AMR Seminar #58 – Short Summary of Cases:

Case 1: 17-year- old male presented with leg mass.

Case 2: Core needle biopsy of the prostate in man with symptoms of urinary obstruction.

Case 3: A 60-year-old man with gastric ulcer "suspected malignant".

Case 4: F.65 with large thyroid mass.

Case 5: M.26 with 2.5 cm. soft tissue mass in right foot.

Case 6: F.38 with ascites and presumptive diagnosis of NH lymphoma has biopsy of retroperitoneal adenopathy.

Case 7: F.45 with multiple lung nodules; had history of renal tumor resected at a different hospital.

Case 8: F.45 with history of Crohn's disease suffered abrupt cardiac arrest and died. Lungs at autopsy.

Case 9: M.59 with sclerotic lesions in long bones and seizure disorder; had a lesion discovered in frontal cortex.

Case 10: F.54 with large plaque (12 x 6 x 2.5 cm) in the visceral pleura.

Case 11: A 75-year-old white female presented with a 0.9 cm lesion on scalp for 1 year.

Case 12: F.56 with bulky mass in the uterus resembling grapes.

Case 13: F.40 with peritonitis showed an ischemic bowel on exploratory laparotomy.

Case 14: F.61 with deep seated soft tissue neoplasm in right forearm.

Case 15: 17-month old boy with 3 cm. soft tissue mass excised from his back.

Case 16: F.40 with a recurrent soft tissue mass in her right biceps.

Case 17: 38-year-old woman with a left adnexal mass.

Case 18: F.50 with anterior mediastinal mass.

Case 19: M.42 with 3 cm. mass in left kidney.

Quiz Case #1: F.50 with cystic lesion in left breast (no slides, only images in the website).

Quiz Case #2: M.13 with soft tissue mass in right thumb.

AMR SEMINAR #58
CASE 1

Contributed by: Volkan Adsay, M.D.

Case History: 17-year- old male presented with leg mass. The lesion was located on the right "posterior knee", and measured 18 cm. Resection was performed. The lesion was mostly solid but had some cystic areas (which is represented in the slides sent to you).

Immunohistochemical Panel: Cam5.2 strong diffuse positive; AE1:AE3 focal; Actin (MSA) negative; INI total loss of nuclear labeling in the tumor cells; S100 negative; CD31 negative; Desmin negative. FISH had been done on the biopsy and was negative for EWSR1 gene rearrangement.

AMR SEMINAR #58
CASE 2

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

Case Description: A 76-year-old man presenting with symptoms of urinary obstruction underwent TRUS biopsies of the prostate for a suspected lesion in the left lobe. PSA was 2.4 ng.
As luck would have it and for reasons perhaps known to the gods of the law of series, 1 month later a 72 year old man underwent TRUS biopsies of a mass that was described as "enormous" and pushing the rectum- the clinical question was whether the mass was prostatic or perhaps extra-prostatic. PSA was 0.66 ng.
Submitted slides come from one or the other of these two cases.

Histology: Needle biopsy cores from both tumors demonstrate a florid spindle cell proliferation.

Diagnosis: Material from the first case was sent off to two consultants: Chris Fletcher and Jonathan Epstein. Both concurred in diagnosing gastro-intestinal stromal tumor, positive for CD117, DOG-1, and CD34. The second case was also diagnosed (by me) as GIST, positive for CD117 and CD34, negative for desmin.

Discussion: As related by Dr Rosai (Seminars in Diagnostic Pathology 20: 247-8, 2003), his mentor Dr Lauren Ackerman would present the problem of recognition (or lack of recognition) of what should be a familiar lesion in an unexpected setting as a metaphor –"the man from Istanbul". A person whom one is used to seeing every day in his home town and would ordinarily recognize instantly would not be recognized in an exotic setting where that person would not be expected to turn up- say Istanbul (the fact that the latest AMR meeting which some of us attended was held in that city is pure coincidence- and despite the location I had no problem recognizing any of the members of the group who attended who were already familiar from the previous meetings).

So this case is my "Istanbul lesion". Obviously a biopsy of a GIST from a mass in the stomach would not arouse the same befuddlement as such a finding turning up in TRUS biopsies performed on a suspicion of prostate disease. Admittedly GISTs can occur anywhere along the GI tract and even outside it in the abdomen, so this shouldn't be totally unexpected. In Markku Miettinen's study of anorectal lesions published in the AJSP in 2001 (25: 1121-1133), GISTs greatly outnumbered smooth muscle tumors of all types in this area (133:11)- however they are only 5% of all GISTs (but in third place after stomach and small intestine). About two-thirds of the GISTs in that study were up to 5 cm in size and many of them were incidental findings treated with local excision. The larger tumors were more often symptomatic. The type of material on which the diagnosis was made - TRUS (in the males who were 71% of the cases) or other needle biopsy, rectoscopy, or from the surgical specimen, - was not specifically mentioned in the article, nor was the specific location in the rectum (anterior wall or not). No mention was made in the article as to what extent these lesions aroused clinical concern for prostatic tumors.
In 2006 Jonathan Epstein, along with our fellow AMR member Elizabeth Montgomery, published 8 cases of GIST diagnosed on prostatic TRUS biopsies. All cases were from Dr Epstein's consultation files. The PSA values were up to 1.4 ng. In some patients the imaging findings were suggestive of tumor originating in the prostate and it was only on pathological dissection of the surgical specimen that it could be determined that the tumor was attached to the rectum or at least separate from the prostate. In one patient the tumor consisted of a small submucosal rectal nodule through which the biopsy needle passed on the way to the prostate.

In a radiological study of anorectal GISTs (Levy et al, Am J Roengtenol. 180: 1607-1612, 2003) one of whose authors is Markku Miettinen, the tumor invaded into the prostate in 1/6 patients included in the study and the authors did point out that in this situation the differential diagnosis with prostatic tumor would need to be made. However in the cases they included in the paper tissue diagnosis was made either on surgical resection material or on rectal biopsies. In another paper cited in the Epstein article- Madden et al, Urol Oncol. 23: 268-272, 2005- three patients were diagnosed with "primary high grade prostatic sarcomas" on the basis of surgical resection, needle biopsies, and TUR material, respectively, with the diagnosis of rectal GIST being made only subsequently on either review of the initial material performed secondarily due to clinical developments or on new material. Thus the cases in the Epstein

paper appear to be the first to be published in which GIST was diagnosed at the onset on TRUS needle biopsy material performed to diagnose or rule out prostatic tumor.
Epstein et al also discuss the possibility of GIST as a primary tumor in the prostate and cite one such case report. However as that determination was made solely on the basis of imaging and the tumor was not resected, the authors were not convinced. I found a citation for a second paper making the same claim for a single case (Lee et al, Hum Pathol. 37: 1361-5, 2006) in which the authors state that the possibility of a rectal GIST involving the rectum secondarily was "excluded by radiological and intraoperative findings".

Epstein et al state at the end of their article that they had examined another two cases since submitting the manuscript for a total of 10 cases. He further informed me that from 2008-2010 he has seen an additional 7 cases (out of a total of 28,000 prostate consults!). I also found another two articles which were subsequently published in the Canadian Journal of Urology (15: 4112-4, 2008; and 16: 4502-6, 2009) for an additional three cases in the literature. In one of the patients the diagnosis was first made on a retropubic prostatectomy resection with the rectal connection being documented only afterwards. Thus rectal GISTs mimicking prostate tumors are rare to say the least.

The differential diagnosis of spindle cell tumors of the prostate is discussed in another article co-authored by Epstein and Montgomery (Hansel et al, Mod Pathol 20: 148-158, 2007) and includes the following entities that are specific for the prostate:

- STUMP: these are benign lesions that come in four categories and are composed of hypercellular stroma with or without atypical degenerative cells mixed with benign glands; hypocellular stroma and benign epithelium in the manner of phyllodes tumor; and myxoid stroma without glands. Sarcoma originating in STUMP is also known. The lack of benign glands amidst the spindle cell proliferation in GIST (unless entrapped at the periphery of the lesion) would be against this, and this lesion is negative;
- Sarcomatoid carcinoma: this consists of a malignant spindle cell proliferation mixed with prostate carcinoma. The latter may be focal and show varying morphologies. Again in cases of GIST carcinoma is not expected (but the differentiation would need to be made with epithelioid differentiation in GIST);
- Sclerosing adenosis: a benign proliferation composed of spindle cells and glands but rarely seen on needle biopsies- the spindle cells stain as basal cells of the prostate would, for HMWK and also S100 and actin.

Soft tissue tumors (besides GIST) that can appear in the prostate as well as in other locations include: Smooth muscle tumors (benign or malignant), inflammatory myofibroblastic tumor, and solitary fibrous tumors, the histology and immunohistochemical properties of which are already familiar to those in the group.

What needs to be stressed again regarding these cases is that clinically these lesions are often assumed to be prostatic clinically and biopsy material will be sent with that expectation to the pathologist who will need to free himself of that predisposition (there may be tourists in Istanbul also) in order to make the correct diagnosis.

AMR SEMINAR #58
CASE 3

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

Clinical History: Multiple hepatic masses in both lobes were detected by ultrasound and CT-scan in a 60-year-old man who complained of weakness, fatigue and weight loss. Liver needle biopsy in June 2009 showed mod. to poorly diff. adenocarcinoma (CK7+, CK20-, CDX2-, TTF1-), consistent with either primary cholangiocarcinoma or metastatic gastric or pancreatobiliary carcinoma. Imaging and upper GIT endoscopy did not reveal a primary tumor. Yttrium-90 selective internal radiation therapy (SIRT) to both hepatic lobes was introduced in June 2009 following a preliminary catheterization with a radioactive marker which showed hepatic-pulmonary shunt of 5%. During the final SIRT catheterization (in June 2009), arterial tributaries to the stomach and duodenum (gastroduodenal artery and left gastric artery) were embolized to prevent transport of the radioactive material to these organs. In September 2009 the patient complained of nausea, vomiting and dysphagia. Endoscopy revealed redness, nodularity and several superficial large ulcers in the gastric fundus and body. Histology showed mucosal edema and focal intestinal metaplasia. Very rare microspheres were present, but not mentioned by the pathologist. In January 2010 repeat endoscopy disclosed a large ulcer in the gastric-body and ulceration in the lower-esophagus. We received the gastric biopsy only with the information of "gastric ulcer, body, suspected malignant". Due to the typical histology of the Yttrium microspheres in the gastric biopsy sections, the diagnosis of Yttrium associated gastritis was made.

Histologic Features: The January 2010 gastric biopsy shows abundant typical round, purple-black microspheres of 20 to 40 μm diameter, which were present also in the esophageal biopsy. The microspheres are present in granulation tissue at the ulcer base and in the inflamed non-ulcerated mucosa. Some of the spheres are within tiny vessels.

Diagnosis: Yttrium associated gastritis.

Discussion: Although I am sure that many of you have seen this pathology, I chose to circulate this slide since the Yttrium microspheres are so unique with "once you see one, you never forget" histologic figure and with no need to rely on immunohistochemistry or molecular biology studies for diagnosis. The internal radiation therapy is based on the divergent blood supply of the hepatic tumors and the normal hepatic parenchyma. While hepatic tumors are supplied almost exclusively by the hepatic artery, the normal liver parenchyma is supplied mainly (70-75%) by the portal vein. Thus, embolization of hepatic artery or its tributaries by the radioactive microspheres, results in a relatively selective tumor damage. The 30-40μm resin microspheres are impregnated with Yttrium-90, a β-emitter with a half life of 64 hours and average tissue penetrance of 2.4 mm. This selective internal radiation therapy enables delivery of high radiation dosage which would be unacceptable by the usual external radiotherapy due to hepatotoxicity. Several clinical studies have shown the efficacy of this selective internal radiotherapy, especially in metastases from colorectal carcinoma.

There are several complications of the SIRT method. The G.I. toxicities range from nausea and abdominal pain to radiation-induced gastroduodenal ulceration and gastritis. The latter affect 5-15% of the treated patients, although most are not biopsied. The latent period from therapy to gastroduodenal clinical symptoms ranges usually from 2 weeks to 3 months. Other, less frequent complications, include pancreatitis, cholecystitis, radiation pneumonitis and pulmonary fibrosis, venoocclusive disease and radiation hepatitis and bone-marrow toxicity.

To prevent these complications, patients undergo pretherapy arteriography for prophylactic embolization (by endovascular coils) of the gastroduodenal artery and other GI collaterals of the hepatic artery. In addition, Technetium-99 macroaggregated albumin in injected to the hepatic artery, followed by nuclear imaging to determine the rate of hepatopulmonary shunting and G.I. extrahepatic deposition. Hepatopulmonary shunting of over 13% excludes patients from SIRT to prevent radiation pneumonitis. Macroaggregated albumin simulates Yttrium-90 microsphere in shape, size and density, thereby mimics the vascular distribution pattern of radioactive microspheres on selective hepatic arterial infusion.

In spite of all these protective measures, extrahepatic toxicity, especially gastroduodenal, cannot be eliminated.

The tissue injury caused by SIRT is likely attributable to radiation rather than ischemia, due to the extensive collateral blood supply in the upper GI tract, to histologic features in some of the cases, and to the chronology of the appearance of symptoms.

References:

(1) Crowder CD et al: Selective Internal Radiation Therapy-Induced extrahepatic injury. An emerging cause of iatrogenic organ damage. Am. J. Surg. Pathol. 33:963, 2009.
(2) Ogawa F et al: Gastroduodenitis associated with Yttrium-90 microsphere selective internal radiation. Arch. Pathol. Lab. Med. 132:1734, 2008.
(3) Silvanto A et al: SIRT-an uncommon cause of gastroduodenal ulceration. Histopathology 55:114, 2009.

AMR SEMINAR #58
CASE 4

Contributed by: Gerald Berry, M.D.

HISTORY: This 65-year-old woman presented with a large right thyroid mass. A hemi-thyroidectomy was performed. By report there is no history or family history of MEN-related disorders.

HISTOPATHOLOGICAL FINDINGS: The lesion is a well-circumscribed neoplasm composed of nests and groups separated by fibrovascular septa. I did not find convincing stromal amyloid. The nests are composed of uniform cells with abundant pale eosinophilic cytoplasm. Centrally, the nests display a cribriform arrangement. The immunostaining profile showed strong staining for calcitonin and absence of staining for thyroglobulin.

DIAGNOSIS: Medullary carcinoma with glandular/cribriform pattern.

COMMENT: The neoplasm for the most part shows an insular pattern. Medullary carcinoma can display a variety of growth patterns and cell types including glandular, trabecular, pseudopapillary (there was a previous AMR Seminar #5 case submitted by John Chan), paraganglioma-like, and carcinoid-like, pigmented, spindle cell, neuroblastoma-like, small cell, etc. I submitted this case on account of the glandular/cribriform pattern that we found in the central part of the tumor. This component was more prominent on the original sections than the recuts I prepared for the group. The nuclear features support neuroendocrine differentiation and the calcitonin provides additional support.

References:

Harach HR, Williams ED. Histopathology 1983; 7:83-97

AMR SEMINAR #58
CASE 5

Contributed by: Michele Bisceglia, M.D.

Case #1 (slides labeled 146141-7)

Clinical History: A 26-year-old male, who had sustained progressive fatigue, muscle weakness, diffuse bone pain, and vertebral fractures for 3 years and was wheel-chair bound for 1 year, was admitted to our hospital in February 2007 for endocrinologic investigation. He had been hospitalized elsewhere because of hypophosphatemic rickets, obesity, diabetes mellitus type II, arterial hypertension, and hypogonadotropic hypogonadism in 2004 and 2005. He was prescribed testosterone, growth hormone, 1,25-dehydroxyvitamin D (aka 1-25-dehydroxy cholecalciferol or calcitriol, the active form of vitamin D3 / cholecalciferol) and vitamin D2 (ergocalciferol) without any clinical-radiologic benefit on his mineral bone metabolism. The patient had no family history of rickets or bone disease. Laboratory investigation in February 2007 confirmed previously documented hypophosphatemia (1.26 mg/dL, reference range 2.7 - 4.5), hyperphosphaturia as indicated by decreased maximum transport of phosphate in renal proximal tubules ($TmPO_4$/GFR, 1.7; normal range 2.5 - 4.2), high serum total alkaline phosphatase (304 u/L, reference range 40 - 129), normocalcemia (calcium-albumin adjusted: 9 mg/dL, reference range 8.1 - 10.4), and – additionally - slightly elevated serum level of parathormone (73.3 pg/mL, normal range 10 - 65). Despite medical treatment, serum level of calcifediol (aka calcidiol, 25-hydroxycalciferol or 25-hydroxivitamin D, the best indicator of blood vitamin D status) was very low (9.9 ng/mL, reference range > 32). Testosterone serum level was marginally low (3.05 ng/mL, reference range 3 - 9). Spine roentgenograms demonstrated osteopenia, thoracolumbar vertebral fractures. Bone scintiscan revealed costochondral uptake suggestive of rachitic rosary. Whole body octreotide scan and computerized tomography scan did not show any additional lesions.

The patient was discharged home receiving phosphate, $1,25(HO)_2$-vitamin D, and calcium supplementation. He was re-admitted six months later. At this time, repeat total body scintigraphy with octreotide and total body CT scan disclosed small, low signal intensity in the heel of his right foot. Fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan revealed high uptake in the soft tissue of the right calcaneal region. Ultrasonogram and magnetic resonance imaging showed a 2.5 cm solid lesion in the subcutaneous panniculus of the right heel. The lesion was excised in September 2007. A preoperative blood sample from median cubital vein to determine serum level of fibroblast growth factor 23 (FGF-23) was submitted to the clinical laboratory. The soft tissue mass was sent to the anatomic pathology laboratory.

Pathologic Findings: A well demarcated 2.5 cm gritty soft tissue mass was surrounded by grossly unremarkable subcutaneous adipose tissue. Histopathologically, the lesion was made up of oval to short spindle-cells set in a collagenous matrix with diffuse lattice-like calcific deposits, focally reminiscent of a chondromyxoid lesion, and exhibited a rich capillary network, microhemorrhages, clusters of multinucleated giant cells, and foci of osseous metaplasia. Cell pleomorphism was not a feature. Mitotic figures were scant (< 1/10HPF). The surgical margins were uninvolved.

Diagnosis: Phosphaturic mesenchymal tumor, mixed connective tissue type.

Follow-up: Just three days after excision of the right heel tumor, both his phosphatemia (3.38 mg/dL) and the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate ($TmPO_4$/GFR, 2.8) normalized. His serum level of fibroblast growth factor 23 (FGF-23) was highly elevated preoperatively (100.7 pg/mL; reference range 10-50), but dropped to normal values (15.5 pg/mL) within 3 days, His postoperative course was uncomplicated and the patient was discharged 8 days after excision of a phosphaturic mesenchymal tumor. Regarding his bone mineralization status, he promptly and completely recovered.

Discussion: We already had such cases circulated in AMR seminars: in fact, Andrew Folpe contributed the first case of phosphaturic mesenchymal tumor in 2001 [AMR Seminar # 36], Kum Cooper contributed his own case in 2006 [AMR seminar # 49], and Goran Elmberger presented the most recent case in 2008 [3rd AMR Int'l Symposium in Mexico City]. All these AMR cases showed peculiar histories and/or clinical-pathological findings. Folpe's case was

located in the soft tissue of the right femoral triangle of a 56-year-old man (of note this case was operated on "*in the hope of identifying a neoplasm*", … since "*no soft tissue or bony masses were apparent by imaging or physical examination*"). Cooper's case was a recurrent soft tissue tumor (of note in this case "*both serum and urinary calcium/phosphate levels were normal*", i.e. it was pertinent to the phosphaturic subset of phosphaturic mesenchymal tumor). Elmberger's case was a sinonasal (ethmoidal sinus) tumor in a 70-year-old woman (of note the fact that this case was of mixed connective tissue type, while most phosphaturic cases in sinonasal location exhibit HPC-like morphology).

Phosphaturic mesenchymal tumor (PMT) is an uncommon tumor causing oncogenic osteomalacia by virtue of overexpressing fibroblast growth factor–23 (FGF-23), a protein capable of inhibiting renal tubular phosphate transport, that is the most important of the four known phosphaturic factors of the "phosphatonin" family, which also includes the secreted frizzled related protein 4 (sFRP-4), the fibroblast growth factor 7 (FGF-7), and the matrix extracellular phospho glycoprotein (MEPE), all acting upon the kidney to reduce phosphate reabsorption.

According to a 2004 review paper on this issue by Folpe et al, a total of 109 cases of PMT had been published up to 2002, to which they added 32 new cases on their own (1). Folpe's paper is still the most exhaustive review paper on this subject and suggestion is given to readers to refer to that paper for clinicopathological details.

The case presented herein is one of my 3 personal cases (the other 2 are on different subjects), which are scheduled to be presented at the 4th AMR Int'l Symposium in Turkey this June 2010. This case gave me the opportunity to update the list of cases published in the world literature so far, and based on a computerized search (PubMed/Medline), from 2002 to the end of March 2010, using [oncocytic osteomalacia], [tumor-induced osteomalacia], and [phosphaturic mesenchymal tumor] as search terms, 108 additional cases of PMT were found (*details in the handouts of that Symposium which will be put onto the AMR official website*).

What is of note in my case? Well, we must say first that - based on ASBMR (American Society for Bone and Mineral Research) criteria - oncogenic osteomalacia can be firmly established even in absence of tumor discovery (tumor-induced osteomalacia of unknown primary) (3). PMT is renown for being sometimes diagnosed after repeat admissions and several clinical searches, due to the small size of tumor and its peculiar location (even intracranial or intraspinal, and also – as it was seen in 3 cases which have recently been published - in visceral organs). The ABMR criteria to assess oncogenic osteomalacia in absence of a known tumor include typical biochemical profile of hypophosphatemic osteomalacia, clinical symptoms of deranged skeletal mineralization, absence of personal or familial history of hypophosphatemic disorders in childhood, normal height at adult age, absence of skeletal deformities, previous documentation of normal fasting phosphate serum levels, exclusion of acquired Fanconi syndrome, and absence of FGF-23 gene mutation (3). The case presented herein was previously diagnosed as oncogenic osteomalacia with unknown primary, which was lastly recognized (at his 3rd admission) by both total body scintigraphy with octreotide and total body CT scan in the superficial calcaneal soft tissue of patient's right foot. This tumor escaped previous investigations because the feet were "technically" excluded from the scanning (it seems that in some imaging services/institutions feet are excluded from scanning unless you specifically request to include *also* the patient's feet in the study).

Foot was affected in 4 of 32 total cases in Folpe's et al own series (1) and in 6 of 109 cases previously published and reviewed up to 2002 by the same authors (1), and in 8 of 106 cases in the 2002-2010 above-mentioned review of the literature for which tumor location was established (sole was the specific site in 3 of these 8 cases). Parenthetically it seems convenient to mention here that I personally saw on consultation also another case of PMT located in the same site as the one herein presented (i.e., even in the subcutaneous tissue of the heel). ***Comment***: Foot (including sole) may be well a good site for PMT to hide.

References:

1. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, et al. Most osteomalacia-associated mesenchymal tumors are a single histopathological entity. An analysis of 32 cases and a review of the literature. Am J Surg Pathol 2004;28:1-30.
2. The 4th AMR Int'l Symposium. Istambul, June 3-4, 2008 (Bisceglia M. case 1). http://www.amr-seminar.org/
3. Jan de Beur SM. Tumor-induced osteomalacia. In: American Society for Bone and Mineral Research (ed) Primer on the metabolic bone diseases and disorders of mineral metabolism. American Society for Bone and Mineral Research, 2006, pp 345–351.

AMR SEMINAR #58
CASE 6

Case contributed by: Michele Bisceglia, M.D.

Case #2 (slides labeled 85197-4)

Clinical History: A 38-year-old female with "ascites" and a presumptive diagnosis of non-Hodgkin lymphoma underwent laparoscopic retroperitoneal paraaortic lymphadenectomy in June 2004. A piecemeal excised 3.0 cm in aggregate mass of soft tissue was submitted fresh for intraoperative consultation and tissue triage.

Intraoperative consultation: Frozen sections revealed total effacement of the lymph node architecture and complete replacement by a bland-appearing leiomyomatous-like proliferation. In places, there were slightly ectatic lymphatic channels as well as scattered, small, round foci of residual lymphoid tissue. The accumulated peritoneal fluid was described as chylous. Both, the histopathological findings and clinical information suggested the possibility of lymphangioleiomyomatosis involving retroperitoneal lymph nodes. Most of the fragments were immersed in 10% buffered formalin for paraffin embedding and standard processing, small tissue fragments were fixed in Karnovsky solution and processed for electron microscopy.

Permanent Sections: H&E stained permanent sections confirmed a spindle cell proliferation with myoid features exhibiting a distinctive peristomatous-arrangement characterized by spindle cell bundles distributed around an arborizing network of endothelium-lined slit-like spaces. Immunohistochemically, the myoid cells were diffusely reactive for vimentin, alpha-smooth muscle actin and desmin. Scattered cells lying in minute clusters or singly were immunoreactive for HMB-45 and melan-A. Additional immunomarkers, such S-100 protein, EMA, cytokeratins, and CD34 all were negative. CD34 highlighted the rich capillary network of lymphatic vessels alternating with the spindle cell fascicles. Based on the coexpression of both smooth muscle markers and melanocytic markers, the myo-melanocytic nature of the spindle cell proliferation mainly composing the lesion was ascertained. Nuclear immunostaining test for estrogen and progesterone receptors was also positive in 40% and 60% of the myo-melanocytic cells, respectively.

Ultrastructural Examination: The myoid cells shared features of both smooth muscle and melanocytes. Their cytoplasms displayed a hybrid phenotype containing intracytoplasmic wisps of actin-like microfilaments in subplasmalemmal localization with dense bodies, and membrane bound granules of variable electron density corresponding to stage 1 and 2 premelanosomes and stage 3 melanosomes with a variety of configurations.

Diagnosis: Lymphangioleiomyomatosis involving lymph nodes – likely systemic – (exclude tuberous sclerosis complex).

Comment: The clinical charts of this patient were reviewed. Her signs and symptoms of lymphangioleiomyomatosis, that had eluded her clinicians for about 9 years, became obvious in view of her newly established diagnosis. The patient had experienced shortness of breath, and its onset coincided with her first pregnancy in 1995. Her dyspnea subsided after delivery. Exacerbation of difficulty breathing became manifest four years later, during her second pregnancy. Therefore, in 1999 she underwent pulmonary function testing for worsening of her respiratory symptoms, which revealed significant airflow limitation. Concomitantly, allergic testing was positive for Dermatophagoides pteronyssinus and Dermatophagoides farinae. With a clinical diagnosis of chronic asthmatiform obstructive pulmonary disease, the patient was treated accordingly with bronchodilators, corticosteroids, and antibiotics. In January 2003 spirometry demonstrated reduced forced expiratory volume (FEV_1) and forced vital capacity (FVC), increased total lung capacity (TLC), increased residual volume (RV), and increased RV/TLC ratio. Computed tomography (CT) scanning revealed diffuse bilateral cystic changes of lung parenchyma, changes that were interpreted as centrilobular pulmonary emphysema. In May 2004 she was hospitalized because of severe dyspnea, cough, and chest pain at our institution. Auscultation revealed reduction of breath sounds. Routine chest X-ray demonstrated hyperinflation. A right pleural effusion was evacuated by repeat thoracenteses. The pleural fluid was described as chylus (opalescent-white). Its chylous nature was proven by biochemical analyses (triglyceride level

1401 mg/ml). Other chemical analyses performed on the chyle were total protein (4.89 g/dl), albumin (2.98g/dl), glucose (108 mg/dl), cholesterol (91 mg/dl). Blood gas analyses documented reduction in diffusing capacity: pH 7.4; pO2=47.9 mmHg; pCO_2= 37.5 mmHg. High resolution chest CT scan (HRCT) confirmed previously documented findings of diffuse, homogeneous, small (< 1.0 cm diameter) thin-walled cysts. No significant mediastinal or hilar lymphadenopathy was identified. CT scan of the abdomen showed multiple enlarged periaortic and pelvic lymph nodes. A periaortic lymph node was biopsied in June 2004. Sections from this lymphadenectomy specimen were used for your review.

No skin, heart, brain, and/or intraabdominal visceral sign or pathological manifestation suggesting tuberous sclerosis complex was discovered, and the definitive diagnosis was that of "sporadic lymphangioleiomyomatosis" (not associated with angiomyolipoma).

Follow-up: Administration of Tamoxifen and luteinizing hormone-releasing hormone analogs (LHRH) resulted in minimal transient clinical benefits. Less than 2 years after the diagnosis, the patient died while in waiting list for lung transplantation. Autopsy was not performed.

Discussion: Lymphangioleiomyomatosis (LAM) (OMIM # 606690) is a systemic condition, affecting almost exclusively women in their reproductive age. It is characterized by an abnormal proliferation of myoid cells (so-called LAM cells) in the lungs as well as in the axial lymphatics and lymph nodes of the thorax and retroperitoneum (1). The disorderly growth of cells with smooth muscle phenotype results in progressive obstruction of airways and lymphatics. LAM most often occurs as a *sporadic disease*, but also occurs in women with tuberous sclerosis complex (TSC) (*syndromic or TSC-related LAM*). There are no pathologic differences between sporadic and syndromic (TSC-related) LAM.

Sporadic LAM is a rare disease with an estimated prevalence of approximately 1 to 2 cases per million women in US and among populations of Caucasian descent (2-3), and is even more rare among Asian and African individuals. Syndromic LAM affects 4-5% of women with TSC, but subclinical involvement is much more frequent than thought (up to 50% [5]). TSC, which occurs up to 1 in 6,000 live births, is an autosomal dominantly inherited systemic malformation syndrome, linked to TSC1 and TSC2 tumor suppressor genes, mapped on chromosome 9q (9q34) and chromosome 16p (16p13.3) respectively, with the former encoding hamartin and the latter - which accounts for the two thirds of mutations - encoding tuberin.

TSC diagnosis is primarily clinical [OMIM # 191100], based on the evidence of *major clinical features* (facial angiofibromas, ungual or periungual fibromas, hypomelanotic macules, shagreen patches, retinal hamartomas and retinal astrocytomas, cortical tubers, subependymal nodules and subependymal giant cell astrocytomas, cardiac rhabdomyomas, lymphangioleiomyomatosis, and renal angiomyolipomas) and *minor clinical features* (enamel dental pits, hamartomatous rectal polyps, bone cysts, cerebral white matter migration lines, gingival fibromas, retinal achromic patches, confetti skin lesions, multiple renal cysts, and "nonrenal hamartomas". The category of "non-renal hamartomas" includes extrarenal angiomyolipomas, pulmonary and extrapulmonary clear cell sugar tumors of visceral organs and somatic soft tissue, and multifocal micronodular pneumocyte hyperplasia.

Histogenesis from epithelioid perivascular cell has been proposed for renal and extrarenal angiomyolipomas, pulmonary and extrapulmonary LAM, pulmonary and extrapulmonary clear cell sugar tumors, which thus at times are collectively called PEComas.

Regarding TSC diagnosis and LAM it might be useful to emphasize the following: i. a definitive clinical diagnosis of TSC now requires two or more distinct types of lesions. ii. multiple lesions of the same type (e.g., multiple angiomyolipomas) in the same organ system are counted as one; iii. in this context and from the clinical point of view, LAM and renal (as well as extrarenal) angiomyolipoma have to be considered as the same lesion and when concomitantly present to be counted as one; iv. foci of LAM have been reported in renal angiomyolipoma (2-3); v. visceral involvement other than lung (e.g., uterus) has been described in TSC-related LAM (4); vi. visceral circumscribed TSC-related LAM (aka, nodular variant of LAM) has also been observed (e.g., in the kidney concomitantly with classic angiomyolipoma); vii. renal angiomyolipoma is the most frequent sign of TSC and is often (50-60%) found also in association with sporadic LAM; viii. LAM associated with angiomyolipoma does not equate TSC.

Although – according to the diagnostic criteria outlined above - LAM is not diagnostic on its own for TSC, it is considered *per se* by some authors to be an incomplete expression (*forme fruste*) of this condition. From the genetic standpoint, syndromic LAM patients harbour germline mutations, but (according to the Knudson theory) the disease is usually caused by a second somatic cellular hit, which inactivates the remaining normal allele ("loss of heterozygosity"

resulting in "two hit" $TSC^{-/-}$ cells). The second hit is not only new in each of several tumors occurring in TSC but may involve TSC1 or TSC2 gene, independently from the germline $TSC1^{-/+}$ or $TSC2^{-/+}$ mutant allele (mechanism of trans-heterozygosity). Analogously, in sporadic LAM patients, who by definition do not have either TSC1 or TSC2 germline mutations, molecular analyses also have found somatic mutations of TSC2 gene in lung and kidney ($TSC2^{+/+}$ / $TSC2^{+/-}$ mosaicism) and loss of heterozygosity in $TSC2^{-/-}$ LAM cells. TSC1 and TSC2 are tumor suppressor genes and their encoded proteins downregulate cell growth and proliferation by inhibiting mTOR (mammalian target of rapamycin), a ubiquitous serine-threonine kinase. Inactivating genetic mutations of TSC1 and/or TSC2 intimately involve the regulation of protein synthesis, cell growth, and cell proliferation.

Some other studies have demonstrated that pulmonary LAM cells are the same cells of lymph nodal LAM and renal angiomyolipoma, thus suggesting the possibility that LAM cells are capable to migrate via lymphatics, and pulmonary LAM is thought to represent "metastatic" disease from other sites (renal angiomyolipomas, and lymph node and lymphatics LAM). This hypothesis has been supported by the demonstration that LAM patients with lung involvement have circulating LAM cells in peripheral blood and that recurrent pulmonary LAM after lung transplantation derive from native LAM.

In descending order of frequency, in sporadic LAM, thoracic (mediastinal and hilar pulmonary), intraabdominal, and cervical lymph nodes can be affected with or without lung involvement.
Lymph node involvement is called extrapulmonary LAM, and extrapulmonary LAM often precedes lung involvement, another point in favour of the capacity of LAM cells to migrate from periphery to lung. When a lymph node is involved in isolation, then the term lymphangioleiomyoma is used.

Other case of LAM which have been circulated in the Club are the case of LAM involving the uterus by Thomas Colby (4) and the case of pulmonary LAM (also showing micronodular pneumocyte hyperplasia) by John KC Chan (5). The case presented herein is one the 3 cases (the other 2 are on different subjects), which are scheduled to be presented this June, 2010, in Turkey during the 4th AMR Int'l Symposium. More details and references will be available in the handouts of that Symposium which will be put on the official AMR website as well (6).

In conclusion LAM is a rare and often unrecognized disease, for which early diagnosis is auspicable. Early therapeutic intervention may improve the symptomatology and slow the disease progression. The mainstay of treatment is based on hormonal manipulation, such as oophorectomy, progestin therapy (medroxyprogesterone acetate), tamoxifen, LHRH analogs. Sirolimus, an immunosuppressive drug, acting as mTOR inhibitor, has recently been also proposed.

References:

1. Travis WD, Colby TV, Koss MN, Rosado-de-Christenson, Müller NL, King TE, Jr. Non-neoplastic disorders of the lower respiratory tract. Atlas of NonTumor Pathology. American Registry of Pathology and Armed Forces Institute of Pathology. Bethesda, Maryland: 2002; pagg. 147-160.
2. Chan JK, Tsang WY, Pau MY, Tang MC, Pang SW, Fletcher CD. Lymphangiomyomatosis and angiomyolipoma: closely related entities characterized by hamartomatous proliferation of HMB-45-positive smooth muscle. Histopathology.1993;22:445-455.
3. Bisceglia M, Galliani C, Carosi I, Simeone A, Ben-Dor D. Tuberous sclerosis complex with polycystic kidney disease of the adult type: the TSC2/ADPKD1 contiguous gene syndrome. Int J Surg Pathol. 2008;16:375-385.
4. Colby TV - Case 2.. Uterine lymphangioleiomyomatosis. Arkadi M. Rywlin 2nd International Symposium in Anatomic Pathology. 10-12 June, 2005. Srni, Czech Republic http://www.amr-seminar.org/ (also in AMR Seminar # 14 case 3 Lymphangioleiomyomatosis of lung).
5. Lymphangiomyomatosis and multifocal micronodular pneumocyte hyperplasia (Seminar 41 – case 3 http://www.amr-seminar.org/).
6. The 4th AMR Int'l Symposium in Anatomic Pathology. Istambul, June 3-4, 2008 (Bisceglia M. - case 2). http://www.amr-seminar.org/

AMR SEMINAR #58
CASE 7

Contributed by: Michele Bisceglia, M.D.

Case # 3 (slides labelled MB-599/A-B-C)

Clinical History and Pathological findings: This is a case I received in July 2009 for second opinion concerning a 45-year-old lady who was admitted to a local hospital with multiple lung metastases, one of which (4 mm in size) was biopsied.

In 1999, at the age of around 35 this woman underwent surgical total left nephrectomy in a different hospital. The histological diagnosis in 1999 was that of a sarcoma-NOS of the kidney. The patient did not receive any adjunctive therapy after surgery in 1999. Tissue blocks from the renal tumor were requested for review, from which the circulated slides were cut.

This past renal tumor (as you can see) was hypercellular and mitotically active, composed of atypical, monomorphic, round to oval closely apposed medium-sized tumor cells, and showed focal HPC-like growth pattern, hemorrhagic foci, necrosis and pseudocystic areas. The greatest tumor diameter was 12.5 cm. The tumor margins were infiltrative, entrapping the surrounding normal renal parenchyma. The renal pelvis was infiltrated, but hilar or perirenal adipose tissues as well as 5 paracaval/periaortic lymph nodes submitted for histological examination were not involved.

On morphology I thought this (primary) renal tumor could be monophasic fibrous primary renal synovial sarcoma. The small lung nodule which was biopsied was consistent with metastasis from the renal primary (but the 10-year long interval was notable).

Immuno in our hands was as follows: vimentin diffusely positive; BCL-2 diffusely +ve; EMA focally +ve; CK (pankeratin, CK7, CK19) all negative; CD99 focally +ve; alpha-SMA, desmin, myogenin negative; CD117 negative; Fli-1 negative; WT1 negative; TTF1 negative; S-100 negative; CD34 patchy +ve.
Electron microscopy showed closely apposed oval-shaped cells lacking epithelial differentiation (no tonofibrils, no desmosomes), with absence of actin-like microfilaments. Basal lamina was not seen.
Molecular analyses (RT-PCR and FISH analyses), which were performed at the Rizzoli Institute, Bologna, Italy, did not demonstrate the t(X;18) (p11;q11) translocation of either SYT-SSX1 or SYT-SSX2 gene fusion. Based on morphology they (Rizzoli Institute) also thought the tumor was suggestive of synovial sarcoma.

Although most unusual finding, CD34 patchy positivity had already been seen in 3 cases of mediastinal synovial sarcoma (Ref. 8 in the list below - *Bégueret H, et al. Primary intrathoracic synovial sarcoma: a clinicopathologic study of 40 t(X;18)-positive cases from the French Sarcoma Group and the Mesopath Group. Am J Surg Pathol. 2005;29:339-46*).

Finally, due to the uncertainty deriving from the CD34 immunoreactivity and the absence of the t(X;18) translocations, I sent this case to Pedram Argani at Johns Hopkins in Baltimore. Dr. Argani got diffuse immunopositivity for CD34, and based on CD34+vity and the absence of the SYT-SSX1 and SYT-SSX2 translocations he concluded for "unclassified non-pleomorphic sarcoma" suggesting the possibility of malignant renal solitary fibrous tumor (verbatim "*I cannot definitely classify this sarcoma in this material. While the morphology certainly suggests synovial sarcoma, arguing against that possibility are 1) the focal presence of a multipolar mitoses, 2) the strong CD34 immunoreactivity we see, 3) the reported negative molecular assay for synovial sarcoma. A malignant solitary fibrous tumor seems possible to me, but I do not see a benign solitary fibrous tumor component which would support such a diagnosis*)".

Discussion: Solitary fibrous tumor of the kidney (SFTK) was first described in 1996 and can originate either in the renal capsule or parenchyma.[1,2] To date 38 cases of SFTK have been reported, most of them described by standard

criteria as histologically benign, and carrying a favourable clinical prognosis (follow-up ranging 2 to 89 months).[1,2,3] Only 2 cases of SFTK exhibiting malignant histological changes were reported, in 2006[1,] and 2008[2], respectively. The tumor in the first case was >10cm in size and diffusely malignant, with the conventional (benign) features found only focally: the patient developed lung metastases 4 months after surgery (*malignant [secondary]* SFTK arising in a pre-existing tumor which had been followed clinically as a stable lesion for 4 years).[1] The tumor in the second case was 9 cm in diameter with a 3 cm nodular malignant area abruptly emerging from the surrounding typically bland SFT tissue (*dedifferentiated* SFTK or SFTK with *sarcomatous overgrowth*); this patient was free of disease 21 months after surgery.[3] Malignant SFTK in the absence of residual histologically benign SFT may be difficult if not impossible to assess as well as to differentiate from primary synovial sarcoma of the kidney (SSK). SSK, a rare neoplasm usually carrying a poor prognosis, was first described in 2000.[4,5] Primary SSK can exist in either a monophasic or a biphasic form, and may be misdiagnosed as another type of sarcomatous or sarcomatoid renal tumor, primary or metastatic. As its soft tissue counterpart, the diagnosis of primary SSK can be confirmed by molecular analysis, showing the characteristic t(X;18) (p11;q11) translocation. To date 54 cases of primary SSK have been reported, including 3 with rhabdoid features[6] (rhabdoid variant of SSK).

Now I agree with Dr Argani's diagnosis, and taking all these findings into account the final diagnosis would be "unclassified non-pleomorphic renal sarcoma" – probably *de novo* malignant SFTK.

Comment: The diagnosis of malignant SFTK in this case is neither straightforward nor would be eventually completely accepted by anyone since no foci of benign SFT were found (areas of usual SFT had been seen so far in both the 2 afore-mentioned cases of malignant SFTK as well as in all cases of the recently recognized dedifferentiated SFT of soft tissue).[7] Furthermore, CD34 may also be positive in sarcomas other than malignant SFTK and is most often lost in the malignant and dedifferentiated areas of SFT in both renal and soft tissue cases.[1,7] Notwithstanding, *de novo* malignant SFT is a real possibility. SSK, which had not yet been described at the time of nephrectomy in this case, was the main consideration on review, but its exclusion is based on both the absence of the specific translocation and presence of CD34 positivity (parenthetically CD34 positivity was also seen in 3 cases of intrathoracic SS[8]); other renal primaries, excluded for more obvious reasons, were sarcomatoid renal cell carcinoma, primary renal fibrosarcoma, malignant nerve sheath tumor, monomorphic angiomyolipoma, extragonadal endometrial stromal sarcoma, inflammatory myofibroblastic tumor, congenital mesoblastic nephroma, malignant mixed epithelial stromal tumor, leiomyosarcoma, anaplastic sarcoma of the kidney with polyphenotypic features[9], of recent identification, and (atypical) congenital mesoblastic nephroma. *Follow-up*: The patient was given several courses of chemotherapy, using Ifosfamide, Epirubicin and MESNA, and temporarily improved. Currently, 10 months following discovery of the lung metastases, she is alive with slight disease progression.

Since I think this case is worth reporting I would be strongly interested in the club members' opinions on it. The tumor was truly uniform and is well represented in the 3 slides which are being circulated.

Any other thoughts? Thanks.

References: **1.** Fine SW, McCarthy DM, Chan TY, Epstein JI, Argani P. Malignant solitary fibrous tumor of the kidney: report of a case and comprehensive review of the literature. Arch Pathol Lab Med. 2006;130:857-861; **2.** Magro G, Emmanuele C, Lopes M, Vallone G, Greco P. Solitary fibrous tumour of the kidney with sarcomatous overgrowth. Case report and review of the literature. APMIS. 2008;116:1020-5. **3.** Hirano D, Mashiko A, Murata Y, Satoh K, Ichinose T, Takahashi S, Jike T, Sugitani M. A case of solitary fibrous tumor of the kidney: an immunohistochemical and ultrastructural study with a review of the literature. Med Mol Morphol. 2009;42:239-244. **4.** Argani P, Faria PA, Epstein JI, Reuter VE, Perlman EJ, Beckwith JB, Ladanyi M. Primary renal synovial sarcoma: molecular and morphologic delineation of an entity previously included among embryonal sarcomas of the kidney. Am J Surg Pathol. 2000;24:1087-1096. **5.** Kim DH, Sohn JH, Lee MC, Lee G, Yoon GS, Hashimoto H, Sonobe H, Ro JY. Primary synovial sarcoma of the kidney. Am J Surg Pathol. 2000;24:1097-1104. **6.** Jun SY, Choi J, Kang GH, Park SH, Ayala AG, Ro JY. Synovial sarcoma of the kidney with rhabdoid features: report of three cases. Am J Surg Pathol. 2004;28:634-637. **7.** Mosquera JM, Fletcher CD. Expanding the spectrum of malignant progression in solitary fibrous tumors: a study of 8 cases with a discrete anaplastic component--is this dedifferentiated SFT? Am J Surg Pathol. 2009;33:1314-1321. **8.** Bégueret H, Galateau-Salle F, Guillou L, Chetaille B, Brambilla E, Vignaud JM, Terrier P, Groussard O, Coindre JM. Primary intrathoracic synovial sarcoma: a clinicopathologic study of 40 t(X;18)-positive cases from the French Sarcoma Group and the Mesopath Group. Am J Surg Pathol. 2005;29:339-346. **9.** Vujanić GM, Kelsey A, Perlman EJ, Sandstedt B, Beckwith JB. Anaplastic sarcoma of the kidney: a clinicopathologic study of 20 cases of a new entity with polyphenotypic features. Am J Surg Pathol. 2007;31:1459-1468.

AMR SEMINAR #58
CASE 8

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

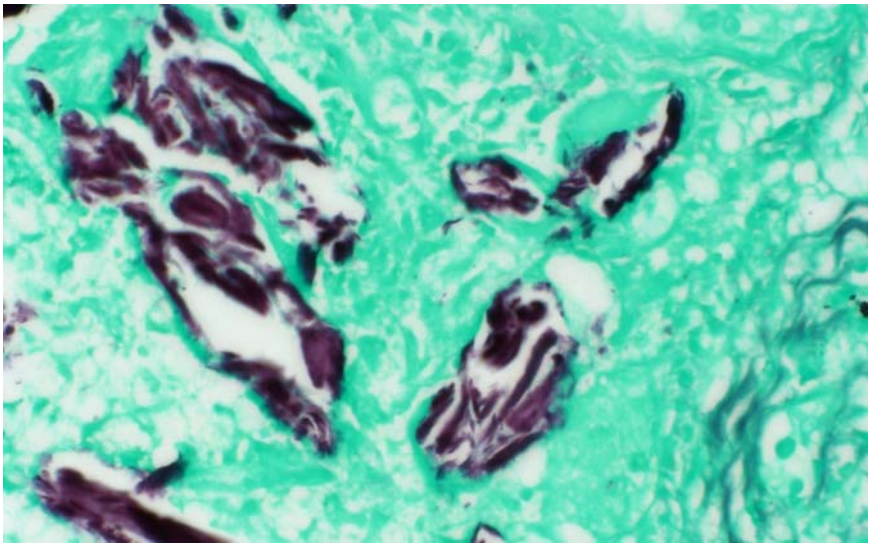
Clinical History (TV10-93): A 45-year-old woman with a long history of Crohn's disease, status-post multiple prior resections, developed dyspnea and suffered an abrupt cardiac arrest and died during workup for her symptoms. This represents tissue from autopsy. The right ventricular thickness was 0.6 cm. The lungs weighed 650 and 640 grams (right and left). They were described as having a "granular cut surface."

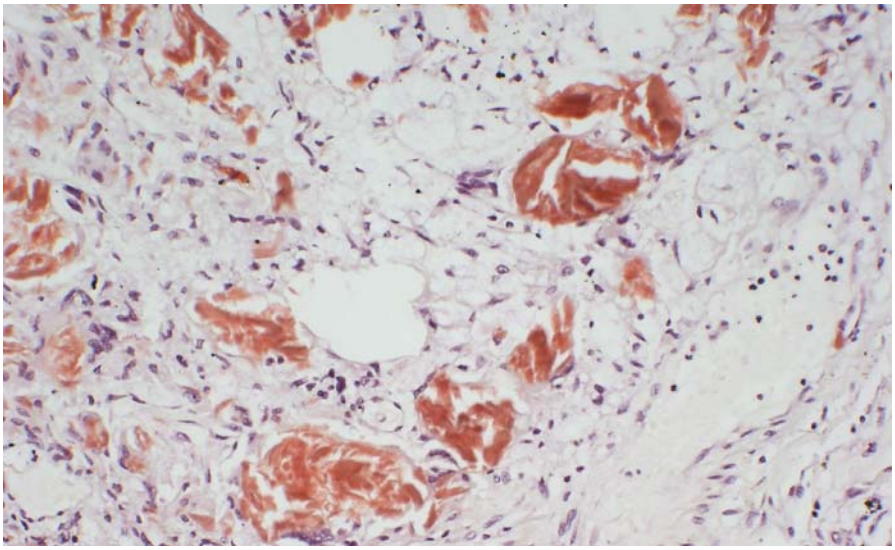
Diagnosis: Massive embolic foreign material consistent with microcrystalline cellulose (from crushed up oral tablets, type unknown) with associated pulmonary hypertension and right ventricular hypertrophy.

Discussion: This case is not a diagnostic problem but is so florid that I thought it would be worthwhile sharing with the group. We see four or five cases like this each year and sometimes there is an obvious history of intravenous exposure, whereas in others such a history can only be obtained with difficulty (and persistence). We could not get details on this patient. I suspect she may have had an intravenous line in, perhaps for hyperalimentation secondary to her intestinal disease. Somehow these patients discover that the effects of pain medications are much quicker when crushed up and injected intravenously compared to oral administration. In my experience, most of these cases are self-administered although I have heard of a few where some other person was doing the injection and one might have to consider more ominous motivations, such as homicide.

In this case the material is obviously within small and large vessels and associated with an exuberant giant cell reaction. One can see rupture of vessel walls in many places. The pulmonary arteries are thickened, indicative of pulmonary hypertension. Given the pathology, the sudden death is not surprising. She probably had severe pulmonary hypertension.

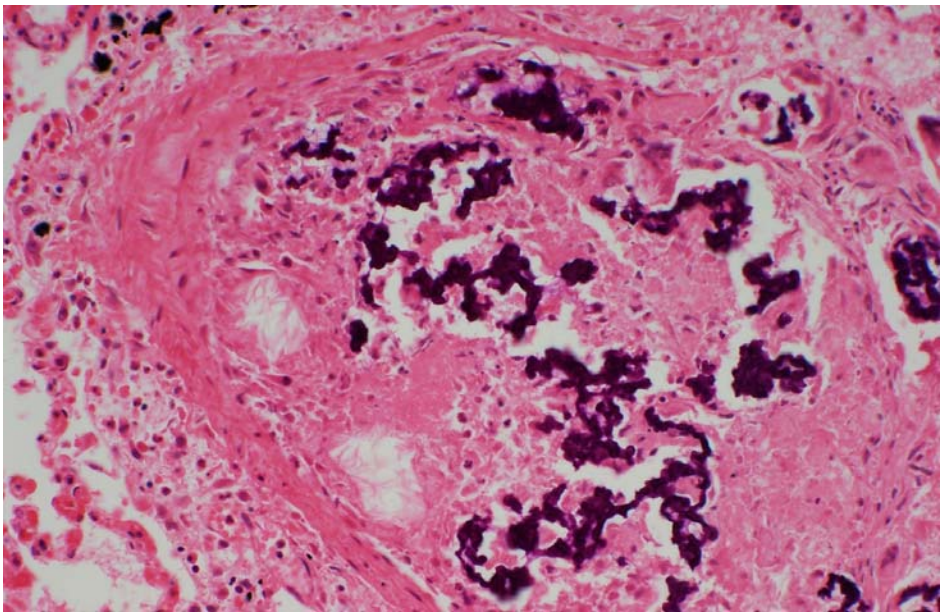
I believe the foreign material here is microcrystalline cellulose, which is a common binder/inert vehicle that is found in many oral tablets these days. In the past, talc had been used and in the past the term intravenous (IV) talcosis was popularized. Microcrystalline cellulose may be positive with PAS, GMS, and Congo red stains. In this case, PAS positivity was not prominent, whereas Congo red positivity and GMS positivity were quite marked and are illustrated below.





When one encounters birefringent material like this in small biopsies, one often has to decide whether the particles are inhaled, aspirated, or injected. In general, inhaled particles are small than 10 microns since particles larger than that do not make it all the way into the alveoli. Aspirated material, obviously can be larger and would tend to be within airspaces as well as airways and food is also often present. Particles injected intravenously that lodge in the lung are typically much larger than 10 microns and in this case the "granular cut surface" seen grossly is probably related to the massive amounts of material within the pulmonary vessels.

Another embolic substance that can be encountered in the lungs of intravenous drug abusers is crospovidone. Crospovidone is a disintegrant used in pharmaceutical tablets. Crospovidone appears as basophilic coral-like particles, sometimes in association with the more chunky microcrystalline cellulose. A picture of crospovidone is shown below.



I hope the group finds this case of interest.

References:

Dettmeyer RB, Verhoff MA, Brückel B, Walter D. Widespread pulmonary granulomatosis following long time intravenous drug abuse-A case report. Forensic Sci Int. 2010 Apr 15;197(1-3):e27-e30. PubMed PMID: 20137873.

Ganesan S, Felo J, Saldana M, Kalasinsky VF, Lewin-Smith MR, Tomashefski JF Jr. Embolized crospovidone (poly[N-vinyl-2-pyrrolidone]) in the lungs of intravenous drug users. Mod Pathol. 2003 Apr;16(4):286-92. PubMed PMID: 12692192.

Hammar SP, Williams MG, Dodson RF. Pulmonary granulomatous vasculitis induced by insoluble particulates: a case report. Ultrastruct Pathol. 2003 Nov-Dec;27(6):439-49. PubMed PMID: 14660283.

Kringsholm B, Christoffersen P. The nature and the occurrence of birefringent material in different organs in fatal drug addiction. Forensic Sci Int. 1987 May-Jun;34(1-2):53-62. PubMed PMID: 3036675.

Ott MC, Khoor A, Scolapio JS, Leventhal JP. Pulmonary microcrystalline cellulose deposition from intravenous injection of oral medication in a patient receiving parenteral nutrition. JPEN J Parenter Enteral Nutr. 2003 Jan-Feb;27(1):91-2. PubMed PMID: 12549606.

Tomashefski JF Jr, Hirsch CS, Jolly PN. Microcrystalline cellulose pulmonary embolism and granulomatosis. A complication of illicit intravenous injections of pentazocine tablets. Arch Pathol Lab Med. 1981 Feb;105(2):89-93. PubMed PMID: 6893924.

Zeltner TB, Nussbaumer U, Rudin O, Zimmermann A. Unusual pulmonary vascular lesions after intravenous injections of microcrystalline cellulose. A complication of pentazocine tablet abuse. Virchows Arch A Pathol Anat Histol. 1982;395(2):207-16. PubMed PMID: 7048728.

AMR SEMINAR #58
CASE 9

Contributed by: Göran Elmberger, M.D., Ph.D. Karolinska University Hospital, Stockholm, Sweden.

Clinical History: This 59-year-old man with congenital aortic insufficiency was healthy until 40 years of age when he suffered from bone pain and increased inflammatory parameters. X-ray revealed lytic and sclerotic multiple lesions in long bones. Bone biopsy from femur condyle interpreted as reactive. On special clinical request to rule out Langerhans cell histiocytosis S-100 IHC was found negative. No Birbeck granulae on EM. Long term treatment with cytotoxic drugs and steroids. Otherwise, symptomatic pericarditis and radiolological signs of coated aorta and perirenal fibrosis. Recently epileptical seizures of grand mal type. CT reveals meningioma-like tumor cerebri in fronto-temporal cortex. Brain biopsy (enclosed slide) externally interpreted as metaplastic-xanthomatous meningioma. General increase in inflammatory parameters and scintigraphically signs of increased activity in distal long bones.

Pathological Findings: Microscopical examination showed a dural based xanthomatous histiocytic proliferation with multiple Touton-like multinucleated giant cells. The Touton-like giant cells regularly showed classical wreath-like arrangement of multiple nuclei. In some sections the histiocytic proliferation was sharply demarcated from surrounding brain tissue even if no capsule formation was seen. The histiocytes generally had abundant pale staining and foamy or finely granular cytoplasm. In minor areas a more eosinophilic granular cytoplasm was present. Focally intracytoplasmic hemosiderin pigment was noted. The nuclei were round to oval and lacked the irregular configurations typical of Langerhans' cells. Pseudocystic and microcystic degeneration was noted centrally in lesion. Parts of lesion showed birefringent collagen sclerosis. Mild lymphocyte dominated focal inflammation was seen. Minor component of plasma cells and rare eosinophilic granulocytes were also noted. Sparsely foci of empty cholesterin-like clefts with suggestive multinucleated foreign-body-type granuloma were seen. Findings not previously described were stromal and intravascular psammoma bodies, HPC-like vessels and a plexiform rich capillary network. Capillaries also focally showed sclerosis. Subdurally, small ball-like proliferates of meningothelial cells were seen. No lymphocytic emperipolesis was identified. No cellular atypia, necrosis, mitosis or granuloma were found.

Special studies:
IHC: CD45+, CD68+, Lysozyme+, MAC387+, vim+/-, CD99-, EMA-, PgR-, MNF116-, S-!00-, GFAP-, NSE-, CD1a-.
Proliferation rate < 1% (MIB1).
Histochemistry: PAS +/- D -.

Review of previous femoral bone biopsies revealed irregularly thickened sclerotic bone trabeculae, bone marrow fibrosis, lymphocytic sparse inflammatory reaction, and a focal infiltrate of foamy cells consistent with late fibrotic phase of Erdheim-Chester disease (ECD). Touton giant cells could not be seen.

Diagnosis: Pseudotumoral intracranial Erdheim-Chester disease (polyostotic sclerosing histiocytosis) mimicking a primary brain-meningeal tumor as manifestation of previously undiagnosed systemic disease.

Discussion: ECD was first described by Chester and Erdheim in 1930 under the name "lipoid granulomatose". To date approximately 200 cases has been described in the literature. ECD is a rare, idiopathic, non-Langerhans cell lipid-storing histiocytosis without detectable serum lipid abnormalities. Histologically ECD is characterized by xanthogranulomatous inflammation, with widespread systemic manifestations. The disease appears to be non-familial and mainly affects middle-aged adults. Clonality studies have yielded mixed results in ECD. A more than rare co-existence of ECD and LCH raise the possibility of a relationship between the two histiocytoses. Typical systemic features of ECD include osteosclerotic lesions of the metaphysial regions of long bones, retroperitoneal and pulmonary fibrosis, cutaneous lesions, fever, and exophthalmos. It may also affect the heart, liver, spleen, sinonasal mucosa, aorta, testis, thyroid, lymph nodes and kidneys. Neurological involvement is most commonly heralded by hypothalamic/pituitary involvement with resultant diabetes insipidus, and occasionally cerebellar symptoms. Involvement of other intracranial regions such as the cerebral cortex, spinal cord, choroid plexus and leptomeninges

is uncommon. By the time the intracranial lesion is discovered, most patients demonstrate evidence of systemic disease. A rare case of isolated intracranial ECD has been described. The most common central nervous system manifestations of ECD in descending order are diabetes insipidus, cerebellar syndromes and orbital lesions. Spinal and extra-dural masses have also been documented in the literature. In general, ECD evolves in a slowly progressive manner and may mimic multiple sclerosis because of the multifocal nature of involvement.

Both preoperative and post-operative anatomical diagnoses of the present case were initially interpreted as consistent with metaplastic-xanthomatous meningioma. The systemic nature of the disease as well as the outcome of IHC with a CD68+, EMA- and PgR- cell population is clearly against meningioma. In addition to ECD, other notable histiocytic disorders that involve the central nervous system and are rarely characterized as a solitary mass lesion include Langerhans cell histiocytosis (LCH) of presumed dendritic Langerhans cell origin and non-Langerhans cell histiocytoses from bone-marrow derived macrophages such as sarcoidosis, Rosai-Dorfman disease (RDD), juvenile xanthogranuloma (JXG) and hemophagic lymphohistiocytosis. In the absence of the characteristic extra-cerebral manifestations, the diagnosis of these disorders is often challenging and is one of exclusion. Awareness of the clinico-pathological spectrum of these entities can be helpful in sorting out the differential diagnosis of cerebral histiocytic lesions that may mimic neoplastic or infectious diseases. Rarely true malignant histiocytic neoplastic disorders such as histiocytic sarcoma or follicular dendritic cell (FDC) sarcoma may primarily involve the leptomeninges and brain.

The prognosis of Erdheim-Chester disease is dependent on the extent of extraosseous disease. Approximately 60% of patients die of the disease, the majority due to respiratory failure or central nervous system involvement. No effective treatment has been discovered, although chemotherapeutic agents, radiotherapy, interferon therapy, and autologous bone marrow transplantation have been employed.

References:

Adem C, Helie O, Leveque C et al. Case 78: Erdheim-Chester disease with central nervous system involvement. *Radiology*. 2005;234:111-115.

Al-Quran S, Reith J, Bradley J et al. Erdheim-Chester disease: case report, PCR-based analysis of clonality, and review of literature. *Mod Pathol*. 2002;15:666-672.

Albayram S, Kizilkilic O, Zulfikar Z et al. Spinal dural involvement in Erdheim-Chester disease: MRI findings. *Neuroradiology*. 2002;44:1004-1007.

Allen TC, Chevez-Barrios P, Shetlar DJ et al. Pulmonary and ophthalmic involvement with Erdheim-Chester disease: a case report and review of the literature. *Arch Pathol Lab Med*. 2004;128:1428-1431.

Andrade VP, Nemer CC, Prezotti AN et al. Erdheim-Chester disease of the breast associated with Langerhans-cell histiocytosis of the hard palate. *Virchows Arch*. 2004;445:405-409.

Augoustides JG, Szeto WY. Unmasked diabetes insipidus after pericardial drainage and biopsy for pericardial effusion in association with Erdheim-Chester disease. *J Thorac Cardiovasc Surg*. 2008;136:217-218.

Barnes PJ, Foyle A, Hache KA et al. Erdheim-Chester disease of the breast: a case report and review of the literature. *Breast J* . 2005;11:462-467.

Bianco F, Iacovelli E, Tinelli E et al. Characteristic brain MRI appearance of erdheim-chester disease. *Neurology*. 2009;73:2120-2122.

Bisceglia M, Cammisa M, Suster S et al. Erdheim-Chester disease: clinical and pathologic spectrum of four cases from the Arkadi M. Rywlin slide seminars. *Adv Anat Pathol*. 2003;10:160-171.

Boralevi F, Leaute-Labreze C, Tison F et al. [Langerhans-cell histiocytosis and Erdheim-Chester disease: probably not a fortuitous association]. *Ann Dermatol Venereol*. 1998;125:335-338.

Brodkin CL, Wszolek ZK. Neurologic presentation of Erdheim-Chester disease. *Neurol Neurochir Pol*. 2006;40:397-403.

Chetritt J, Paradis V, Dargere D et al. Chester-Erdheim disease: a neoplastic disorder. *Hum Pathol*. 1999;30:1093-1096.

Chung JH, Park MS, Shin DH et al. Pulmonary involvement in Erdheim-Chester disease. *Respirology*. 2005;10:389-392.

Clerico A, Ragni G, Cappelli C et al. Erdheim-Chester disease in a child. *Med Pediatr Oncol*. 2003;41:575-577.

Colin P, Ballereau C, Lambert M et al. Retroperitoneal infiltration as the first sign of Erdheim-Chester disease. *Int J Urol*. 2008;15:455-456.

Cruz AA, de A, V, Falcao MF et al. Association between Erdheim-Chester disease, Hashimoto thyroiditis, and familial thrombocytopenia. *Ophthal Plast Reconstr Surg*. 2006;22:60-62.

De FM, Ingegnoli A, Carloni A et al. Erdheim-Chester disease: clinical and radiological findings. *Radiol Med*. 2009.

Dickson BC, Pethe V, Chung CT et al. Systemic Erdheim-Chester disease. *Virchows Arch*. 2008;452:221-227.

Dinkar AD, Spadigam A, Sahai S. Oral radiographic and clinico-pathologic presentation of Erdheim-Chester disease: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007;103:e79-e85.

Dion E, Graef C, Miquel A et al. Bone involvement in Erdheim-Chester disease: imaging findings including periostitis and partial epiphyseal involvement. *Radiology*. 2006;238:632-639.

Eble JN, Rosenberg AE, Young RH. Retroperitoneal xanthogranuloma in a patient with Erdheim-Chester disease. *Am J Surg Pathol*. 1994;18:843-848.

Egan AJ, Boardman LA, Tazelaar HD et al. Erdheim-Chester disease: clinical, radiologic, and histopathologic findings in five patients with interstitial lung disease. *Am J Surg Pathol*. 1999;23:17-26.

Enriquez R, Cabezuelo JB, Martinez M et al. Nephrotic syndrome and amyloid A amyloidosis in a patient with Erdheim-Chester disease. *Nephron*. 2000;86:195-196.

Evans S, Williams F. Case report: Erdheim-Chester disease: polyostotic sclerosing histiocytosis. *Clin Radiol*. 1986;37:93-96.

Ferrozzi F, Bova D, Tognini G et al. Pseudotumoral bilateral involvement of the breast in Erdheim-Chester disease: CT appearance. *J Comput Assist Tomogr*. 2000;24:281-283.

Fortman BJ, Beall DP. Erdheim-Chester disease of the retroperitoneum: a rare cause of ureteral obstruction. *AJR Am J Roentgenol* . 2001;176:1330-1331.

Freed GL, Sinacori JT. Subglottic stenosis in Erdheim-Chester disease: a previously unrecognized site of involvement. *Laryngoscope*. 2006;116:663-664.

Garg T, Chander R, Gupta T et al. Erdheim-Chester disease with cutaneous features in an Indian patient. *Skinmed*. 2008;7:103-106.

Gong L, He XL, Li YH et al. Clonal status and clinicopathological feature of Erdheim-Chester disease. *Pathol Res Pract*. 2009;205:601-607.

Green I, Dorfman RF, Rosai J. Breast involvement by extranodal Rosai-Dorfman disease: report of seven cases. *Am J Surg Pathol*. 1997;21:664-668.

Gundling F, Nerlich A, Heitland WU et al. Biliary manifestation of Erdheim-Chester disease mimicking Klatskin's carcinoma. *Am J Gastroenterol*. 2007;102:452-454.

Gupta A, Kelly B, McGuigan JE. Erdheim-Chester disease with prominent pericardial involvement: clinical, radiologic, and histologic findings. *Am J Med Sci*. 2002;324:96-100.

Haroche J, Amoura Z, Touraine P et al. Bilateral adrenal infiltration in Erdheim-Chester disease. Report of seven cases and literature review. *J Clin Endocrinol Metab*. 2007;92:2007-2012.

Haroche J, Cluzel P, Toledano D et al. Images in cardiovascular medicine. Cardiac involvement in Erdheim-Chester disease: magnetic resonance and computed tomographic scan imaging in a monocentric series of 37 patients. *Circulation*. 2009;119:e597-e598.

Ivan D, Neto A, Lemos L et al. Erdheim-Chester disease: a unique presentation with liver involvement and vertebral osteolytic lesions. *Arch Pathol Lab Med*. 2003;127:e337-e339.

Johnson MD, Aulino JP, Jagasia M et al. Erdheim-chester disease mimicking multiple meningiomas syndrome. *AJNR Am J Neuroradiol*. 2004;25:134-137.

Karcioglu ZA, Sharara N, Boles TL et al. Orbital xanthogranuloma: clinical and morphologic features in eight patients. *Ophthal Plast Reconstr Surg*. 2003;19:372-381.

Khamseh ME, Mollanai S, Hashemi F et al. Erdheim-Chester syndrome, presenting as hypogonadotropic hypogonadism and diabetes insipidus. *J Endocrinol Invest*. 2002;25:727-729.

Kong PM, Pinheiro L, Kaw G et al. Erdheim-Chester disease: a rare cause of interstitial lung disease. *Singapore Med J*. 2007;48:e57-e59.

Kovacs K, Bilbao JM, Fornasier VL et al. Pituitary pathology in Erdheim-Chester disease. *Endocr Pathol*. 2004;15:159-166.

Kumandas S, Kurtsoy A, Canoz O et al. Erdheim Chester disease: cerebral involvement in childhood. *Brain Dev*. 2007;29:227-230.

Lachenal F, Cotton F, smurs-Clavel H et al. Neurological manifestations and neuroradiological presentation of Erdheim-Chester disease: report of 6 cases and systematic review of the literature. *J Neurol*. 2006;253:1267-1277.

Lau WW, Chan E, Chan CW. Orbital involvement in Erdheim-Chester disease. *Hong Kong Med J*. 2007;13:238-240.

Madroszyk A, Wallaert B, Remy M et al. [Diffuse interstitial pneumonia revealing Erdheim-Chester's disease]. *Rev Mal Respir*. 1994;11:304-307.

Marsot-Dupuch K, Le HP. Erdheim-Chester disease: a sinonasal lesion mimicking rhinoscleroma. *Neuroradiology*. 2000;42:625.

Mergancova J, Kubes L, Elleder M. A xanthogranulomatous process encircling large blood vessels (Erdheim-Chester disease?). *Czech Med*. 1988;11:57-64.

Moore FO, Berne JD, Fox AD. Mesenteric panniculitis and Erdheim-Chester disease: xanthogranulomatous diseases confused with malignancy. *J Am Coll Surg*. 2007;204:326-327.

Mounach A, Nouijai A, Achemlal L et al. Erdheim-Chester disease: a case report with pulmonary, kidney involvement and bone lesions. *Rheumatol Int*. 2009.

Nagatsuka H, Han PP, Taguchi K et al. Erdheim-Chester disease in a child presenting with multiple jaw lesions. *J Oral Pathol Med*. 2005;34:420-422.

Nicholson AG, Anderson E, Saha S et al. Progressive dyspnoea, pleural effusions and lytic bone lesions. *Thorax*. 2008;63:492, 554.

O'Rourke R, Wong DC, Fleming S et al. Erdheim-Chester disease: a rare cause of acute renal failure. *Australas Radiol*. 2007;51 Spec No.:B48-B51.

Ozdemir MA, Coskun A, Torun YA et al. Cerebral Erdheim-Chester disease: first report of child with slowly progressive cerebellar syndrome. *J Neurooncol*. 2007.

Perlat A, Decaux O, Sebillot M et al. Erdheim-Chester disease with predominant mesenteric localization: lack of efficacy of interferon alpha. *Joint Bone Spine*. 2009;76:315-317.

Petrikowski CG, McGaw WT. Erdheim-Chester disease of the jaws: literature review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90:389-398.

Protopapadakis C, Antoniou KM, Nicholson AG et al. Erdheim-Chester disease: pulmonary presentation in a case with advanced systemic involvement. *Respiration*. 2009;77:337-340.

Rao RN, Chang CC, Uysal N et al. Fulminant multisystem non-langerhans cell histiocytic proliferation with hemophagocytosis: a variant form of Erdheim-Chester disease. *Arch Pathol Lab Med*. 2005;129:e39-e43.

Rhodes B, Jawad AS. Erdheim-Chester disease. *J R Soc Med*. 2005;98:296.

Romm S. Jakob Erdheim. Eminent pathologist of Vienna. *Am J Dermatopathol*. 1987;9:447-450.

Rush WL, Andriko JA, Galateau-Salle F et al. Pulmonary pathology of Erdheim-Chester disease. *Mod Pathol*. 2000;13:747-754.

Rushing EJ, Kaplan KJ, Mena H et al. Erdheim-Chester disease of the brain: cytological features and differential diagnosis of a challenging case. *Diagn Cytopathol*. 2004;31:420-422.

Rushing EJ, Bouffard JP, Neal CJ et al. Erdheim-Chester disease mimicking a primary brain tumor. Case report. *J Neurosurg*. 2004;100:1115-1118.

Saboerali MD, Koolen MG, Noorduyn LA et al. Pleural thickening in a construction worker: it is not always mesothelioma. *Neth J Med*. 2006;64:88-90.

Scheer M, Hon M, Fruauff AA et al. Perinephric xanthogranulomatosis: CT diagnosis and confirmation by CT-guided percutaneous biopsy. *Clin Imaging*. 2000;24:64-67.

Schmidt HH, Gregg RE, Shamburek R et al. Erdheim-Chester disease: low low-density lipoprotein levels due to rapid catabolism. *Metabolism*. 1997;46:1215-1219.

Serratrice J, Granel B, De RC et al. "Coated aorta": a new sign of Erdheim-Chester disease. *J Rheumatol*. 2000;27:1550-1553.

Shamburek RD, Brewer HB, Jr., Gochuico BR. Erdheim-Chester disease: a rare multisystem histiocytic disorder associated with interstitial lung disease. *Am J Med Sci*. 2001;321:66-75.

Sheu SY, Wenzel RR, Kersting C et al. Erdheim-Chester disease: case report with multisystemic manifestations including testes, thyroid, and lymph nodes, and a review of literature. *J Clin Pathol*. 2004;57:1225-1228.

Shimada S, Ono K, Hashizume Y et al. Intracranial lesion of Erdheim-Chester disease. *Hum Pathol*. 2007;38:950-951.

Spyridonidis TJ, Giannakenas C, Barla P et al. Erdheim-Chester disease: a rare syndrome with a characteristic bone scintigraphy pattern. *Ann Nucl Med*. 2008;22:323-326.

Stoppacciaro A, Ferrarini M, Salmaggi C et al. Immunohistochemical evidence of a cytokine and chemokine network in three patients with Erdheim-Chester disease: implications for pathogenesis. *Arthritis Rheum*. 2006;54:4018-4022.

Taguchi T, Iwasaki Y, Asaba K et al. Erdheim-Chester disease: report of a case with PCR-based analysis of the expression of osteopontin and survivin in Xanthogranulomas following glucocorticoid treatment. *Endocr J*. 2008;55:217-223.

Thorns V, Zajaczek J, Becker H et al. Extracerebral subdural manifestation of Chester-Erdheim disease associated with a giant adenoma of the pituitary. *Clin Neuropathol*. 2003;22:246-251.

Vaglio A, Corradi D, Maestri R et al. Pericarditis heralding Erdheim-Chester disease. *Circulation*. 2008;118:e511-e512.

Vencio EF, Jenkins RB, Schiller JL et al. Clonal cytogenetic abnormalities in Erdheim-Chester disease. *Am J Surg Pathol*. 2007;31:319-321.

Venkatanarasimha N, Garrido MC, Puckett M et al. AJR teaching file: A rare multisystem disease with distinctive radiologic-pathologic findings. *AJR Am J Roentgenol*. 2009;193:S49-S52.

Vick VL, Wilson MW, Fleming JC et al. Orbital and eyelid manifestations of xanthogranulomatous diseases. *Orbit*. 2006;25:221-225.

Wang CW, Colby TV. Histiocytic lesions and proliferations in the lung. *Semin Diagn Pathol*. 2007;24:162-182.

Wittenberg KH, Swensen SJ, Myers JL. Pulmonary involvement with Erdheim-Chester disease: radiographic and CT findings. *AJR Am J Roentgenol*. 2000;174:1327-1331.

Yahng SA, Kang HH, Kim SK et al. Erdheim-Chester disease with lung involvement mimicking pulmonary lymphangitic carcinomatosis. *Am J Med Sci*. 2009;337:302-304.

AMR SEMINAR #58
CASE 10

Contributed by: Giovanni Falconieri, M.D., Udine, Italy

Clinical History: The patient is a 54-year-old lady complaining of mild chest pain. Instrumental investigations reveal a pleural opacity associated with effusion. A CT scan shows a left pleural mass which is felt suspicious of a primary pleural tumor. No other clinical features are noted. Past medical history is unremarkable as well.

Pathologic Features: A 12 x 6 x 2.5 cm plaque is resected from the visceral pleural sheath. It is firm, white-grey, with no areas of necrosis or hemorrhage. Microscopically, tumor sections appear fairly comparable showing a cellular proliferation of polygonal, large cells, with abundant, often vacuolated cytoplasm and vesicular nuclei. The ground substance is variably fibrous or sclerotic. In several sections the tumor does not appear circumscribed. Yet the underlying pulmonary parenchyma is questionably infiltrated. Scattered mitoses can be recognized. Residual mesothelial elements with variable degree of hyperplasia are noticed as well. Tumor cells are positive for keratins, vimentin, and calretinin, and negative for CEA, BerEp4, CD34, CD99, desmin, actins, podoplanin.

Microscopic Interpretation: Don't know! The surgeon told me that the tumor was relatively easy to resect and that the remainder of the pleura was unremarkable, although no extra tissue was submitted. I just signed this as atypical mesothelial tumor, not otherwise specified, and recommended a close clinical monitoring. Alternative ideas?

Follow up: The patient did not receive any further treatment. There was no clinical or instrumental evidence of tumor recurrence in the past 11 months.

AMR SEMINAR #58
CASE 11

Contributed by: Franco Fedeli, M.D.

Clinical History: A 75-year-old white female presented with a 0.9 cm lesion on scalp for 1 year.

Pathologic Findings: The histologic findings were characterized by cell clusters or short papillae of well-differentiated epithelium floating in multilocular mucin pools that were often separated by thin fibro-connective tissue septae. Tumor cells showed little cytoplasmic mucin vacuoles despite abundant mucin in the surrounding tissue. Rarely, the tumor cells were directly in contact with connective tissue stroma. Myoepithelial cells (stained by CK5/6 and P63) were rarely found in the periphery of the clusters of neoplastic cells bordered by non-mucinous connective stroma. ER, PR, and CK7 were positive in the tumor cells. There was a strong positivity for synaptophysin and focally for chromogranin. CK 20 and CDX2 were negative. The clinical work-up for metastatic carcinoma was negative. The presence of an in situ component bounded by myoepithelial cells, which were highlighted by immunostains for CK 5/6 and p63, in association with invasive mucinous carcinoma is evidence for considering the lesion as a primary carcinoma of the skin. The presence of strong positivity for synaptophysin suggests neuroendocrine differentiation. The clinical significance lies in the fact that this lesion needs to be differentiated from metastatic mucinous carcinoma, particularly from breast. Immunoreactivity of primary cutaneous mucinous carcinoma with CK7, ER and PR makes this distinction impossible.

Diagnosis: Mucinous carcinoma of the skin.

Comment: Primary mucinous (colloid) carcinoma of the skin is a rare neoplasm. In the skin, approximately 180 cases have been reported and most describe pure mucinous carcinoma without an in situ component. There is a female predominance (2:1). The mean age is 65. Commonly it arises in the head or neck, with scalp and eyelid being the most common sites. It is also found on the axilla and trunk. Painless, gray or reddish nodules, measuring 0.5 to 7cm in diameter are the most common presentation. Cut surface has a gelatinous appearance. Dermal tumour demonstrates large pools of basophilic mucin separated by thin fibrovascular septa. Small islands of epithelial cells are present in the mucinous pools. Cells are dense at the periphery. Tumour cells are small, cuboidal and bland and may have vacuolated cytoplasm arranged in cribriform, papillary, tubular or glandular patterns. Almost no mitotic figures are present.

Mucinous carcinomas can originate from in situ lesions. The presence of an in situ component defines the neoplasm as primary cutaneous, but its absence does not exclude that diagnosis. Cytologic diagnosis of primary mucinous carcinoma of the skin is possible; however, correlation of clinical, radiologic and pathologic features is necessary to obtain an accurate diagnosis. By immunohistochemistry this tumour is positive for low- molecular weight cytokeratin, CEA, EMA and sometimes S100. ER and PR are also positive. CK20 is negative, which might significantly contribute to the differentiation from metastatic colonic cancer. In rare cases there is positivity for neuroendocrine markers. Neuroendocrine differentiation occurs in other mucinous carcinomas, such as mucoid carcinoma of the breast, but the significance of this finding and its potential role in the histogenesis of primary mucinous carcinoma of the skin is still controversial. Treatment for primary mucinous carcinoma of the skin is wide local excision. Recurrence is about 15%. Very few cases show metastatic spread to local lymph nodes.

REFERENCES:

Bellezza G, Sidoni A, Bucciarelli E. Primary mucinous carcinoma of the skin. Am J Dermatopathol. 2000;22:166–170.

Friedrich B, Markus C, Wolfgang P, et al. Primary mucinous carcinoma of the scalp. *Dermatology*. 2000;200:250–253.

Hanby AM, McKee P, Jeffrey M, et al. Primary mucinous carcinomas of the skin express TFF1, TFF3, estrogen receptor, and progesterone receptors. *Am J Surg Pathol*. 1998;22:1125–1131.

Kazakov D, Suster S, LeBoit P, et al. Mucinous carcinoma of the skin, primary, and secondary. Am J Surg Pathol. 2005;29:764–782.

Qureshi HS, Salama ME, Chitale D, et al. Primary cutaneous mucinous carcinoma: presence of myoepithelial cells as a clue to the cutaneous origin. *Am J Dermatopathol*. 2004;26:353–358.

AMR SEMINAR #58
CASE 12

Contributed by: Masaharu Fukunaga, M.D.

History: A 56-year-old, gravida 1, para 1, female presented with constipation. CT, Echogram and physical examination revealed a bulky mass in the pelvic cavity. At laparotomy, the mass showed an exophytic, deep red tumor resembling cotyledons of the placenta or grapes extending from the uterine surface and projecting into the pelvic cavity. She underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. The patient is alive with no evidence of disease at 20 months after surgery.

Macroscopic Features: A 30 cm bulky mass was noted associated with the posterior wall of the uterine body. The cut surface of the mass showed a white a multilobulated tumor (Figures 1 and 2, Arrow indicates uterine body). Small veins were identified in the interlobular regions. The tumor was characterized by an extrauterine, exophytic growth pattern, multinodular cotyledonoid appearance, and the absence of massive necrosis or invasive growth. The extrauterine tumor is continuous with intrauterine myomatous nodules.

Immunohistochemical studies: vimentin, asma, HHF35, desmin, CD10, ER :(+). H-caldesmon, CD34, c-kit, PgR: (-).

Diagnosis: Cotyledonoid dissecting leiomyoma of the uterus (Sternberg tumor).

Comments: The characteristic macroscopic feature is a diagnostic clue of this neoplasm. In 1996, Roth et al. (1) described a series of four cases of unusual uterine leiomyoma termed 'cotyledonoid dissecting leiomyoma of the uterus'. As they were collected by Dr. Sternberg, they are often called "Sternberg tumors". Histologically in this case, the tumor had two components, a cotyledonoid extrauterine component and an intramural component, and the former was interpreted as intramural in origin. The intramural component demonstrated an irregularly dissecting growth pattern with elongated processes (the distributed slides may not contain this component). The lesion consisted of a proliferation of smooth muscle cells with intra- and extrauterine tumor components with marked hyalinization. Adipose differentiation was focally seen in the dissecting leiomyoma component. Almost all reported cases arose in the fundus or posterior aspect of the cornus of the uterus; perhaps there is more space for serosal growth in these areas (2). To date, there has not been any malignant behavior or recurrence described in association with these lesions with the longest reported follow-up period being 41 years (1). Intraoperatively, the worrisome appearance of the gross specimen is often mistaken for malignant or non-uterine lesions, which may result in overtreatment. Practically, the most important is the indication for intraoperative pathologic consultation (frozen section diagnosis). Total hysterectomy with close follow-up may be an appropriate treatment.

References:

1. Roth LM, Reed RJ, Sternberg WH. Cotyledonoid dissecting leiomyoma of the uterus: the Sternberg tumor. Am J Surg Pathol 1996; 20: 1455-61.
2. Cheuk W, Chan JKC, Liu JYS. Cotyledonoid leiomyoma: a benign uterine tumor with alarming gross appearance. Arch Pathol Lab Med 2002; 126: 210-3.

AMR SEMINAR #58
CASE 13

Contributed by: Thomas Krausz, M.D.

Clinical History: 40-year-old, morbidly obese female with long standing history of pulmonary arterial hypertension and cor pulmonale, who was admitted with dehydration, weakness, muscle stiffness and hyperkalemia. A few days later she developed worsening abdominal pain, distention, peritonitis and sepsis. Exploratory laparotomy revealed ischemic bowel. Right hemicolectomy with ileostomy was performed.

Additional Clinical History: Apart from idiopathic pulmonary hypertension, the past medical history includes: panhypopituitarism secondary to pituitary adenoma excision, secondary adrenal insufficiency, chronic kidney disease, hyperthyroidism status post radioablation, atrial fibrillation and gout. She was taking dopamine, remodulin, coumadin, spironolactone, pepcid, hydrocortisone, allopurinol, fexofenadine, amiodarone, folic acid, Lasix, midodrine, klor-con, and revatio as home medication. She had been called, the day prior to admission, by the nurse who told her to reduce her Lasix dose. She presented to the emergency department with several days of profound weakness and muscle stiffness, progressing to inability to walk. She states at admission that she feels "my potassium is high". At admission potassium was 7.7 and sodium 122. Following admission she received several doses of Kayexalate to treat her hyperkalemia.

Pathology: The resected specimen consisted of terminal ileum (18.5 cm), cecum with appendix and ascending colon (45.0 cm). The cecum and the ascending colon was dilated with areas of serosal dark purple discoloration. The colonic mucosa showed areas of ulceration covered by fibrinous exudate. Histologic examination (including the submitted section) showed ischemic necrosis, which focally was transmural. In the luminal inflammatory exudate there are scattered angulated, rhomboid or triangular, basophilic, non-birefringent crystals with mosaic pattern, consistent with Kayexalate medication. Neither vasculitis nor thromboembolism was detected. The histologic features are consistent with ischemic intestinal necrosis in association with Kayexalate medication.

Diagnosis: Colon with focal transmural ischemic necrosis following Kayexalate treatment for hyperkalemia.

Comments: There are numerous drugs that may cause injury to the gastrointestinal tract. The associated injury patterns can prompt consideration of drug-induced etiology. In the submitted case the morphologic clue to the diagnosis is the presence of angulated, basophilic crystals with mosaic pattern which are typical for Kayexalate (sodium polystyrene sulfonate) medication for hyperkalemia. The only differential diagnosis is cholestyramine, a bile acid binding resin sometimes used in the treatment of Clostridium difficile colitis. However, the cholestyramine crystals which are also basophilic and angulated, have greater opacity, and lack a mosaic pattern.

Sodium polystyrene sulfonate (SPS, Kayexalate) is usually administered in sorbitol and is a recognized cause of intestinal necrosis. SPS is a cation-exchange resin. When administered orally, SPS releases sodium ions in the acidic stomach, binds hydrogen ions, and subsequently exchanges hydrogen for potassium in the small and large intestine. In its early use, SPS was administered as a suspension in water, however, it caused constipation and fecal impaction. In order to prevent constipation, the practice changed in administering SPS with hypertonic sorbitol, an osmotic laxative agent. Sorbitol, rather than SPS resin itself, has been implicated in the development of intestinal injury. It has been shown that it is the sorbitol component that leads to ischemic necrosis and that uremic patients are most susceptible to the vascular shunting, induced by the osmotic load. Erosive and ulcerative injury of the esophagus, stomach and duodenum, in patients taking oral SPS (Kayexalate) preparations have also been described. However, these upper GI lesions seem to be reversible and are not associated with mortality.

Less than seventy cases of intestinal necrosis secondary to SPS in sorbitol have been reported. Initial reported cases were described in the renal transplant literature and most of these cases occurred postoperatively, in critically ill patients with end-stage renal disease, and in those with uremia. However, increasing number of cases have also been documented in less-ill and/or nonsurgical patients. The incidence of SPS (Kayexalate) in sorbitol-mediated

intestinal necrosis has been estimated as 0.27% to 1.8%. In view of high overall mortality (between 30 -40%), when treating hyperkalemia, alternative means of potassium reduction should be considered.

References:

Lillemoe KD, Romolo JL, Hamilton SR et al. Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. Surgery 1987; 101: 267-272.

Abrahams SC, Bhagavan BS, Lee LA et al. Upper gastrointestinal tract injury in patients receiving Kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic and histopathologic findings. Am J Surg Pathol 2001; 25: 637-644.

Parfitt JR, Driman DK. Pathologic effects of drugs on the gastrointestinal tract: a review. Human Pathology 2007; 38: 527-536.

McGowan CE, Saha S, Chu G, Resnick MB, Moss SF. Intestinal nerosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. Southern Medical Journal 2009; 102: 493-497.

AMR SEMINAR #58
CASE 14

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

Clinical Features: A 61-year-old female patient developed a deep seated neoplasm on the right forearm that was completely excised. There is no sign of recurrence at 4 months.

Pathological Features: Histologically, a deep seated, encapsulated mesenchymal neoplasm composed of cytologically bland spindled and stellated tumour cells is seen. The neoplastic cells are set in a prominent myxoid stroma containing numerous blood vessels with fibrosed vessel walls and focal microcystic spaces. Immunohistochemical stainings revealed a homogenous expression of S-100 protein by neoplastic cells, whereas the remaining antibodies (EMA, Claudin-1, ASMA) were all negative.

Diagnosis: Reticular schwannoma.

Comments: Reticular schwannoma represents a rare and recently described variant of biologically benign schwannoma. The majority of the reported neoplasms arose in visceral location, especially in the gastrointestinal tract, where often unencapsulated and infiltrative neoplasms are seen; in soft tissues the lesions are encapsulated. Histologically, reticular schwannoma is characterized by a prominent myxoid stroma with microcysts and neoplastic cells are arranged in a net-like fashion. A number of myxoid mesenchymal neoplasms has to be considered in the differential diagnosis including reticular perineurioma, myoepithelioma and extraskelatal myxoid chondrosarcoma

References:

Lee SM, Goldblum J, Kim KM. Microcystic/reticular schwannoma in the colon. Pathology. 2009;41(6):595-6

Liegl B, Bennett MW, Fletcher CD. Microcystic/reticular schwannoma: a distinct variant with predilection for visceral locations. Am J Surg Pathol. 2008 Jul;32(7):1080-7

Agaimy A, Märkl B, Kitz J, Wünsch PH, Arnholdt H, Füzesi L, Hartmann A, Chetty R. Peripheral nerve sheath tumors of the gastrointestinal tract: a multicenter study of 58 patients including NF1-associated gastric schwannoma and unusual morphologic variants. Virchows Arch. 2010 Apr;456(4):411-22

Graadt van Roggen JF, McMenamin ME, Belchis DA, Nielsen GP, Rosenberg AE, Fletcher CD. Reticular perineurioma: a distinctive variant of soft tissue perineurioma. Am J Surg Pathol. 2001 Apr;25(4):485-93

AMR SEMINAR #58
CASE 15

Contributed by: Elizabeth Montgomery, M.D. - Case S09-43545

History: This 3 cm mass was excised from the mid back just to the right of midline from a 17-month-old white boy whose parents had noted the lesion when the baby was 2 months old. At the time of excision, the lesion was remarkable for an overlying "crop" of coarse hairs and was quite firm.

Diagnosis: Fibrous hamartoma of infancy.

Comment: This is not a diagnostic problem but it is just so classic and lovely that it seems nice to have in a slide collection! It shows the relationship to the overlying skin since it is nicely oriented These lesions are rare and typically arise in the superficial soft tissue of the axillary fold area but also the shoulder girdle, thigh, groin, back, or forearm. The ones in the groin are put there for you to misdiagnose as rhabdomyosarcoma on frozen sections. Most present in baby boys younger than 2 years and some are noted at birth. Microscopically they are composed of an admixture in variable proportions of adipose tissue, bundles of spindle cells with fibroblastic and/or myofibroblastic features reminiscent of fibromatosis, and cells that appear more primitive. On immunolabeling, there is variable actin expression in the fibromatosis-like component but desmin expression is unusual. Beta catenin nuclear labeling is absent.

References:

1: Thway K, Gibson S, Ramsay A, Sebire NJ. Beta-catenin expression in pediatric fibroblastic and myofibroblastic lesions: a study of 100 cases. Pediatr Dev Pathol. 2009 Jul-Aug;12(4):292-6.

2: Michal M, Mukensnábl P, Chlumská A, Kodet R. Fibrous hamartoma of infancy. A study of eight cases with immunohistochemical and electron microscopical findings. Pathol Res Pract. 1992 Dec;188(8):1049-53.

3: Fletcher CD, Powell G, van Noorden S, McKee PH. Fibrous hamartoma of infancy: a histochemical and immunohistochemical study. Histopathology. 1988 Jan;12(1):65-74.

4: Popek EJ, Montgomery EA, Fourcroy JL. Fibrous hamartoma of infancy in the genital region: findings in 15 cases. J Urol. 1994 Sep;152(3):990-3.

AMR SEMINAR #58
CASE 16

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

Clinical History: 43-year-old woman with recurrent mass on right biceps.

Pathology: Morphologically a multi-lobulated neoplasm formed by mature chondroid tissue is identified, with some myxoid areas and minimal calcifications. No evident atypia is seen, however scant mitosis can be found with occasional binucleated cells.
Surgical margins are involved.

Diagnosis: Soft tissue chondroma vs chondroid tumor of unknown malignant potential.

Discussion: This was a referral case that we got after the recurrence. The initial neoplasm was resected in 2007 and the second one in 2010. Both show similar morphological features.

What I would like to address with this case is the confusion that can arise from these entity, being called chondroma according to the WHO classification, and therefore benign, even with atypia and mitosis if present in a distal location away from bone. This same morphology if in contact with bone would be called chondrosarcoma grade 1 or 2. We really think that the malignant potential of cartilaginous tumors is still not well defined and the fact that the anatomical location is even more important than the histological features means that we are missing something. Should we be calling these neoplasms as of unknown malignant potential? I would like to hear your comments on this subject.

AMR SEMINAR #58
CASE 17

Contributed by: Joshua Sickel, M.D.

Clinical History: 38-year-old woman with a left adnexal mass.

Gross Examination: Ovarian cyst with multiple papillary excrescences measuring from 1 to 5 cm. Some nodules have a fleshy consistency on cut section. Others have a distinct finely papillated surface covered with light tan cheesy material.

Microscopic Examination: Both nodular lesions described above have been included on the submitted slide. Sections from the fleshy nodules show characteristic features of clear cell adenocarcinoma with tubulocystic growth pattern. Immunostains for AE1/AE3, CK7 and EMA are positive, while stains for AFP, Sall-4 and Glypican-3 are negative, the latter results arguing against a diagnosis of yolk sac tumor. Sections from the papillated nodules show a dermoid cyst with striking verrucous growth pattern. In-situ stains for HPV performed at UCSF med center were negative.

Diagnosis: Clear cell adenocarcinoma arising in association with a dermoid cyst with striking verrucous hyperplasia.

Discussion: The vast majority of epithelial-type malignancies arising in mature cystic teratomas are squamous cell cancers. Only rare examples of clear cell adenocarcinoma arising in this setting have been reported in the literature. I was especially intrigued by the distinctive warty features in the dermoid cyst and strongly considered an HPV-related lesion (strangely enough, HPV-related squamous cell carcinoma has been report in the ovary, although I've never seen it). I was not able to find a report of true condylomatous lesions in a dermoid (I was hoping mine was the first case, oh well…). Have any AMR club members encountered this peculiar combination of ovarian lesions in your practice?

References:

Verguts J, et al. HPV induced ovarian squamous cell carcinoma: case report and review of the literature. Arch Gynecol Obstet. 2007 Sep;276(3):285-9.

Mai KT, et al. Bilateral primary ovarian squamous cell carcinoma associated with human papilloma virus infection and vulvar and cervical intraepithelial neoplasia. A case report with review of the literature. Am J Surg Pathol. 1996 Jun;20(6):767-72.

AMR SEMINAR #58
CASE 18

Contributed by: Dominic Spagnolo, M.D. - PathWest Laboratory Medicine, Nedlands, Western Australia (Accession Q10B12347N). Case seen in consultation, courtesy of Dr. L Ng, Western Diagnostic Pathology (accession 10-6376533).

Case History: 50–year-old female presented with chest tightness, shortness of breath and an enlarged submandibular node following a viral-like illness. Because the node was hard, and clinically a Kuttner tumour was suspected, a FNA was performed resulting in a paucicellular, non-diagnostic yield. At the time she was also noted to have a suprasternal notch swelling merging with an anterior mediastinal mass, confirmed on CT scan. PET scan did not show any focal abnormal metabolic activity in the submandibular gland, while the mediastinal mass revealed heterogeneous, moderate intensity FDG avidity. There is no history of HIV, sepsis, rheumatoid arthritis, Sjogren syndrome, SLE or myasthenia gravis.

A radical thymectomy was performed. Intraoperatively there was found a hard non-invasive thymic mass extending into the root of the neck to the base of the thyroid gland, with some associated adenopathy. There was no vascular or soft tissue invasion. Complete resection was effected.

Post-operatively she is well, but developed a hard right anterior orbital swelling, incisional biopsy of which (outside laboratory) has shown a necrotizing granulomatous process suggestive of deep granuloma annulare, without any suspicion of lymphoma or other neoplasia.

Pathological Changes: Paraphrasing the outside laboratory report, the specimen was described as an irregular piece of firm tissue 110x100x30mm weighing 98 gm, invested by a thin membrane and with some rubbery nodes attached. The cut surface showed central cysts with thick fibrous walls ranging in size from 2-3mm up to 15mm in size and containing cream/tan degenerate material. The intervening tissue had a uniform pale tan appearance. The gross images that were sent to me are not great but are appended for your interest.

The circulated slides derive from 3 different blocks but should be representative of the features described below. The enlarged thymus gland shows islands of residual unremarkable parenchyma at its periphery and lacks the lobulation and fibrous septation of a conventional thymoma. There are 3 salient elements here - cysts, proliferation of epithelium (medullary) and a prominent lymphoid infiltrate including many reactive follicles. The cysts vary in size, some are lined by continuous attenuated or stratified (squamous) epithelium, others have a partly ulcerated epithelium accompanied by inflammation and fibrosis in their walls. The cysts variously contain altered blood, keratinous material and cholesterol clefts. The intervening tissue is notable for a striking proliferation of irregular, often angulated and branching islands of somewhat spindly, bland thymic epithelium clearly continuous with, centered around, and radiating from Hassal's corpuscles undergoing progressive cystic change; this relation to Hassal's corpuscles imparts an orderly, repetitive appearance to the epithelial proliferation as opposed to a more diffuse and crowded pattern of proliferation. At least focally these islands of epithelium merge with the cyst walls (though this may not be apparent in all sections). The epithelial elements are often liberally infiltrated by small lymphocytes (largely CD20+). The final component is a striking follicular lymphocytic and plasmacytic stromal infiltrate, which is polyclonal (by both immunostaining and IgH and IgK gene rearrangement studies by capillary electrophoresis/GenScan). The reactive lymphoid follicles are often intimately related to the proliferating epithelium and also occur in the cyst walls. Rare follicles have a Castleman-like morphology. The plasma cells do not show an aberrant total IgG/IgG4 ratio. Included are photomicrographs of double keratin/CD20 immunostains which nicely illustrate these relationships. The T-cells in between the B-cell elements are mature T cells (negative for CD99, CD1a, TdT). There are no features to suggest secondary development of a thymoma or carcinoma. The attached lymph nodes showed nonspecific reactive changes only.

Diagnosis: Acquired thymic multilocular cyst with epithelial hyperplasia (medullary) and prominent lymphoplasmacytic and follicular lymphoid hyperplasia.

Discussion: We would all be familiar with the seminal publications on the subject by Drs Suster and Rosai. The main differential diagnoses are congenital thymic cyst, extranodal marginal zone lymphoma and micronodular thymoma with B-cell hyperplasia.

Uncomplicated congenital cysts are usually thin-walled, uni- or multilocular and lined by attenuated, cuboid or columnar epithelium which may be ciliated, or stratified squamous epithelium. They lack the accompanying epithelial hyperplasia and lymphoid reaction seen here. Extranodal marginal zone lymphoma of the thymus is a more difficult consideration as these are often cystic and may have a prominent element of reactive follicles. However there is more diffuse B-lymphoid proliferation, marginal zone cells in clusters or sheets are found, lymphoepithelial lesions are more discrete and clustered and contain at least mildly irregular lymphocytes and monoclonality is demonstrable in all cases by at least one or more ancillary modes of testing. Micronodular thymomas with lymphoid B-cell hyperplasia are also frequently multicystic and given the degree of epithelial proliferation here, also needed serious consideration. Micronodular thymoma, while also lacking the gross lobulation and broad fibrous septa of conventional thymoma, however has a greater profusion of multiple, small epithelial nodules creating a space-occupying effect, intraepithelial lymphocytes are scanty and the cysts typically lack an epithelial lining, rather appearing to arise from dilatation of perivascular spaces and not from Hassal's corpuscles.

The degree of medullary epithelial hyperplasia in this case I found striking. It seems to be different from the hyperplastic change occurring in the lining epithelium of the cysts described Drs Suster, Rosai and Michal (refs 2 &3). Various carcinomas are described arising in association with multilocular cysts, and some have also been associated with germ cell tumors. A rhabdomyomatous component has been described in one case.

Assuming this is indeed an acquired multilocular cyst, I have no idea what may have caused it. My main concerns throughout the process of formulating my ideas have been the possibility of an underlying autoimmune disorder, but there is no clinical evidence for this, and also not to miss a marginal zone lymphoma. I am hoping not to have under called an unusual thymoma, but I really don't think it is. Am looking forward to comments!

REFERENCES:

1. Multilocular thymic cyst: an acquired reactive process. Suster S, Rosai J. Am J Surg Pathol 1991; 15(4):388-398.
2. Multilocular thymic cysts with pseudoepitheliomatous hyperplasia. Suster S, Barbuto D, Carlson G, Rosai J. Hum Pathol 1991; 22:455-460.
3. Pseudo-epitheliomatous hyperplasia in thymic cysts. Michal M, Havlicek F. Histopathol 1991; 19:282-282.
4. Multilocular thymic cyst associated with follicular hyperplasia: clinicopathologic study of 4 resected cases. Izumi H, Nobukawa B, Takahashi K, et al. Hum Pathol 2005; 36(7):841-844.
5. Carcinomas arising in multilocular thymic cysts of the neck: a clinicopathologic study of three cases. Moran CA, Suster S, El-Naggar A, Luna MA. Histopathol 2004; 44(1):64-68.
6. Micronodular thymoma with lymphoid B-cell hyperplasia: clinicopathologic and immunohistochemical study of eighteen cases of a distinctive morphologic variant of thymic epithelial neoplasm. Suster S, Moran C. Am J Surg Pathol 1999; 23(8):955-962.

AMR SEMINAR #58
CASE 19

Contributed by: Paul Wakely, Jr., M.D. (Case #45530)

History: A 42-year-old man presented with flank pain. Gross examination revealed a 3 cm. mass in the superior pole of the left kidney.

Diagnosis: Metanephric Adenoma.

Comment: The tumor was positive with WT1 stain and negative for CK7 and EMA. An incidental angiomyolipoma was also found in this case.

AMR SEMINAR #58
QUIZ CASE 1

Contributed by: Joshua Sickel, M.D.

(note: there are no slides – images only which are on the AMR website)

Clinical History: 50-year-old woman with cystic lesion of left breast. Fine needle aspiration is performed.

Diagnosis: Myospherulosis

An analysis was made of 19 cases of myospherulosis seen on fine needle aspirates of mammary and subcutaneous tissue masses. Myospherulosis, best seen with the Papanicolaou stain, appeared as 4 microns to 7 microns spherules that were homogeneously smooth or contained one or more internal dense bodies. The spherules were dispersed singly or aggregated into sac-like structures. Myospherulosis accompanied 16 benign and 3 malignant conditions. In two aspirates, myospherulosis was seen simultaneously with breast carcinoma; in another, fat necrosis with myospherulosis masked an underlying breast malignancy.

In 10 of the 12 aspirates from patients with previous tissue trauma, it accompanied evidence of fat necrosis and mesenchymal repair; in 4 aspirates, no other underlying condition was apparent. These findings indicate that myospherulosis is not an uncommon finding in fine needle aspirates of fatty sites; it often accompanies fat necrosis and mesenchymal repair. The presence of myospherulosis in aspirates of clinically suspicious masses does not exclude an underlying malignancy.

Reference:

Shabb N, et al. Myospherulosis. Fine needle aspiration cytologic findings in 19 cases. Acta Cytol. 1991 Mar-Apr;35(2):225-8.

AMR SEMINAR #58
QUIZ CASE 2

Contributed by: Saul Suster, M.D.

Clinical History: A 13-year-old boy is seen for a slowly-growing soft tissue tumor approx. 3cm. in greatest diameter in his right thumb. The tumor was excised.