesenteric mass along with a segment of proximal ileum was resected (the mass was not contiguous to adhesions of the previous laparotomy, but was in the radiation field). Histology showed typical mesenteric fibromatosis (the slide is not distributed). The patient presented again at age 20 with a left axillary mass (slide A, from 1997). This year the patient (age 29) presented with persistent right pleural effusion. CT showed a large right pleural effusion with right pleural coarsely calcified masses. Thoracoscopic pleural biopsy showed small nodules (slide B, from 2006, courtesy of Dr. Hector Cohen from Western-Gallilee Hospital, Naharia). Postoperative bone-scan showed prominent pathological absorption in the right hemithorax, probably pleural, involving also the right ribs, the sternum and the vertebrae.

Pathologic Findings: The 1997 left axillary mass was 2.5x2x1.5 cm showing a spindle cell tumor with central ossifications and myxoid areas with epithelioid cells, focal nuclear atypia and rare mitoses. The tumor infiltrates the skeletal muscle and extends up to the surgical margins (reexcision was not performed).

The 2006 pleural tumor has features of osteosarcoma, high-grade. Calretinin and cytokeratin were negative in tumor cells, vimentin was positive. P53 stain was diffusely positive in the pleural tumor, but was negative (retrospectively) in the 1997 axillary tumor.

Beta-catenin (retrospectively performed) was positive in the mesenteric fibromatosis, while negative in the axillary and pleural tumors.

Comments: There are several unusual aspects of this case:

1. Postradiation mesenteric fibromatosis. This case was described by us in a previous report along with another case[(1)] . This patient's fibromatosis had the regular histologic features of fibromatosis, and did not have the "bizarre cells with large hyperchromatic nuclei" of postradiation fibromatosis (Rosai's textbook, 9th ed., p. 2252).
2. The axillary mass, also in the radiation field, 10 years postradiation. I do not know the nature of this tumor. Probably an atypical myofibroblastic cell proliferation with ossification?
3. (a) Pleural osteosarcoma. Extraskeletal osteosarcoma of the pleura is exceedingly rare [(2) (3)] . Most pleural tumors with histology of osteosarcoma are either metastatic [(4)(5)] or represent areas resembling osteosarcoma in sarcomatoid mesothelioma [(6)].
   (b) Postradiation osteosarcoma.

This sarcoma arising 19 years following radiation in the radiation field is consistent with postradiation sarcoma. Children treated with high-dose radiotherapy which is combined with chemotherapy are at the greatest risk for developing postradiation osteosarcoma [(7)]. The mean latency period for the development of postradiation sarcoma in a large series was 15.5 years [(8)].

I would be grateful to have your opinions regarding this patient's tumors:
- What is the nature of the axillary mass. Is it benign? Low-grade malignant?
- Could there be an association between the axillary tumor and the subsequent pleural tumor?

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AMR SEMINAR #50
CASE 3

Contributed by: Gerald Berry, MD

History: This 76-year old woman presented with a short history of new onset neck mass in March 2006. An ultrasound was obtained by her primary care physician, which showed a 5x7x1 cm mass in the left lobe of the thyroid. A preoperative serum thyroglobulin level was not obtained. She underwent total thyroidectomy. Postoperatively the CT scan of the neck and thorax showed small mediastinal lymph nodes measuring less than 0.5cm and no hilar adenopathy. A 0.7 cm nodule was found in the LUL, along with a 0.6 cm nodule in the RLL.

Microscopic Findings: As the surgery was performed elsewhere we don't have any details about the gross appearance of the left thyroid lobe lesion. Microscopic sections display an anaplastic carcinoma with sarcomatous features. The mesenchymal component consists of osteosarcoma with abundant chondroid differentiation. The epithelial component is distributed around the peripheral of the neoplasm. Focal weak immunoreactivity against EMA and cytokeratin CAM5.2 is present. TTF-1 and thyroglobulin staining are negative.

Diagnosis: Sarcomatoid variant of anaplastic carcinoma of the thyroid

Comment: We seem to be seeing more cases of anaplastic carcinoma of the thyroid these days. I thought this was a nice example of the sarcomatoid or metaplastic variant. The patient will receive adjuvant chemotherapy consisting of 6 cycles of cisplatinum, adriamycin and cytoxan followed by radiation therapy. The prognosis unfortunately continues to be quite dismal except for the small subset of patients with demonstrable anaplastic carcinoma arising in a differentiated type such as papillary or follicular carcinoma.

AMR SEMINAR #50
CASE 4

Contributed by: Michele Bisceglia

History: The patient is a 47-year old lady, who was investigated for a systemic arterial hypertension. Her renal function was normal. At ETG-scan she was found harbouring a small left kidney as well as a sacciform aneurysm of the homolateral renal artery. Intravenous pyelography was not performed. The patient underwent angiography of abdominal arteries which confirmed the left renal artery aneurysm, also disclosing "hypertrophy and elongation of homolateral adrenal arteries", and further revealed an aneurysm of the splenic artery. The angiographic study of the supra-aortic vessels discovered morphologic findings consistent with "bilateral dysplasia of carotid arteries". The patient was otherwise normal. The arterial hypertension was ascribed to nephrovascular pathogenesis, and the patient underwent surgery. A total left nephrectomy was performed, but the section on the renal artery was made just immediately distal to (or adjacent to) the aneurysm, which was so not included in the surgical specimen (i.e. the renal artery aneurysm was surgically tied, but not resected as far as I could learn from the surgeon).

Pathologic Findings: The left kidney was 6x4x3 cm in size. The renal artery was abnormally ramified, almost arborizing, with 8 total arterial branches seen at the level of the renal sinus, before entering the renal parenchyma. The diameter of the main renal artery was 4 millimetres. The venous system was also abnormal and 5 veins were seen coming out of the kidney at the hilum. On cut surface the kidney did not disclose any macroscopic abnormality, which I could grossly recognize, but the number of pyramids was lower than normal (I count only 4 minor calyces).
Histologically (slide labelled 122148-6), at the level of the medulla many, radially arranged, small cystically dilated collecting ducts are seen, some of which can also be seen emptying into the corresponding minor calyx, which is represented in the slide. The epithelium lining the dilated ducts is immunoreactive for CK7 and EMA (and negative for CK20). No cyst or cystic dilation in the cortex is seen, but some degree of interstitial nephritis is present. The pelvis as well as the short ureteral segment, included in the surgical nephrectomy specimen, were hypoplastic, but histologically normal. The renal arteries as well as the veins were histologically normal.

Diagnosis: The cystic dilation of the collecting ducts was considered as expression of the condition known as medullary sponge kidney. The kidney was also considered as congenitally hypoplastic (both hypoplasia of the main renal artery and on the low number of minor calyces/pyramids are strongly in support of the congenital pathogenesis).

Comment: Medullary sponge kidney is a non-genetically transmitted disease -usually asymptomatic- characterized by the presence of ectasia of papillary collecting ducts(ducts of Bellini) in the renal medulla, congregating at the papillary tips, and involving one to all of pyramids (hence the alternative name of cystic disease of renal pyramids) (1). Papillary duct ectasia (or precalyceal canalicular ectasia) is likely a congenital anomaly which is not discovered until complications have supervened. It is commonly radiographically detected in adults, although pediatric cases are even on record (2). Kidneys are bilaterally affected, with normal size and intact function, which on intravenous urography show characteristic radial linear streaking in the renal papillae as contrast medium collects in the ectatic or cystic papillary collecting ducts analogized with a "bouquet of flowers". The main clinical symptom is given by renal lithiasis, which –in contrast with expectations- only occasionally has the staghorn morphology (3)>>>>. Renal infections (ascending pyelonephritis) may occur, and hematuria may also be the presenting symptom; and even a tumor may be mimicked on occasion (4). The true prevalence of the disease is unknown; however estimates range from 1 in 5,000 to 20,000. There is no sex predilection, and the risk of renal failure is modest, and related to renal infections and the formation of struvite stones.

Medullary sponge kidney is also eponymically known as Lenarduzzi (radiologist)-Cacchi (urologist)-Ricci (pathologist) disease. The best review of the disease in point has recently been published by an Italian group from Padua and Verona (5), i.e., the same Universities where the eponymic authors also used to work between the late thirties and early seventies of the last century (actually Lenarduzzi was radiologist in Padua at the time of the first descriptions of the disease in 1939-1949; Cacchi was a fellow of the Institute of Urology in Padua, and then was

appointed as a professor at the University of Ferrara in 1950; Ricci, who was assistant at the Anatomic Pathology Institute in Padua at that time, then became professor of Otorrhinolaryngology in Verona in 1970s).

The case herein presented is one of the rare cases (around 10%) in which other congenital abnormalities affecting the kidney are found in association with medullary sponge kidney: a list of congenital disorders associated with medullary sponge kidney is presented as a Table in the quoted ref. 5. Those authors distinguish 3 groups of these congenital disorders occasionally associated with the disease in point: congenital hemihypertrophy and Beckwith-Wiedemann syndrome; congenital dilation of intrahepatic bile ducts and hepatic fibrosis, and ADPKD; and uncommon or anecdotal abnormalities (among which Ehlers-Danlos syndrome, renal artery fibromuscular dysplasia, and few others).

Thus, although the pathogenesis of medullary sponge kidney has yet to be elucidated, its association with these malformative conditions supports the idea that it is a developmental disorder.

The hypothesis has been proposed that the disease is the consequence of a disruption of the ureteral bud / metanephric blastema interface: normally the ureteral bud from Wolff's mesonephric duct is induced to branch thanks to the glial-derived neurotropic factor (GDNF) which is produced by the metanephric blastema, which binds to RET, a GDNF receptor expressed by the ureteral bud itself. The correct interaction induces normal nephrogenesis, morphogenesis and normal kidney growth (5). The above mentioned authors conclude that "*molecular studies are needed to confirm the hypothesis but, if it proves correct, we would expect to find other renal developmental abnormalities of the processes depending on RET/GDNF binding (i.e. unilateral renal agenesia, or unilateral or bilateral renal hypoplasia, or renal district duplication, …) ……. We ourselves have observed six cases of congenital, monolateral small kidneys in a systematic analysis of 72 medullary sponge kidney patients*>>> (5). <u>The hypoplasia associated in the case herein presented must be one of these expected abnormalities</u>.

The RET receptor involvement in this hypothesized mechanism might also explain the association of this condition with primary hyperparathyroidism as well as the (so far) unique case of MEN-2a patient (combining medullary thyroid carcinoma with primary hyperparathyroidism) in which RET protooncogene gene mutation is documented. From the differential point of view we would like just to mention the condition known as *medullary cystic kidney disease***,** which is also quite semantically misleading. <<<<<Medullary cystic kidney disease (MCKD), has common pathologic features with juvenile nephronophtisis (JNPHP), and is characterized by the presence of small cysts located at the corticomedullary junction and deeper in the renal medulla, arising from the distal convoluted and collecting tubules, alongwith some tubulointerstitial damages (1). Medullary cystic kidney disease as well as juvenile nephronophtisis usually lead to end-stage kidney disease (hence the alternative term of uremic medullary sponge kidney to refer to the entire dual group). JNPHP, an autosomal recessive condition linked to mutations in more than one gene, occurring at different ages, has been mapped to chromosome 2q (juvenile form –NPHP1, with nephrocystin as a gene product [OMIM #256100), chromosome 9q (infantile form –NPHP2 [OMIM #602088]), chromosome 3q (adolescent form –NPHP3 [OMIM #604387]), and chromosome 1p36 (juvenile form –NPHP4 [OMIM #606966]), accounting for the 70% of all cases of the JNPHP/MCKD group. JNPHP usually presents in the 1st decade of life. Between 10-20% of cases are associated with tapeto-retinal degeneration (so-called Senior-Loken syndrome for the most severe cases [OMIM #266900]). Less frequently, JNPHP is associated with skeletal abnormalities, central nervous system malformations and oculo-motor apraxia of Cogan-type. Kidneys are bilaterally affected and are usually small at presentation. Patients with JNPHP present with polyuria, polydipsia, functional concentration tubular defects, Fanconi syndrome, growth retardation, and renal function impairment leading to early end-stage renal disease, at median ages of 1 year, 13 years, 19 years, and at a mean age of 22 years, respectively. JNPHP is usually associated also with hepatic portal tract fibrosis with biliary ductular enlargement and proliferation ("nephronophtisis-congenital hepatic fibrosis"). MCKD usually occurs in the 3rd-4th decades of life, sharing the same clinical renal presentation with JNPHP, except for the growth retardation and extrarenal malformations, which are absent in MCKD, and for the later age of occurrence of uremia. Two forms of MCKD are recognized, MCKD1 [OMIM %174000] and MCKD2 (OMIM #603860), which are transmitted as autosomal dominant traits, the corresponding genes of which have been identified and mapped to chromosome 1q and chromosome 16p, respectively. Uremia supervenes after 60 years of age in MCKD type 1 and around 30 years in MCKD type 2. MCKD type 2 is often associated with hyperuricemia and gout and on occasion hyperuricemia has been also observed in association with JNPHP (familial juvenile hyperuricemic nephropathy –FJHN [#162000]), with this latter phenotype being considered a likely allelic variant of MCKD type 2 in that its responsible gene, which encodes uromodulin, is apparently located on Chr.16p in a region overlapping with the locus of MCKD2. In about 15% of the cases of JNPHP/MCKD complex no family history is found, possibly representing a new mutation.>>>> (1)

Note: the latter paragraphs have been taken from the referenced sources.

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AMR SEMINAR #50
CASE 5

Contributed by: Thomas V. Colby, M.D.

History: A 64-year-old ex-smoker presented with chest pain and dyspnea and was found to have a pneumothorax. A (? causative) giant bulla was noted in the right upper lobe. Chest CT also showed emphysema. A bullectomy was performed as part of the treatment for the pneumothorax.

Diagnosis: Malignant mesothelioma with invasion of the lung and associated pneumothorax.

Follow-Up: Two months later the patient had peritoneal biopsies showing mesothelioma. PET scan was positive in the diaphragm.

Comment: Dr. Rossi noted the peculiar bland-appearing polyglonal cells scattered around in the lung lining alveoli. These proved to be strongly positive with calretinin and negative with TTF-1, and the histology and the immunohistology is typical of mesothelial cells. Careful examination of the visceral pleural surface shows a mesothelial proliferation that is at least atypical if not invasive; the recuts sent to the club are not the best to show this. It was difficult to find convincing pleural invasion although I took the involvement of the lung parenchyma (as did my colleagues, Drs. Kevin Leslie and Henry Tazelaar) as indicative of tissue invasion and we interpreted this as a mesothelioma with a very unusual presentation (i.e. pneumothorax). The patient subsequently was found to have biopsy-proven mesothelioma in the peritoneum

Dr. Rossi is an occasional visitor here in Scottsdale and while here a couple of months ago he went through other mesotheliomas that I had and there were three more that had presented with a pneumothorax. On retrospective review, these three cases showed similar intraparenchymal lung involvement by mesothelioma that was relatively inconspicuous and which I had not seen on initial review. Dr. Michael Koss recently had an identical case.

It is known that an occasional presenting manifestation of mesothelioma is pneumothorax. Based on these several anecdotal cases, I suspect the cause of the pneumothorax is invasion of the lung tissue by a mesothelioma. The involvement is quite subtle (at least that is how I rationalize the fact that I missed this on the three prior cases).

I present this as an interesting and unusual case for the club's enjoyment.

An image of the calretinin staining is shown on the website.

AMR SEMINAR #50
CASE 6

Contributed by: Hugo Dominguez-Malagon, M.D.

History: A 77 year-old female with a tumor in the left kidney, focally calcified by image studies.

Pathological Findings: Grossly, a 10 cm partly necrotic tumor located in the lower pole of the kidney was present. The cut surface showed solid pink to yellowish areas with hard gray translucent nodules of cartilaginous appearance.

Histologically, areas of clear cell carcinoma are recognized from which merged extensive zones of spindle-shaped sarcoma, embryonal rhabdomyosarcoma and nodules of cartilage.

Immunohistochemistry: Positive for CD10 and vimentin (epithelial cells and sarcomatous areas), cytokeratin cocktail (epithelial cells), S100 (cartilage), and desmin (rhabdomyosarcoma only)

Diagnosis: sarcomatoid renal cell carcinoma with overgrowth of the sarcomatoid component (Clear cell carcinoma with sarcomatous areas of divergent differentiation) (WHO: renal carcinoma, unclassified).

To my knowledge there is only one case report of a renal tumor with such a broad phenotype in the sarcomatous component (Li L. Arch Pathol Lab Med 2005;129:1057-60).

I would like to hear from the club members their opinions and their experience with similar cases, especially Michal Michal, who has recently published several papers on morphological variants of renal tumors.

AMR SEMINAR #50
CASE 7

Contributed by: Andrew L. Folpe, M.D.

History: A 51-year-old man was found to have an incidental 3.8cm solid mass in the right upper quadrant of the abdomen on an abdominal ultrasound performed as part of the workup of elevated liver function tests. A subsequent CT scan revealed a 3x4cm homogeneous mass located immediately anterior to the right kidney, thought to arise from the posterior aspect of the 2nd portion of the duodenum, as well as a 1.4x3 cm mass in the lumen of the 3rd portion of the duodenum. A Whipple resection was performed.

Gross description: A standard pancreaticoduodenectomy specimen was received, within which was identified a 2.5 x 1.5 x 1.5 cm peri-ampullary mass (slide a) with 2 adjacent satellite submucosal nodules, 0.8 and 1.2 cm in diameter. The tumor also formed a separate peripancreatic mass, 4.6 x 4.5 x 3.5 cm, and was present within two peripancreatic lymph nodes (slide b).

Microscopic description: Sections from the peri-ampullary mass and from the peripancreatic lymph node showed a neoplasm with three components: 1) nests and “zellballen” composed of cells with abundant clear to amphophilic cytoplasm, resembling paraganglioma/ pheochromocytoma, 2) ganglion cells, and 3) abundant schwannian stroma, resembling that seen in ganglioneuroma. Mitotic activity and necrosis were absent. A “carcinoid-like” component was absent.

Immunohistochemical results: The paragangliomatous and gangliomatous components were strongly synaptophysin and chromogranin positive. The schwannian stroma expressed S100 protein. A variety of cytokeratin antibodies were negative.

Diagnosis: Multifocal gangliocytic paraganglioma with extensive ganglioneuromatous differentiation, with lymph node involvement.

Discussion: Gangliocytic paraganglioma is a very rare, benign tumor that almost always occurs in the second portion of the duodenum, in proximity to the Ampulla of Vater. Multiple lesions in the periampullary region of the duodenum and in the peripancreatic tissue have been reported under the term of multiple "paraganglioneuromas" (Virchows Arch A 1985; 406:373). Cases with localization in peripancreatic lymph nodes have also been reported. It is unclear if these rare cases represent an example of mucosal tumors of neural crest derivation with multifocal localization or metastasis to regional lymph nodes. Follow-up has been very limited on these extremely rare cases with nodal involvement, and the significance of this finding is uncertain.

I hope the AMR members enjoy having an example of this rather rare phenomenon (and agree with our diagnosis!). Interestingly, this patient was also found to have a Grade 1 follicular lymphoma of the small intestine (sections not submitted here), for which he is currently receiving therapy. There is no evidence of progressive gangliocytic paraganglioma at approximately 6 months follow-up.

AMR SEMINAR #50
CASE 8

Contributed by: Göran Elmberger M.D., Ph.D.

History: A 73 year old woman presented with a pigmented skin lesion on the capilitium. She had a previous medical history including multiple actinic keratoses and squamous cell carcinomas in-situ in skin of thorax and H&N.

Pathological Findings: Microscopy shows a pigmented combined tumor consisting of a basal cell carcinoma and a melanoma. The basal cell carcinoma is typically of low-grade nodulocystic and adenoid basal cell type. The melanoma is a vertical growth phase type with an intraepidermal component and an invasion to Clark III-IV and Breslow depth 2.6mm. The intimate relationship between basal cell phenotype and melanocyte phenotype is well appreciated in IHC of various melanocyte and basal cell markers (Melan A, HMB 45, MITF, CK high, CK 5, p63) (Figure enclosed). I believe that cells are partially showing bi-directional differentiation but partially there is more of a close but excluding intermingling. Transition areas exist.

Diagnosis: Malignant basomelanocytic tumor (combined basal cell carcinoma and malignant melanoma of the skin).

Follow-Up: No evidence of local recurrence or metastatic spread after 2 years follow-up.

Discussion: Cutaneous combined tumors showing bi-directional differentiation towards basal cell carcinoma and malignant melanoma are rare. To my knowledge only three cases has been published to date (1-2). The term malignant basomelanocytic tumor has been suggested and is the preferred nomenclature in last WHO classification. One of three published cases showed a metastatic behavior of the melanoma component. A true biphasic tumor shows an intimate blending of the basaloid and melanocytic phenotype and this relationship can be further visualized using IHC. The fact that the melanoma shows some epidermal radial phase activity indicates that both tumor components in present case are arising in the primary location.

Important differential diagnoses are collision tumor, metastatic melanoma to pre-existent basal cell carcinoma (3), colonization of basal cell carcinoma by non neoplastic dendritic melanocytic cells, antigen transfer and aberrant keratin expression within a melanoma.

I admit that ideally the IHC should have been performed by dual staining technique with red chromogen for melanoma markers but seeing the complete picture I am still for the suggested diagnosis. I will keep track of case and expand follow up. Vysis are now starting to sell multi-FISH probes for melanoma diagnosis and I will try this technique on present sample as soon as I get the kit in the lab. This could be an ideal way to differentiate between various differential diagnoses such as colonization, collision versus combined tumor.

A unique feature of the present case is that the basal cell carcinoma component is of conventional low-grade type as opposed to previously published cases.

The limited published data seem to suggest that the biologically worst component – the melanoma – will determine the biology of the lesion but grading and staging of these tumors are still a matter of opinion. We staged the melanoma component a an unusual melanoma but discussed the limited experience of a tumor like this.

The pathogenetic mechanisms behind a phenotypic infidelity are not known to me but I see it more and more often not at least in my favorite areas of lung salivary gland pathology. I guess it is just an aspect of loss of genetic imprinting control along with tumor dedifferentiation.

Comment: Hope everyone got representative material on slides.

Question: Do members agree on the diagnosis of this rare specimen?

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AMR SEMINAR #50
CASE 9

Contributed by: Giovanni Falconieri, M.D.

History: A 50-year-old woman was evaluated for vague abdominal discomfort and epigastric pain. Gastroscopy showed minute raised granular areas within the antral mucosa. Random biopsies were performed.

Microscopically, two fragments of gastric mucosa showed superficial, mild chronic inflammation and occasional spiral-shaped bacteria consistent with Helicobacter pylori. The lamina propria of another superficial fragment, of antral mucosa, features hyaline pink bodies that (depending on the plane of section) were intracytoplasmic and appeared to be pushing the cell nuclei toward the periphery. A clear halo was often seen surrounding the inclusions, which varied in shape, being either round to oval or squared, they were more tingible centrally. Cell nuclei were usually hyperchromatic. No significant atypia or mitotic activity was noted. A mixed inflammatory infiltrate was focally seen. The cytoplasmic inclusions were PAS-positive, diastase insensitive, CD79a-positive, polytypic (kappa/lambda), and negative for keratins and LCA. Congo red stain was negative as well. Also submitted, to complement the circulating glass slide I am also submitting some digital pictures obtained from the initial levels of the tissue block, before it was almost entirely cut for the stains.

Diagnosis: Russell body gastritis

Comment: Although the significant diagnostic material is scant, I believe that the diagnostic features of this unusual condition may be observed in most (although unfortunately not all) of the sections of antral mucosa presented in the circulating slides. Although Russell bodies have been described earlier in either neoplastic and nonneoplastic endoscopic gastric biopsies, it was not until recently that Russell body gastritis (RBG) became the focus of several reports and that it was delineated as a possible microscopic entity or “pseudotumoral” condition. The pathogenesis of RBG is unclear; *H. Pylori* infection may play a role in some cases, as in the present instance, however the total number of cases is too small to permit any conclusions.

The importance of recognizing RBG rests on the potential interpretative pitfalls involving the cytoplasmic inclusions, including signet-ring carcinoma or plasmacytoma or lymphoplasmocytic lymphoma. The differential diagnosis may be difficult, especially for those who are unaware of the microscopic entity (as we were initially!). Amyloid deposits may also enter the differential diagnosis since the plane of tissue section may not include the cell nucleus. Thus the inclusions appear to lie in the stroma surrounding the cells and not within the plasma cell’s cytoplasm.

I shall look forward to reading the opinion of the Club members and learning about their experience with this condition.

I apologize for the poor quality of some of the sections that a few members will unfortunately receive. So little tissue was left in the paraffin block that it was difficult to obtain 50 good sections, considering that the diagnostic features were present in only one of the fragments originally submitted. As a follow-up note, during the past 6 months, the patient was also evaluated for possible plasma cell dyscrasia. So far, the pertinent laboratory examinations have been within the normal limits. She is currently scheduled to have a new endoscopic examination, and we have suggested that the gastroenterologist obtain a generous sampling of the gastric mucosa, especially within the antral region. Should we obtain adequate material from this new biopsy, we hope to provide additional glass slides and a follow-up.

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AMR SEMINAR #50
CASE 10

Contributed by: Giovanni Falconieri, M.D.

History: A 40-year-old woman was evaluated for abdominal pain and pruritus. Her laboratory examinations were within normal limits and markers for viral hepatitis were all negative. An ultrasound scan of the liver revealed a lobulated, inhomogeneous mass, and a core needle biopsy showed a nodular architectural distortion as well as increased fibrosis and nonspecific inflammatory changes. These observations, however, were deemed inconclusive. A wedge resection of the mass was therefore performed.

Macroscopically, the resected portion of liver contained a 10- by 6-cm lobulated, firm, pale-brown mass with a fairly nodular cut surface and a central stellate scar (see digital gross pictures).

Diagnosis: Focal nodular hyperplasia of liver, with sarcoid-like epithelioid granulomas.

Comments: Focal nodular hyperplasia (FNH) is still a largely unexplained though well- known condition initially described almost half a century ago by Edmonson in the first AFIP series**.** It is still unclear whether it reflects a local hyperplastic response of hepatocytes to a vascular abnormality. Systemic or hepatic diseases—such as autoimmune, myeloproliferative, or lymphoproliferative disorders and primary biliary cirrhosis—as well as hormone replacement therapy and some chemotherapeutic agents may play a role. It has been suggested that fibrolamellar carcinoma of the liver is the malignant counterpart of FNH, although the relationship between the two is far from certain. Most patients are asymptomatic and the lesion is discovered incidentally; clinical manifestations may be those of portal hypertension, including splenomegaly and esophageal varices with or without bleeding. During the last few years, a number of cases of FNH exhibiting deviant morphologic patterns have been published and segregation within microscopic categories has been proposed (classic and non-classic, the latter further subdivided into the following types: telangiectatic, mixed hyperplastic adenomatous, and atypical with large cells). The current case is characterized by numerous noncaseating epithelioid granulomas, an unexplained finding that has rarely been seen in FNH. Classic features—such as the central scarring with abnormal vessels in myxoid stroma; hyperplastic, thick wall of medium- to small- sized arteries; nodular arrangement of thick, disorderly liver plates along with disorderly biliary canaliculi—may be recognized in almost all tissue blocks. The adjacent “normal” liver also included some irregularly thick vessels, suggesting that hepatic vascular abnormalities may be the anatomic background for the development of FNH.

I hope that this sophisticated group will enjoy this case, although it is not as challenging as most of those generally presented. However, I believe it to be of potential interest to young residents and medical students.

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AMR SEMINAR #50
CASE 11

Contributed by: Masaharu Fukunaga, M.D.

History: A 32-year-old, gravida 0, para 0, Japanese woman presented with lower abdominal and left leg pain that had been present for 11 months. MRI revealed a 5-cm subserosal mass in the uterine fundus. Intraoperatively, a rubbery solid uterine mass attached to the left broad ligament was found and locally excised. The patient did not have the tuberous sclerosis complex. Fortunately, she gave a birth at 24 moths postoperatively. The patient had no evidence of tumor at 31 months.

Immunohistochemical studies: Vimentin, h-caldesmon, HMB45, alpha-smooth muscle actin: (+). Desmin, HHF35, CAM5.2, EMA, S-100 protein, CD34, CD10, Melan A, synaptophysin, chromogranin A, GFAP, CD117: (-).

Diagnosis: Perivascular epithelioid cell tumor (PEComa) of the uterus.

Histology and Comments: Its preoperative diagnosis was a subserosal leiomyoma. A clinician asked me for an intraoperative consultation. He said that the lesion looked like 'a carcinoma'not a leiomyoma and it was soft and hemorrhagic. My frozen section diagnosis was 'epithelioid smooth muscle tumor, borderline, most likely'

Grossly, the mass was fragmented and measured 5.0cm in aggregate. Its sectioned surface was tan-pin, unencapsulated, rubbery, and solid with foci of hemorrhage and necrosis. Microscopically, the tumor was composed of round to polygonal cells with a round nuclei and abundant clear to slightly eosinophilic cytoplasm and the cells were arranged in short fascicles and focally in a perivascular location. No melanosomes or premelanosomes were found in EM studies.

Because of the presence of coagulative necrosis, infiltrative growth and the size of the mass 5cm, I think that it is a PEComa with an uncertain malignancy potential (1, 2).

There is controversy about relationship between PEComa and epithelioid leiomyosarcoma with clear cells (3). I would appreciate very much if I could hear your diagnosis and comments on malignancy.

References:

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AMR SEMINAR #50
CASE 12

Contributed by: Thomas Krausz, M.D.

History: An infant with a bulging blue-purple congenital scalp mass which was resected at the first day of life. The resected 7.8 x 2.6 cm. specimen was partly covered by skin. The tumor was found to partly fed by meningeal arteries and partly drained into the superior sagittal sinus. The bone was, however, not involved by the mass.

Pathology: The tumor exhibits rather variable histomorphology. The main components of the tumor are: a nodule of rounded/epithelioid cells with moderate amount of vacuolated cytoplasm (strongly/extensively S-100 positive and focally EMA positive), areas of spindle cells with focal schwannian (some re S-100 positive) and focal myoid/myofibroblastic features (focal immunoreactivity for SMA, MSA and rare cells for desmin), cellular areas of immature mesenchyme (rare S-100 positive cells), and a few pigmented melanocytes (Melan-A, HMB45 positive) located near one edge of the section. In addition, there was focal immunoreactivity for CD34, CD99, synaptophysin and rare cells stained for neurofilament. The following markers were negative: Cam 5.2, AE1/AE3, GFAP and chromogranin.

Diagnosis: Neurocristic cutaneous hamartoma.

Comment: I received this case in consultation with a suggested diagnosis of "hamartoma with ectopic meningothelial component". In my opinion it does not express a true meningothelial phenotype even though there is focal whirling. A number of entities were considered in the differential diagnosis but it is not easy to find a good fit. The lesion shows areas of melanocytic, schwannian, myofibroblastic and immature mesenchymal differentiation. Even though not evident on the received material the tumor is reported to involve the overlying dermis. The diagnosis of neurocristic cutaneous hamartoma (NCH) appears to capture best the multiphenotypic components. The location as well as the congenital nature of the mass also fits for this entity.

NCH is a rare entity which involved the dermis/subcutis and is thought to result from aberrant development of cells derived from the neural crest. Neural crest-derived cells may differentiate along melanocytic, neurosustentacular, fibroblastic lines and contribute to the formation of local mesenchyme especially within cephalic areas. Although melanocytic cells have been reported to be the dominant cell population, neurosustentacular and neuromesenchymal cells may be the principle component (Smith at al, 1998). Malignant dermal melanocytic tumors, with a distinctive biologic behavior, may develop in some cases of NCH (Pearson et al, 1996).

I think, this is a diagnostically difficult case. I would greatly appreciate comments and suggestions from the members on this unusual case.

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AMR SEMINAR #50
CASE 13

Contributed by: Thomas Mentzel, MD

Clinical Findings: A 73 year old male patient developed a 2.3 x 1.2 x 1.2 cm. measuring dermal nodule on his chest wall. A cylindroma has been excised at that side twelve years previously.

Histological Findings: Histologically, a multinodular, plump invasive, epithelial neoplasm involving the dermis and subcutis is seen. The neoplasm is composed of enlarged, slightly atypical epithelial cells with enlarged, often vesicular nuclei showing different growth patterns. In some areas the neoplasm resembles atypical eccrine spiradenoma, in other areas a trabecular as well as a pseudopapillary growth pattern is noted, and focally myxoid stromal changes are present (in fact the neoplasm was sent to us with the diagnosis of adenoid cystic carcinoma by the referring pathologist).

Diagnosis: Polymorphous sweat gland carcinoma.

Comment: The classification of benign, atypical, and malignant skin adnexal neoplasms including sweat gland neoplasms is complex and somewhat of confusing given problems in the distinction of apocrine and eccrine neoplasms as well as the fact of overlapping clinicopathological features of so-called distinct entities (ie. Eccrine spiradenoma and cylindroma). The presented neoplasm shows in our opinion different growth patterns and is characterized by an infiltrative growth, most consistent with polymorphous sweat gland carcinoma, that has been nicely described by Saul Suster. Polymorphous sweat gland carcinoma represents a low-grade carcinoma characterized by a variety of growth patterns and shows up to moderate atypia of epithelial cells and mitoses.

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AMR SEMINAR #50
CASE 14

Contributed by: Elizabeth Montgomery, MD

History: A 93 year old male with symptoms of diarrhea undergoes flexible sigmoidoscopy with biopsy of an "unremarkable" segment of sigmoid colon. There were no biopsies or manipulation of the right colon. By the next day, the patient had perforated in the ascending colon, which necessitated surgical intervention.

Diagnosis: Mucosal tear/ "fractured colon" in collagenous colitis with perforation.

Comment: Sections from the resection specimen show focal areas of ulceration characterized by a population of predominantly neutrophils. The bowel shows patchy areas of mucosal injury without intervening ischemic damage or vascular injury (thrombus, vasculitis, etc.) Even though the biopsy was performed on the left side of the colon, the patient experienced perforation of the right side, suggesting a diffuse disorder. No visible abnormalities of the mucosa were seen on endoscopic exam. The mucosa adjacent to the perforation shows collagenous colitis.

There is thickening of the subepithelial collagen table with increased intraepithelial lymphocytes and no crypt distortion, consistent with collagenous colitis. Examples of perforation after colonoscopy (and thus after colon insufflation) in patients with collagenous colitis have been reported in the literature. Barium enema causing perforation in these patients has also been reported, but the accepted mechanism is a thickened tubular colonic mucosa that is over-distended during air insufflation, resulting is linear mucosal tears, pneumatosis, and ultimately perforation. Taylor et al. described nine cases of perforation in collagenous colitis patients, and found that the right colon was the preferred site. Linear bleeding ulcers were found on initial endoscopic examination in three of these patients (and five at later resection).

The actual rate of perforation in collagenous colitis is low (less than 1%). However, it is important to be aware of it, as the potential consequences of peritonitis may be devastating.

References:

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AMR SEMINAR #50
CASE 15

Contributed by: Cesar A. Moran, M.D.

Clinical History: A 47 year old man was evaluated for symptoms of dysuria and hematuria. Radiographic examination revealed a right kidney mass. A right partial nephrectomy was performed.

Diagnosis: Mixed epithelial and stromal tumor (MESTK).

Comment: This another example of an entity originally described by our friend, Michal Michal, a few years ago. The case is rather typical but I'm sending it because despite increased awareness of this entity, it is still a very rare tumor. Here at M.D. Anderson we see a fair number of renal tumors every year and very few correspond to this particular histologic variant. The ovarian-like stroma is nicely displayed in this case and I though the members of the Club would enjoy having another good example of this entity.

AMR SEMINAR #50
CASE 16

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

History: A 67 year old woman had a 7x6 cm. mass of the parietal and visceral diaphragmatic pleura and a 2.5 cm. pleural tumor at the right lower lobe. On macroscopic examination, the masses had a whitish appearance and firm consistency. The adjacent pulmonary parenchyma showed no signs of infiltration. In addition, a 1.5 cm. pericardial nodule was detected.

A TruCut biopsy of the diaphragmatic pleural mass was performed and a diagnosis of malignant pleomorphic tumor, possibly mesothelioma, was established. The tumor was removed surgically and after a 5 month follow up, the patient remained stable with no progression of the disease.

Pathological Data: As can be seen in the section we received, microscopic examination shows a sarcomatous pattern with areas of spindle-shaped cells and pleomorphic cells. Hyalinized areas with a collagenized extracellular matrix are also visible. The mitotic activity is very high. The lesion affected the parietal and visceral pleura, but showed a semi-expansive pattern of infiltration and growth.

On immunohistochemical study the tumor cells were positive for vimentin and smooth-muscle actin, focally positive for CD99, and weakly and focaaly positive for low molecular weight keratins. EMA and BcI2 also showed weak, focal positivity. The remaining makers (CEA, calretinin, WT1, TTF-1, pancytokeratins, CK19, B7.23, CD31, CD34, S100, c-Kit, lysozyme, thrombomodulin and desmin) were negative. Are the marked ones right? Can't find them.

Diagnosis: High-grade malignant pleomorphic tumor.

Discussion: The differential diagnosis for this tumor includes pleomorphic sarcomatoid mesothelioma and high-grade pleomorphic sarcoma. The diagnosis of pleomorphic sarcomatoid mesothelioma could be concordant from the histochemical viewpoint. Nevertheless, the absence of mesothelial markers and the minimal focal positivity for keratins, as well as the expansive macroscopic growth and relatively good clinical course do not favor this diagnosis. As an alternative, pleomorphic sarcoma, probably secondary to a single, local, fibrous, mesenchymal tumor is a potential option. Electron microscopy findings were not conclusive because the available material was not in optimal conditions.

I would greatly appreciate your comments on this case, your impressions with regard to the diagnosis and your suggestions for other diagnostic options.

AMR SEMINAR #50
CASE 17

Contributed by: Josh Sickel, M.D.

History: A 53 year old woman presented with a 4 cm distal pancreatic mass and surgical resection was performed. Histologic sections revealed moderate to poorly differentiated adenocarcinoma. We subsequently discovered that six months prior to her admission, she had surgery at another hospital for bilateral ovarian tumors. Both ovaries were originally interpreted as "mucinous borderline tumors with foci of stromal invasion by signet-ring cells". Metastatic tumor was also found in the omentum and capsule of the liver. We requested materials from the outside facility for review. AMR seminar slides are submitted from the original ovarian tumor.

Histology: Sections show a multiloculated cystic ovarian lesion lined by mucinous epithelium with bland nuclear features and intestinal differentiation. Much of the lesion is typical for mucinous cystadenoma. Adjacent tissue shows abrupt transition to invasive signet-ring cell adenocarcinoma.

Diagnosis: Metastatic pancreatic adenocarcinoma simulating a primary mucinous tumor of the ovary.

Comments: This case was from several years ago and immunostains were not performed. Both pancreatic and ovarian mucinous tumors are typically positive for CK7, CK20 and MUC-5AC. CDX-2 is occasionally positive in pancreatic tumors and always negative in ovarian lesions. The clinical history, bilaterality of the ovarian tumors and histologic resemblance of the pancreatic and ovarian neoplasms, favor a metastatic lesion in this case. I was amazed by the innocuous appearance of the ovarian tumors and striking resemblance to benign mucinous cystadenoma. Have club members encountered this phenomenon in the past?

References: Young RH and Hart WR. Metastases from carcinoma of the pancreas simulating primary mucinous tumors of the ovary: a report of seven cases. Am J Surg Pathol 13(9): 748-756, 1989.

AMR SEMINAR #50
CASE 18

Contributed by: Dominic Spagnolo, M.D.

History: This skin lesion was taken from a 74 year old female in 1999. It was a roughly 12mm diameter nodule present at the end of a scar on the abdominal wall, said to be the site of a previous lymph node biopsy. This female has had countless squamous and basal cell carcinomata removed from sun-exposed skin, going back in our records for 18 years, but also antedating our computerized records. In 1996, she was diagnosed elsewhere with stage IV, grade 1 follicular lymphoma on a right groin node biopsy (on review, also showing marginal zone differentiation). She was originally treated with chorambucil and prednisolone, and was said to have achieved a clinical remission. According to the clinical notes, the patient said her skin tumors were "more aggressive" during her chemotherapy. Several skin biopsies over the next 2 years revealed the collision of BCC or SCC with follicular lymphoma (reviewed). Early in 1998 she was found to have extensive central and peripheral adenopathy, was recommended on chorambucil/Pred, achieved only partial remission, developed splenomegaly and pleural effusions. She continued to develop further cutaneous and subcutaneous, presumed lymphomatous deposits but not further biopsied, and refractory to treatment. She died of progressive lymphoma in November 2000; there was no post-mortem examination.

Pathological Findings: There is a diffuse infiltrate of cells with dendritic morphology occupying dermis and extending into subcutis, compressing epidermis, but with little or no epidermal involvement. Mononuclear cells predominate but there are also considerable multinucleated forms. Nuclei are often deeply cleft and some contain prominent nucleoli. There is variable nuclear pleomorphism. Cytoplasm is abundant and eosinophilic. The multinucleated cells often show a peripheral wreath-like disposition of their nuclei. Smaller cells with more reniform, "histiocytoid" nuclei are also numerous. Mitoses abound, in many areas numbering in excess of 25/10hpf (field area 0.237mm^2), and include atypical forms. There is a sprinkling of small lymphocytes but eosinophils are conspicuously absent.

Immunophenotype:
Positive: S-100 diffuse, strong; CD1a, focal, <10% overall; lysozime (majority of cells; mainly "Golgi distribution); CD4, weak; CD45, focal, weak; MIB-1 variable 40-50%.
Negative: CD20; CD3; CD30; ALK-1; CD21; CD35; placental alkaline phosphatase; PGM-1(CD68) and CD163-scattered positively thought to reside in reactive histiocytes, but can't be absolutely sure.

Ultrastructure: (See attached jpg. Images) Revealed no Birbeck granules after intensive scrutiny. The cytoplasm was generally voluminous and organelle-rich but without specific features. In the Golgi region of some cells, small lysosomal granules could occasionally be seen but there was no phagocytosis or endocytosis seen. Nuclei were deeply indented and sometimes convoluted, and typically eccentrically disposed. Cell surface morphology varied and included cells demonstrating parallel arrays of flattened lamellipodia between cells, to others which formed broader, spatulate, complex interleaving processes. There were no desmosomal attachments, and very rarely could areas of apposing suplasmalemmal linear densities be resolved between cell processes, at most representing "primitive" or "intermediate" junctions resembling zonula adherens type junctions. But there were isolated findings. The ultrastructural features I thought presented features that could be seen both in Langerhans cell (Birbeck granules excepted) and in interdigitating cells (the complex interleaving broad processes).

Diagnosis: Indeterminate cell tumor/sarcoma; indeterminate cell histiocytosis; dendritic cell sarcoma, not otherwise specified (WHO).

Discussion: I submitted this case for several reasons: (i) what to call it (cell lineage); (ii) is it benign, "atypical", "malignant"; (iii) its association with a low grade non-Hodgkin lymphoma; (iv) its rarity.
While in 1999 I signed this case out as an "indeterminate cell tumor", it is still a diagnosis open to question and individual interpretation, and there is no unanimity on what constitutes an "indeterminate" cell in the context of

dendritic cell proliferations. Some equate this cell type to the veiled cell (S100+, CD1a+, no Birbeck granules) though it is not known whether this represents a Langerhans cell precursor, or a Langerhans cell in transit to lymph node after contacting antigen, prior to becoming an interdigitating reticulum cell (S100+, CD1a-, no Birbeck granules). Indeed, these cells may represent different functional states of the same basic cell type. Others would adopt a broader definition to include cells with overlapping histiocytic and dendritic morpho-immunophenotypes, not strictly conforming to accepted definitions of Langerhans cells, histiocytes, and interdigitating reticulum cells, which share a common haemopoietic progenitor. A unifying concept of the M-PIRE (mononuclear phagocyte and immunoregulatory effector) system has been proposed by Foucar and Foucar (1990) to encompass these phagocytic and on-phagocytic cells putatively derived from a common marrow stem cell. Follicular dendritic cells are of different derivation and have distinctive morphology and immunophenotype. A very useful review of tumors of histiocytes and accessory dendritic cells was published by the ILSG in 2002. (Pileri SA et al).

The first case of indeterminate cell histiocytosis was reported by Wood et al (1985) as a detailed immunophenotypic and ultrastructural study of a case previously published by Winkelmann et al (1982). Patients may have multiple skin lesions, or sometimes occur as a solitary nodule, composed of S100+, CD1a+ Langerhans-like cells which lack Birbeck granules ultrastructurally. They lack other histological and clinical features of Langerhans cell histiocytosis. Recently a spindle cell variant resembling a FDC sarcoma was described (Rosenberg AS 2001). It is not possible to generalize about the behavior of these lesions owing to their small numbers. Some have behaved in a clearly indolent fashion, even with spontaneous regression, while others have been more aggressive. There is no reproducible correlation as far as I can tell, between the presence of cytological atypia and mitotic activity and behavior. These are not common tumors, and relatively few cases are reported in the literature (ref below). Limited data based on HUMARA gene inactivation assays indicate that these dendritic cell proliferations are clonal (Wu et al, 1999).

There has been an interesting association, as in this case, in a minority of indeterminate cell tumors with antecedent low grade B-cell lymphomas (Bonetti et al 1985; Segal GH et al 1992; Vasef MA et al) which have included SLL/CLL and follicular lymphoma. In one report, a patient developed mast cell leukemia 7 years after the diagnosis of cutaneous indeterminate cell histiocytosis (Kolde et al 1986), while another who had follicular lymphoma, developed AML.

I look forward to colleagues' opinions on nomenclature. Has anyone encountered a similar case in association with a lymphoma?

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