

AMR Seminar #62

Case – 1

Quiz Case

Contributed by: Volkan Adsay, M.D.

History: 62 year old female presented with vomiting, bloating and pain in left quadrant. CT scan showed a soft tissue mass involving the wall of sigmoid colon. Colectomy was performed and serial sectioning revealed a white, fibrous lesion located in the middle of the color; not involving the mucosa.

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Case - 2

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

Clinical History: A 75 year old man underwent total thyroidectomy for a tumor in the right lobe. Previous FNA showed sheets of atypical cells with finely granular cytoplasm.

Pathological Findings: The right lobe contained a well-circumscribed mass homogeneously pale tan in color measuring about 2.2 cm. Histology shows neoplastic follicles lined by cuboidal or columnar cells with clear or pale cytoplasm and containing some dense colloid in the lumens. The nuclei are for the most part round, vesicular, with small nucleoli. At one side there is a focus consisting of more rounded eosinophilic cells forming nests rather than follicles. In this area some of the cells contain vacuoles reminiscent of signet ring cells. There is invasion into the capsule and into multiple capsular veins. TTF-1 and Pax-8 showed positive nuclear staining.

Diagnosis: I called this encapsulated Hurthle cell carcinoma with extensive cytoplasmic clear cell changes.

Discussion: Dr Rosai's thyroid tumor fascicle from the third AFIP series, the most recent one available as far as I know (maybe another is in the works at this moment?), dedicates a full chapter to thyroid tumors with clear cytoplasmic changes. It states that clear cell tumors should not be considered as a separate entity, but rather as the result of changes which can develop in any other tumor type, and also in non-neoplastic conditions such as Hashimoto disease, dyshormonogenetic goiters, and nodular hyperplasia. This change can result from accumulation of glycogen, lipid, thyroglobulin, mucin, and cytoplasmic vesicles, these latter representing massively dilated mitochondria, secretory vesicles, endoplasmic reticulum, or Golgi apparatus. Dr Rosai points out that in the latter circumstance (clearing resulting from vesicles) the cytoplasm is not perfectly clear but in reality shows a fine granularity when examined closely, which I think is the situation here. He calls these "washed out oncocytes".

The most likely cell type to undergo this change is the oncocyte, whether neoplastic or non-neoplastic. The clear cell change can be seen to a greater or lesser extent, and the oncocytes and clear cells can be segregated or mixed. Dr Rosai also describes transitional forms which he qualifies as "spectacular", in which only part of the cytoplasm is clear. In this particular case, on low power the clear cell aspect stands out, but the follicles seem to have a thick eosinophilic rim. On high power examination it becomes evident that this impression is a result of the tumor cells (at least in part) which are columnar or tall cuboidal in shape showing clearing of the apical portion, and eosinophilia of the basal portion, with the nuclei in the center (this is illustrated in figure 173 on page 185 of the fascicle).

Cytoplasmic clearing can also be seen in non- oncocytic follicular tumors though if the clearing is extensive enough evidence of previous oncocytosis may not be appreciated. In many of these cases in fact ultrastructural examination shows cytoplasmic vesicles but in others the clearing may result from glycogen accumulation. Though clear cell tumors can be benign widespread clear cell change in thyroid tumors should raise the suspicion for malignancy which is determined on the basis of the accepted criteria for determining malignancy in follicular thyroid tumors.

Accumulation of those cytoplasmic substances which can give rise to clear cell change can also produce signet ring cell change. This is often the result of thyroglobulin accumulation.

Though cytoplasmic clearing can be seen in papillary carcinomas I didn't consider the nuclei of this tumor to be typical for that type. Interestingly the columnar cell carcinoma considered at least by some as a variant of papillary carcinoma is described as showing cytoplasmic clearing but this is often subnuclear (mimicking secretory

endometrium) unlike in the case I am demonstrating where in those cells where the clearing only involves part of the cytoplasm it is in the apical portion. In these tumors while the nuclei are not typical for papillary carcinoma, typically there is nuclear hyperchromasia, elongation, and stratification which are not seen in this case.

Of course, the finding of a clear cell carcinoma in the thyroid begs the question of a metastasis from a renal tumor. An authoritative fairly recent series of 36 cases of renal clear cell carcinomas metastatic to the thyroid was published by Bruce Wenig and collaborators. These cases can be deceptive in that the metastasis can sometimes follow by decades or else precede recognition of a tumor in the kidney. They can form solitary nodules even involving an adenomatous tumor of the thyroid itself and can show capsular and vascular invasion. All the primary renal tumors were classical clear cell carcinomas in that they either didn't form follicles or else formed "pseudofollicles" containing red blood cells in the centers (not seen in this case), and the cytoplasm showed absolute "water-clearing" without the pale subtle granularity of the clear cell tumors arising in the thyroid (as I believe is demonstrated in my case). In any case the tumors reported in this series didn't show follicles producing colloid. Along with these histological differences the differential diagnosis can be confirmed using immunohistochemistry for thyroglobulin or TTF-1, with the caveats expressed by Dr Rosai that while staining for the former can be weak in clear cell tumors of the thyroid, it can be spuriously present in metastatic renal cell carcinomas due to adsorption from surrounding parenchyma.

A different can of worms is opened by the rare recently described entity of thyroid like follicular carcinomas of the kidney (Amin et al). For the most part these tumors are colloid producing but are not composed of clear cells (with the exception of the one case reported by Jung et al, and one other rather unique one by Fadare et al, which showed papillae lined by clear cells and also macrofollicles containing colloid). While as far as I could discover no such cases of this entity metastatic to the thyroid have yet been reported, in the event of such an occurrence the differential diagnosis would not be with the type of tumor I am presenting.

I'll admit that I didn't think of the correct diagnosis on FNA. I also didn't appreciate the follicular nature of the tumor. In her text Kini mentions that the cytology of clear cell thyroid tumors is reported infrequently. The cytoplasm of the tumor cells in cytological preparations does not show the clearing seen in histology but can be very pale to granular. The cell borders are often indistinct and when not intact the naked nuclei can appear as lymphocytes. On second look at the smears in places the cytoplasmic granularity seems relatively sparse (I'm including two photos from the smears stained with H and E- I'm not sure to what extent the photos do justice to them).

References:

AFIP Atlas of Tumor Pathology, Tumors of the Thyroid, Third Series Fascicle 5 (Washington D.C. 1992), ed. Juan Rosai et al, "Tumors with Clear Cell Features" pgs 183-193 ; also "Secondary Tumors" pp 291-293.

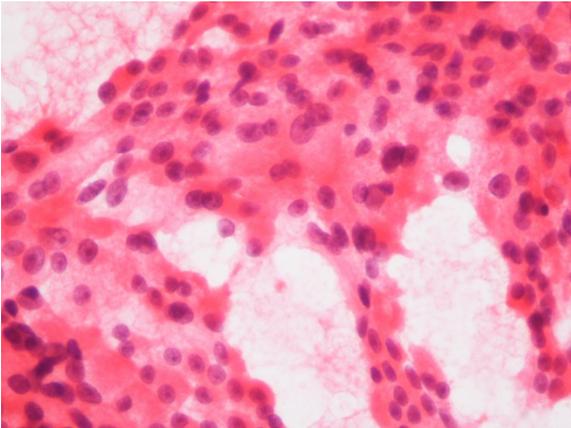
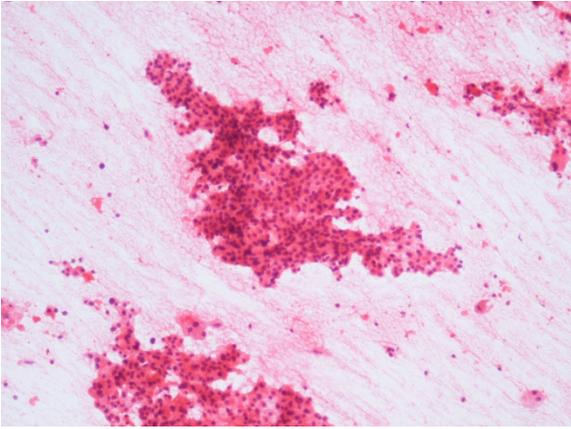
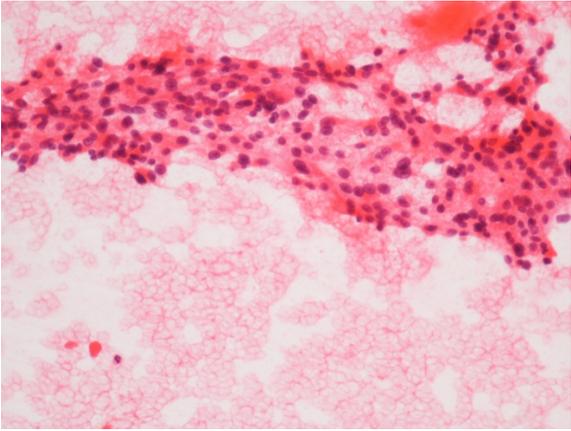
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Jung S.J. et al, Thyroid follicular carcinoma like tumor of kidney, *Am J Surg Pathol* 30: 411-451, 2006

Fadare et al, Papillary renal cell carcinoma with diffuse clear cells and thyroid like macrofollicular areas, *Ann. Diag. Pathol* 14: 284-291, 2010

Thyroid Cytopathology: an atlas and text, by S. R. Kini, Wolters- Kluwers Lippincott: Philadelphia 2008, pp 429-431



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Case - 3

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

Clinical History: A 68 y.o. woman had renal transplant 5 years ago and since then she is treated with tacrolimus and mycophenolate-mofetil. Colonoscopy was performed due to diarrhea and revealed two rectal polyps (1.2 cm and 0.7 cm) which appear in the slide. The larger polyp shows tubular adenoma with focal high-grade dysplasia and underlying aggregates of large macrophages with granular-eosinophilic cytoplasm associated with neutrophils, few plasma cells and small lymphoid follicle. The smaller polyp is a non-neoplastic polyp with the some macrophages. PAS and von-Kossa stains highlight the concentric, sometimes "target-like" inclusions in the macrophages. Repeat colonoscopy 6 months later (this month), revealed only a small tubular adenoma.

Diagnosis: Malakoplakia.

Discussion:

1. Malakoplakia: Malakoplakia (a combination of "malakos" = soft and "plax" = plaque, both in Greek), is a rare inflammatory reaction/disease characterized by aggregates of large granular eosinophilic histiocytes (von Hansemann cells) which contain the typical Michaelis-Gutmann (MG) laminated calcific spherules. The latter are highlighted by PAS, calcium and iron stains. It is associated with Gram-negative bacterial infections, particularly Escherichia Coli. Its typical histology is probably related to defective lysosomal processing of microorganisms by macrophages and accumulation of debris in lysosomes with subsequent mineralization. It's most common location is in the genitourinary tract, followed by the gastrointestinal tract (GIT), and has been reported also in the respiratory tract, skin, soft tissue and in other organs and tissues.

2. Malakoplakia of the GIT and association with colorectal tumors: Colorectal involvement by malakoplakia (MAP), the most common location of GIT MAP, can be either segmental or diffuse. It appears as soft, flat lesions in early stages, which progress to raised, tan-gray and yellowish lesions. A literature review in 1995^{1,2} reported 95 cases of colonic MAP, 24 of which had a coexistent colonic adenocarcinoma. All of these 24 cases were detected in surgical specimens, and half of them occurred as a pericolic mass. Thus, the association of MAP with colonic adenocarcinoma maybe an incidental finding in many of these cases. MAP associated with colonic adenomas is very rare, and I found only 4 previously reported cases.³

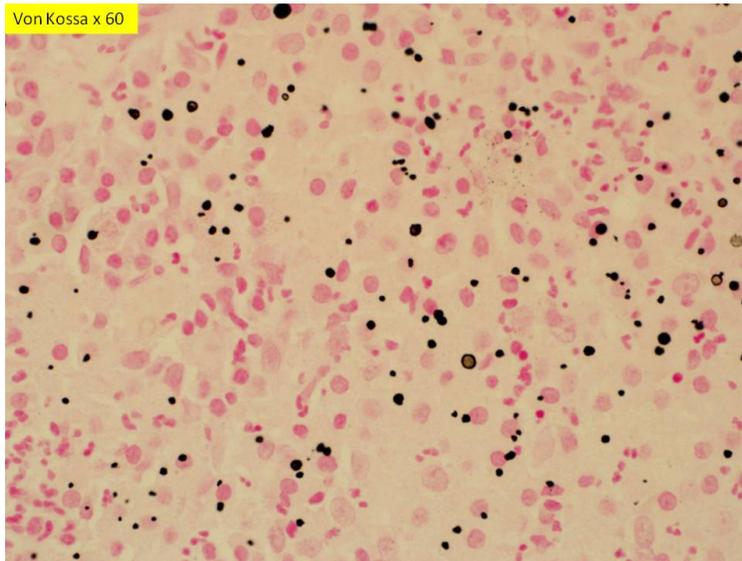
3. Malakoplakia in Renal Transplant recipients: Immunosuppression is a predisposition to development of MAP and was reported in up to 40% of the cases.⁴ Although MAP in renal transplant recipients involves most frequently the genitourinary tract, including the transplanted kidney⁵, MAP of GIT was also reported in patients with renal transplant^{6,7} and liver transplant.⁸ In renal transplant recipients, MAP may be one of the causes for diarrhea, in addition to the mycophenolate-mofetyl induced diarrhea and to opportunistic infections including CMV and stryngyloides. Rarely, MAP may pursue an aggressive course and fatal outcome in transplanted patients.⁷

4. Therapy of malakoplakia: The medical treatment of MAP is based on both bacterial eradication and augmentation of macrophage function. Bacterial eradication is mediated by prolonged therapy with antibiotics having efficient intracellular penetration. Augmentation of macrophage function is mediated by reducing immune-suppression⁹ and maybe by cholinergic agonists which raise macrophage intracellular cyclic GMP.⁶ The latter mode is controversial.

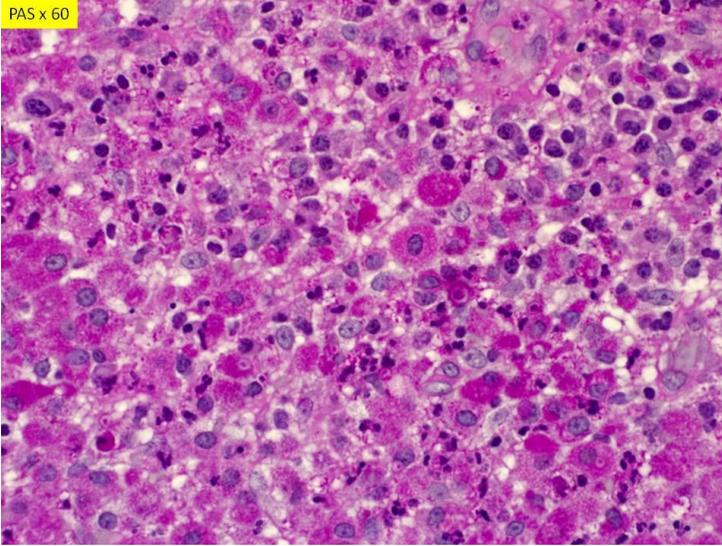
Conclusion: Malakoplakia in colorectal adenomas of a patient with renal transplant who presented with diarrhea is a rare combination which highlights the clinical aspects of malakoplakia.

References:

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- ² Karasavvidov F et al: Malakoplakia of the colon associated with colonic adenocarcinoma diagnosed in colonic biopsies. *World J Gastroenterol* 13:6109-11, 2007.
- ³ Rizzo E et al: Malakoplakia and colonic adenoma: A rare association. *Ann Diagn Pathol* 8:364-6, 2004.
- ⁴ Long JP, Althausen AF: Malacoplakia: A 25 year experience with review of the literature. *J Urol* 141:1328-31, 1989.
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- ⁶ Shah MB et al: Malakoplakia induced diarrhea in a kidney transplant recipient. *Transplantation* 90:461-2, 2010.
- ⁷ Berney T et al: Malakoplakia of the cecum in a kidney transplant recipient: presentation as acute tumoral perforation and fatal outcome. *Transplant Int* 12:293-6, 1999.
- ⁸ Kim PTW et al: Colonic malakoplakia in a liver transplant recipient. *Can J Gastroenterol* 21:753-5, 2007.
- ⁹ Biggar et al: Malakoplakia and immunosuppressive therapy. Reversal of clinical and leukocyte abnormalities after withdrawal of prednisone and azathioprine. *Am J Pathol* 119:5-11, 1985.



PAS x 60



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Case - 4

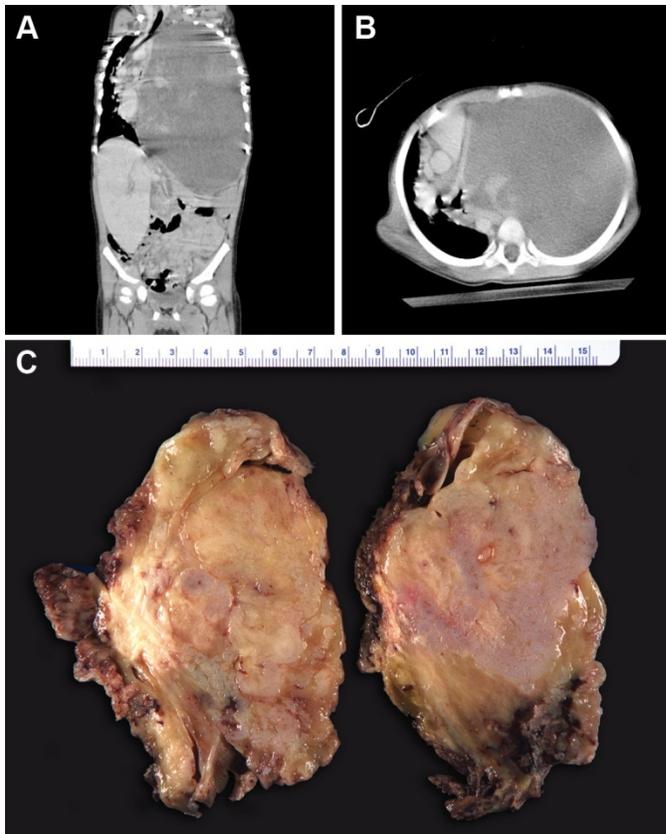
Contributed by: Gerald Berry, M.D.

History: This 2-year old previously healthy male child presented with a 1-week history of progressive respiratory distress, fever and lethargy. He was seen by his primary care physician and a diagnosis of viral URI was made. With progressive symptoms he was brought to the ER. CT imaging of the thorax showed complete opacification of the left hemithorax and displacement of the heart and mediastinal structures into the right chest. (See images) There was tracheal deviation and inferior displacement of the spleen and liver. Following a small incisional biopsy tumor debulking including a left pneumonectomy was performed.

Pathological Findings: The pneumonectomy specimen reveal a 24 x 20 x 7 cm mass weighing 1400gm that involved the lower lobe. The cut surface exhibited a solid tan-yellow mass admixed with foci of cartilaginous appearing tissue and foci of hemorrhage and necrosis. (See images) Sections displayed a biphasic malignant neoplasm composed of undifferentiated and fibrosarcomatous blastema and trabeculated islands of neoplastic cartilage. Microscopic zones of anaplasia were present but were a minor finding. In the monomorphic-spindled areas the mitotic count was 7/10 hpf while in the anaplastic areas up to 22/hpf were found.

Diagnosis: Pleuropulmonary Blastoma, Type III.

Follow-Up: Following staging procedures (Bone marrow and brain MRI were negative) the patient was placed on IPPBT Type III Study and is receiving chemotherapy consisting of vincristine, ifosamide, dactinomycin, doxorubicin.



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Case - 5

Contributed by: Gerald Berry, M.D.

Clinical History: This 4-year old male toddler with a history of asthma and recurrent respiratory infections underwent CT imaging of the chest in Sept 2011. Multilocated cysts were seen in the both lungs with a predominant cyst in the left lower lobe measuring 5.7 x 4.8 x 6.5 cm (see images). Additional cysts in the left upper lobe measured up to 2.3 x 1.8 x 1.8 cm and in the right upper lobe up to 2.3 x 1.8 x 1.8 cm. In light of the large dominant LUL cyst concern was raised for pleuropulmonary blastoma. Left lower lobectomy was performed.

Pathological Findings: The lobectomy specimen revealed a subpleural smooth walled cyst containing serous fluid (see image). It was extensively sampled. The lesion was lined by flattened or cuboidal epithelium (not seen in all slides). The wall was fibrotic with focal regions arranged as fibrous nodules. No cambium layer of primitive mesenchymal or cartilaginous elements were found in the lesion (entirely submitted in 22 sections). The differential diagnosis included Type 4 congenital pulmonary airway malformation (CPAM) and involuted/regressed Pleuropulmonary blastoma, Type I. The case was seen by both Ashley Hill and Louis Dehner who thought that the radiological findings together with the histological findings (even in absence of immature mesenchyme) supported the diagnosis of involuted/regressed Type I PPB.

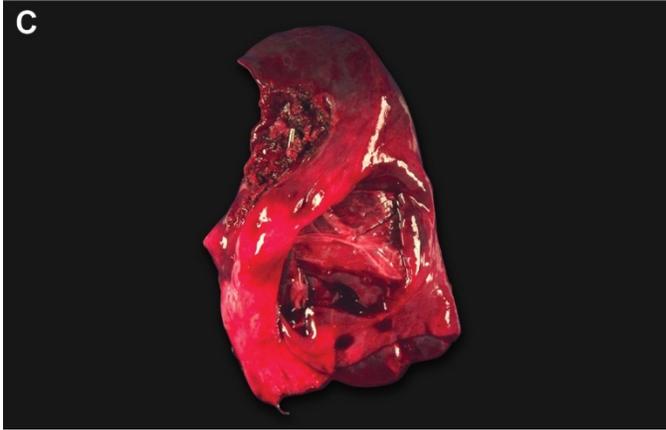
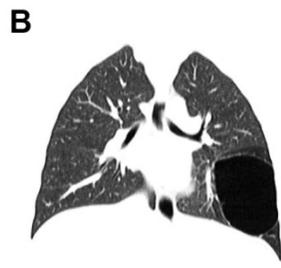
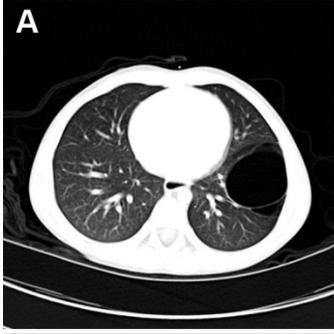
Diagnosis: Pleuropulmonary Blastoma, Type I, Regressed

Follow-Up: After discussion with the pediatric oncologists it was decided that adjuvant chemotherapy was warranted on account of the other cystic lesions.

Comment: I thought that the group would be interested in the spectrum of changes in PPB. Both cases came to us within a couple of months of each other. PPB is rare with equal gender distribution and the majority of cases presenting before age 7. It is thought to be part of the hereditary predisposition syndrome and additional associations include familial cystic nephroma, medulloblastoma, germ cell neoplasms, Hodgkin lymphoma, leukemia thyroid neoplasms and GI polyps. The lesions are classified as: Type I (cystic; 14%), Type II (cystic and solid; 48%) & Type III (solid; 38%). Type I PPB (see John Chan's case in AMR Seminar 31) typically presents as a multiloculated cyst with a cambium layer containing primitive mesenchymal elements along with rhabdomyoblasts (49%), and/or cartilaginous nodules (40%). Regression is thought to be a common occurrence and may explain, in part, the better outcome (5-year survival of 83% for Type I and 42% for Types II & III). Local recurrence occurs in 10-15% of Type I PPB but in 50% of Type II and III. Metastases develop in 25% of Type II & III cases with brain, spinal cord and bone comprising the common sites.

References:

1. Stocker JT. Cystic lung disease in infants and children. *Fetal Pediatr Pathol*. 2009;28(4):155-84.
2. Dishop MK, Kuruvilla S. [Primary and metastatic lung tumors in the pediatric population: a review and 25-year experience at a large children's hospital.](#) *Arch Pathol Lab Med*. 2008 Jul;132(7):1079-103.
3. Hill DA, Jarzembowski JA, Priest JR et al. Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the International Pleuropulmonary Blastoma Registry. *Am J Surg Pathol* 2008; 32:282-295.
4. Indolfi P, Bisogno G, Casale F, Cecchetto G, De Salvo G, Ferrari A, Donfrancesco A, Donofrio V, Martone A, Di Martino M, Di Tullio MT. [Prognostic factors in pleuro-pulmonary blastoma.](#) *Pediatr Blood Cancer*. 2007 Mar;48(3):318-23.
5. Priest JR, Magnuson J, Williams GM, et al. Cerebral metastasis and other central nervous system complications from pleuropulmonary blastoma. *Pediatr Blood Cancer* 2007; 49:266-273.



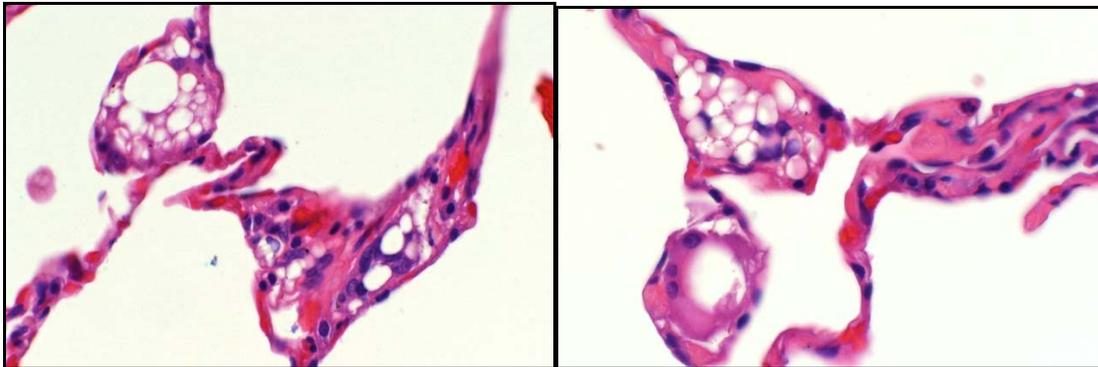
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Case - 6

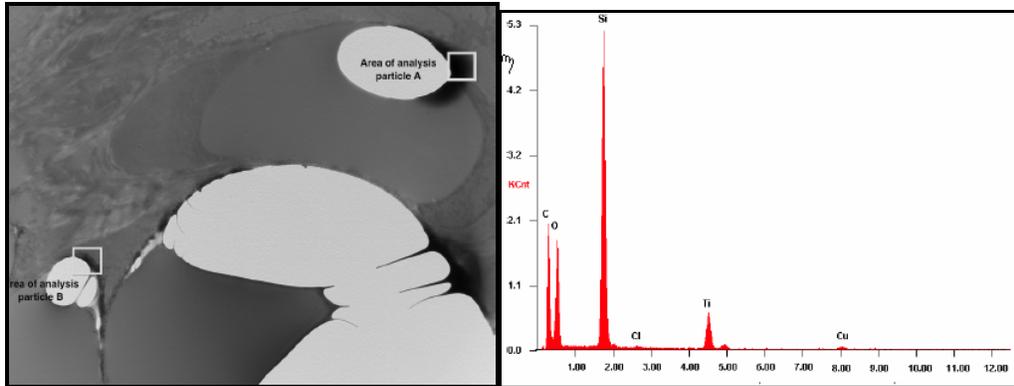
Contributed by: Thomas Colby, M.D.

Clinical History: A 54-year-old woman with a history of silicone breast implants noted a change in the configuration of one of the implants and a subsequent evaluation revealed that the implant had ruptured. She then noted axillary lymphadenopathy and pulmonary infiltrates were noted on radiologic studies. When questioned, she admitted to having some dyspnea. The implants were removed and an axillary lymph node was biopsied. Implant rupture was confirmed by the surgeon and the pathologist and evaluation of the lymph node showed typical features of silicone lymphadenopathy. The patient's pulmonary infiltrates and dyspnea persisted and she came to surgical lung biopsy.

Pathologic Findings: The lung biopsy (below) shows very subtle changes with overall preservation of lung architecture and occasional alveolar capillaries containing vacuolated histiocytes identical to those seen in the lymph node. These involve sufficient numbers of pulmonary capillaries to compromise lung function and cause dyspnea. The findings are distinctive and allow the pathologist to make a definitive diagnosis of an embolic process that allows explanation of this patient's dyspnea and pulmonary infiltrates.



In this case, energy dispersive analysis was performed (SEE BELOW) of the material associated with the vacuoles and there was a high peak for silicon as one would expect with silicone in the lung.



Epon-embedded plastic section of lung tissue (left) taken from the paraffin block shows regions of vacuolization and dark material surrounded by a square box (upper). The boxed area represents the region/material analyzed by energy dispersive electron microscopy, the graph of which is shown at right. There large peak is for silicon, one of the major components of silicone. The energy dispersive analysis and appearance on Epon-embedded sectioning is typical of silicone.

Comments: In a world where individuals want to enhance themselves in many ways, silicone has been widely used, both in sanctioned medical procedures such as breast implants, as well as in illicit situations where non-medical practitioners perform silicone injections.

Silicone is among many things that may embolize to the lung and many of them may be specifically identified on the basis of the pathologic findings in biopsies. Some of these include bone marrow emboli, other forms of fat emboli, tumor emboli, foreign body emboli (such as material from intravenous drug injections), amniotic fluid, parasites and a number of other materials.

Silicone has been considered a relatively inert compound. It is relatively water repellent, heat resistant and very resistant to chemical attack; hence, its appeal as a relatively inert substance to use in implants and for other cosmetic procedures. Silicone is best known for its use in breast implants. Liquid silicone is also injected by non-medical practitioners at a variety of sites for various forms of "enhancement."

There have been many reports of lung disease related to embolic silicone from illicit injection at a variety of sites: primarily subcutaneous (eg. buttocks) or submucosal (eg. vagina). A radiologic example is shown below; this was the CT appearance 1 week after subcutaneous injections of silicone..Lung disease related to silicone emboli from ruptured breast implants has been only rarely reported.

In most cases of silicone-induced embolic lung disease, the symptoms are acute and temporally related to the injections; they gradually subside with supportive care with or without steroid therapy. In the patient presented symptoms were persistent and became chronic despite removal of the implants and the relationship between symptomatology and implant rupture was less clearcut. The possibility that this patient may have had an occult source of silicone left behind was being considered clinically, but the presence of silicone in the lung needed to be confirmed pathologically. A definitive diagnosis was made on the basis of the lung biopsy. In the case presented, the additional benefit of energy dispersive analysis to confirm the morphologic findings was also demonstrated.

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AMR Seminar #62

Case – 7

Quiz Case

Contributed by: Thomas Colby, M.D.

Case History: A 61-year-old man had dyspnea, diffuse pulmonary infiltrates and a history of deep vein thrombosis. Lung biopsy was performed for diagnosis. When the Comments go around I will share the answer and some pertinent immunostains that will amaze a lot of people.

AMR Seminar #62

Case - 8

Contributed by: Jonathan Epstein, M.D.

Clinical History: A 74 year old man was found to have an incidentally detected 3.5 cm renal mass.

Pathologic Description: On sectioning the mass, it was tan-brown with hemorrhage and focal cystic areas. Histologically, the tumor is characterized by cells with densely eosinophilic cytoplasm. A minor component of the lesion consists of small nests of cells in a fibromyxoid background, where the nests have uniform bland cytology. The majority of the cells have significant nuclear pleomorphism, yet of a degenerative nature, also in many areas within a fibromyxoid matrix. The lesion lacks necrosis or mitotic figures. Immunohistochemistry performed at the outside institution was positive for ck7 with scattered positive cells, CD117, AMACR, and negative for RCC. Ki67 showed less than 1% positive cells.

Diagnosis: Oncocytoma with marked diffuse degenerative atypia.

Discussion: It is not uncommon for a classic oncocytoma to have focal collections of cells with pleomorphic nuclei, often clustered but occasionally scattered more diffusely. The atypia is degenerative in nature with smudged chromatin, pseudonuclear inclusions, and lack of other findings (mitotic figures, necrosis) that would be seen with a high grade malignancy. This case is unusual for the extensive and diffuse nature of the degenerative atypia with only small islands of more classic oncocytoma. In other slides there was more of the classic oncocytoma, although still admixed with a lot of the atypical cells. Other "atypical" findings that can be seen with oncocytoma is involvement of perirenal adipose tissue and vascular (including large vessel) invasion. Findings that rule out oncocytoma are necrosis, papillary formation (other than pseudopapillary tufting in cystically dilated glands as seen in hyperplastic thyroid nodules), and cells with clear cytoplasm (other than seen in the central scar with shrunken cells). In general, I find most immunohistochemical stains to be worthless in the assessment of oncocytoma. The typical differential diagnosis is between oncocytoma and chromophobe renal cell carcinoma. Hales colloidal iron is variably useful but not sufficiently reliable to routinely use. The only stain I will sometimes use is CK7 which tends to be more diffuse in chromophobe RCC and only patchy in oncocytoma. IN this case the low Ki67 supported the H&E impression that the atypia was degenerative in nature. In signing out oncocytoma, I only give the size (even though it is of no prognostic significance) and the margins. I do not comment if oncocytoma is confined to the kidney as in cases where it involves the perirenal adipose tissue, the lesion is still 100% benign.

AMR Seminar #62

Case - 9

Contributed by: Giovanni Falconieri, M.D.

History: A 52 year old woman is evaluated for a diffuse opacity of the left lung. A few years previously, she had been treated with mastectomy for malignant phyllodes tumor of breast at another medical center (slides not available for review). CT scans revealed multiple, confluent nodular masses virtually replacing the entire left lung. A percutaneous needle biopsy was non-diagnostic. Pneumonectomy was carried out. No other lesions were recognized after extensive medical work up.

The specimen showed massive replacement of lung by rubbery, grey-yellow glistening masses surrounded by scant remnants of pulmonary tissue. Some gross pictures are submitted.

Diagnosis: Pleomorphic sarcoma, NOS

Comment: Tumor cells were negative for all markers (keratins, desmin, actins, S100, H-caldesmon, bcl1, CD10, CD99, EMA, ER, PR, c-kit). No areas of gland differentiation could be recognized.

I am not totally sure about the nature of this tumor. Although the lung is one of the most common sites of metastases from malignant Phyllodes tumor and isolated, large metastases have been described, near-total pulmonary neoplastic replacement sounds bizarre. In addition, tumor cells were negative for all markers, including CD10 which is often expressed by borderline and malignant Phyllodes tumor.

I would still go for metastatic Phyllodes tumor; however, do the club members have any additional ideas or suggestions?

References:

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AMR SEMINAR #62

Case - 10

Contributed by: Franco Fedeli, M.D.

Clinical History: A 57 year old male presented with a nodular mass in his right testis. Abdominal computed tomography (CT) showed an unremarkable pancreas.

Macroscopic Findings: In the right testis was found a well-circumscribed nodular mass, 3.2 cm in diameter, lies beneath the tunica albuginea surrounded by testicular tubules and rete testis, with a homogeneous gray-brownish cut surface, hard in consistency. No follow-up is available.

Microscopic Findings: The tumor was composed of epithelioid round cells arranged in single cells, cords, and nests separated by collagen bundles, with round-to-oval nuclei with distinct nucleoli and evenly dispersed chromatin. In some areas, the tumor showed a diffuse growth pattern interspersed with dehiscent areas, delicate pseudopapillae and hemorrhagic foci. The cytoplasm was pale and granular with variable-sized vacuoles. Many cells had single large cytoplasmic vacuoles that pushed the nuclei to the periphery and showed a signet-ring feature. Scattered eosinophilic hyaline globules could be seen in the cytoplasm. No tumor necrosis, nuclear atypia or mitotic figures was found.

Immunohistochemical Findings: The tumor cells were positive for Vimentin, CD10, β -Catenin, Synaptophysin, NSE, focally positive for Calretinin and negative for E-cadherin, Melan-A, CD30, CK AE1-AE3, EMA, Ck7, Ck20, Cam5.2, β -Inhibin, PSA, S-100 protein, CD31, CD34, CD99, HMB45, CDX-2, CD117, Chromogranin, Cd56 and Progesterone β -HCG, PLAP. MIB1 rate was very low.

Diagnosis: We could not render a definite diagnosis. The closest diagnosis we could reach is Signet-ring stromal tumor of the testis Vs Pancreatic Type solid/papillary tumor of testis.

Comments: Signet-ring stromal tumor (SRST) is a rare type of ovarian tumor belongs to the category of the fibroma/thecoma group of the sex cord stromal tumor by WHO.

Only two cases have been described in the literature in the testis (1 – 2). Most of the cytoplasm of the tumor cells was seen to be replaced by an empty clear vacuoles which pushed the nuclei to the periphery of the cells. Sharp circumscription, mild cellular pleomorphism and low mitotic rate all indicate the benign nature of SRSTs.

The occurrence of pseudo-papillae, the finding of eosinophilic hyaline globules in the cytoplasm of some cells, the lack of immunoreactivity for β -Inhibin, the presence of nuclear-cytoplasmic β -Catenin and the positivity for Synaptophysin and NSE in conjunction with loss of E-cadherin may also be supportive to consider a pancreatic type solid/pseudopapillary tumor, recently described in the ovary (3) but never described in the testis.

There are very few lesions from which signet-ring stromal tumor of the testis should be differentiated.

Metastasis of gastric adenocarcinoma with signet ring cell morphology is an extremely rare event in the testis; the immunoreaction to vimentin rather than EMA and cytokeratins distinguish the visceral metastases from the primary signet-ring stromal tumor of the testis.

Adenomatoid tumors may consist of well-defined fibrous nodules with epithelioid tumor cells arranged in single cells, cords, and nests separated by collagen bundles; tumor cells of adenomatoid tumors have glandular or tubular structure and react to cytokeratins and mesothelial cells markers.

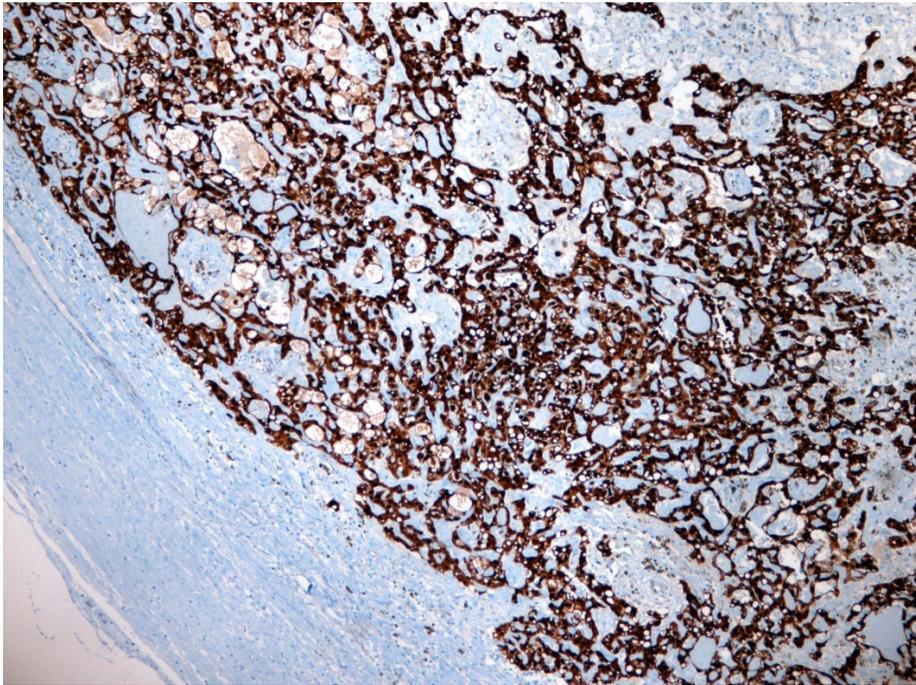
Although very rare, epithelioid hemangioendotheliomas of the testis have been reported; histologically it shows solid nests and short cords of rounded or slightly spindle endothelial cells with intracytoplasmic lumens or vacuoles.

Intracytoplasmic lumens of epithelial hemangioendotheliomas contain erythrocytes, and these cells express endothelial markers such as CD31 and CD34.

In the testis, although the distinction of Leydig cell tumors and SRSts is not critical because both tumors lack malignant features, Leydig cell tumors with lipomatous changes should be included in the differential diagnosis; intense immunoreactivity for inhibin of Leydig cell tumors are different from SRSts.

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Beta-catenin

AMR SEMINAR #62

Case - 11

Contributed by: Masaharu Fukunaga, M.D.

Clinical History: A 68-year-old male presented with discomfort of the oral cavity. A hard mass was found in the left hard palate and gingiva. CT and MRI revealed a 2cm solid tumor with infiltrative growth and bone destruction in the left maxilla. Under a clinical diagnosis of malignant tumor. Excision was performed. The patient is well with no evidence of disease at seven months after surgery.

Macroscopic Features: A submucosal, white, solid mass measuring 20x16mm without a capsule. No hemorrhage or necrosis was seen.

Immunohistochemical Studies: CAM5.2 (++). S100 protein focally (+).
vimentin, alpha-smooth muscle actin, EMA: (-).

Diagnosis: Canalicular adenoma

Comments: Canalicular adenoma is one of monomorphic adenoma and is considered a benign minor salivary gland tumor with luminal cell differentiation. Canalicular adenoma occurs most commonly in the older patients (mean age of 65yrs) and it is primary an oral lesion (the upper lip (74%), buccal mucosa, palate, major salivary glands). Bone destruction may be seen. Recurrence does not occur after complete excision (1-3). Cases with distant metastasis have not been reported. Histologically, canalicular adenoma is characterized by interconnecting strands of cuboidal to columnar epithelium forming canalicular, pseudopapillae and tubules with collagenous stroma. Bone destruction is seen the slide. Immunohistochemically this type of tumor is positive for CAM5.2, S-100 protein, and infrequently EMA. Myoepithelial or basal cell participation is not observed.

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AMR Seminar #62

Case - 12

Contributed by: Thomas Krausz, M.D.

History: 6 week old male, who was originally admitted through the emergency room at age 3 weeks for tachypnea, fussiness, decreased appetite, runny nose and cough. He was born after a full term pregnancy via uncomplicated vaginal delivery and was immunized for HepB in hospital after birth. He was treated with clindamycin and azithromycin for what was thought to be a chlamydia infection and discharged after 7 days. He continued to have persistent cough and recurrent tachypnea with bilateral airspace opacities for which a lung biopsy was performed. A representative section (from one of two blocks with similar histology) is submitted for your review.

Histology: There is extensive multifocal pneumonitis with interstitial and intraalveolar infiltrates composed of a mixture of inflammatory cells predominantly neutrophils, eosinophils and histiocytes with focal intraalveolar fibrinous exudate. There are foci of microabscesses and distinct granulomas. The histologic differential diagnosis is rather broad in a 6 week old and includes Langerhans cell histiocytosis, eosinophilic pneumonia, drug reaction and infection. Some of the granulomas contain sparse fungal organisms highlighted by GMS and PAS stains (*Aspergillus fumigatus* on culture). Histiocytes are positive for CD68 and negative for S100 and CD1a. He also developed a hyperpigmented papular rash on his head and neck which was biopsied and showed pustular and perivascular dermatitis with eosinophils (no organisms).

Initial Diagnosis: Suppurative/eosinophilic granulomatous pneumonitis due to fungal infection. Consider chronic granulomatous disease (CGD) of childhood (proven by subsequent test, see discussion).

The key question is why should a full-term baby develop a fungal pneumonia? I am submitting this case because it highlights the role of pathologists in suggesting further laboratory tests to reveal the etiology and pathogenesis of this rare condition without which appropriate curative treatment of the disease rather than just the fungal infection would not be possible.

Additional Tests: Dihydrorhodamine (DHR) assay (for neutrophil oxidative burst): Abnormal. 92% of neutrophils found to exhibit no oxidative burst activity. Remaining 8% of neutrophils have minimal activity. Negative tests: HIV, CMV, bone marrow aspirate and biopsy, T and B cell immune deficiencies.

Final Diagnosis: Chronic granulomatous disease presenting as fungal pneumonia

Discussion: CGD is an inherited disorder which comprises five genetic defects, each impairing one of five essential subunits of the phagocyte (neutrophil, monocyte, macrophage and eosinophil) NADPH oxidase generating reactive oxygen species. Adult-onset CGD is increasingly observed, even in the elderly. The overall prevalence of the disease is reported from 1:250,000 to 1:120,000. X-linked defects in NOX2 account for about 70% of the cases, autosomal-recessive defects in p47 for about 20% and the remainder for the very rare p22 and p67 defects with only one p40phox deficient CGD patient reported so far. Clinically, the NOX2 deficient form of CGD runs a more severe course than the p47 deficient form, with earlier presentation and earlier death.¹

Loss-of-function mutations abrogate oxidase activity and compromise host immunity against certain bacteria and fungi. However, there is now increasing evidence for excessive inflammation with elevated IL-1 release from

monocytes in CGD even in the absence of infectious agents with increased frequency and severity of granulomatous inflammatory reactions, notably colitis.²

CGD may present to histopathologists in a wide range of tissue specimens (including upper and lower GI tract, liver, bladder, bone, lung, skin, soft tissue, bone marrow and lymph node) most often demonstrating features of active chronic inflammation with or without granuloma formation. In some cases, the presence of numerous pigmented macrophages in association with such inflammation should raise the suspicion of the diagnosis. In addition, diffuse granulomatous inflammation of the lung and hepatic abscess formation should be regarded as suggestive of the diagnosis.³

Antifungal and antibiotic therapies (combined with steroids and other anti-inflammatory agents) have increased survival to a median of 35 years. Hematopoietic stem cell transplantation is a potential cure for CGD and has shown impressive results in early childhood using matched, unrelated or cord blood donors. Gene therapy, however, still has major limitations, remaining experimental.⁴

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AMR SEMINAR #62

Case – 13

Quiz Case

Contributed by: Alberto Marchevsky, M.D.

Clinical History: The patient is a 47 year old man with a history of smoking up to 5 packs of cigarettes a day, for a total smoking history of 70 pack year. His previous medical history included panhypopituitarism secondary to pituitary tumor, COPD, asthma, hypertension, cardiomegaly and blindness in one eye. He presented with increasing shortness of breath over several years. Chest computerized scans showed multiple, bilateral cystic spaces throughout both lobes, more prominent in the upper lung zones, and associated with some nodularity in the upper lung zones. There was no evidence for hilar or mediastinal lymphadenopathy. He was diagnosed at another hospital with Langerhans histiocytosis. We have no records of how this diagnosis was rendered and whether the patient had previous lung biopsy. Our radiologist also favored the diagnosis of Langerhans histiocytosis. The patient underwent bilateral lung transplant.

AMR SEMINAR #62

Case - 14

Contributed by: Thomas Mentzel, M.D.

Clinical History: A 76-year-old male patient developed an indurated, and plaque-like lesion on his left upper arm. Clinically, multiple slowly enlarging skin lesions have been reported.

Pathological Findings: Histologically, a skin biopsy with dermal fibrosis and a cellular granulomatous infiltrate composed of lymphocytes, enlarged lymphoid cells and numerous histiocytes including multinucleated giant cells is seen. Numerous CD30 positive, activated and enlarged lymphoid cells and neutrophils are noted in the dermal infiltrate. In addition, a striking epidermotropism is present and enlarged lymphocytes with enlarged and hyperchromatic nuclei are detected in the epidermis. The majority of atypical lymphoid cells including the intraepithelial lymphocytes stain positively for CD4 whereas only few CD8 positive cells are present.

Diagnosis: Granulomatous mycosis fungoides.

Comments: Primary cutaneous lymphomas of B- or T-cell differentiation may show a prominent granulomatous reaction, which represents a potential diagnostic pitfall. Granulomatous mycosis fungoides is the most common form of granulomatous cutaneous T-cell lymphoma and occurs predominantly in patients in their fifth decade of life with a male predominance. Clinically, erythematous patches and plaques are noted and the clinical features are not suggestive for granulomatous histological findings. Histologically, a diffuse infiltration of the dermis (and the subcutis) by atypical lymphocytes with epidermotropism is seen. The associated granulomas usually show a sarcoid-like pattern, however, also granuloma annulare-like, palisaded or necrobiotic granulomas can be seen more rarely. In addition to radiotherapy psoralen-UV-A and interferon alfa are most commonly used therapeutic approaches in granulomatous mycosis fungoides. Prognostically, complete tumour regression is seen in the minority of patients only, whereas half of patients show a slowly progressive clinical course. Extracutaneous spread is seen in about a third of patients and is associated with transformation into CD30 positive anaplastic large T-cell lymphoma in a significant number of patients. It can be argued that the presence of clusters of enlarged and atypical CD30 positive lymphoid cells in the discussed case represents an early sign of transformation.

In contrast granulomatous slack skin is a very rare form of granulomatous cutaneous T-cell lymphoma with bulky skin lesions, and is characterized by a better clinical prognosis and extracutaneous spread is exceedingly rare. Unfortunately, granulomatous mycosis fungoides and granulomatous slack skin show overlapping histological features and cannot be separated reliably by histological examination alone. Probably, granulomatous mycosis fungoides and granulomatous slack skin are considered variants of a single disease. The reported genetic alterations with t(3;9)(q12;p24) in a case of granulomatous slack skin have to be confirmed.

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AMR SEMINAR #62

Case - 15

Contributed by: Elizabeth Montgomery, M.D.

History: A splenectomy on a 32 year old man showed multiple hemangiomatous lesions. The spleen weighed 734 grams. One of the nodules is submitted for your review.

Diagnosis: Littoral cell angioma

Comments: These tumors are presumably known to club members, with their tendency to manifest as multinodular spongy lesions as first described by Stephan Falk and Glauco Frizzera at the former AFIP in 1991. The nodular lesions are located in the red pulp, well marginated, and compress the adjoining splenic parenchyma. The endothelial cells lining the vascular spaces in the nodules have a plump histiocytoid appearance and a characteristic immunophenotype, expressing CD68 and CD31 but not CD34, as did this lesion. The clinical outcome was reported as benign in the initial series, although Fernandez et al reported a case that metastasized. The latter case displayed solid areas in the initial sample.

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AMR SEMINAR #62

Case - 16

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

Clinical History: A 35-year-old man presented with history of shortness of breath and chest pain of several weeks duration. The patient stated that he has always been in good health and has not had any medical problem in the past. Radiographic examination revealed a pleural mass with some thickening of the continuous pleura. A biopsy was obtained.

The initial biopsy (very small biopsy) was referred to me with the possible diagnosis of mesothelioma. The histology of the tumor was of a spindle cell proliferation with scattered mitotic figures. As you can imagine, numerous stains were performed obtaining positive staining for EMA, and negative staining for different keratins, S-100 protein, Bcl-2, and muscle markers. At this point I was almost convinced that this tumor did not represent mesothelioma but was not sure of the diagnosis either. I suggested the possibility of meningioma and asked if this patient had been evaluated for a CNS tumor. I guess at this point, the treating physicians really did not believe the diagnosis and the patient started treatment with chemotherapy. The patient subsequently came to our institution for medical evaluation and once again I went through the headache of viewing the biopsy again and was not able to make an unequivocal diagnosis.

At this point, the radiographic imaging showed a tumor involving the pleura, the costophrenic sulcus and diaphragm. There was no evidence of a CNS involvement. Surgical removal of the tumor was performed. That is the sample that you have.

By histology, one is able to see different growth patterns and in some of the sections, necrosis was extensive and mitotic figures were present up to 20x10hpf. The immunohistochemical stains very much show similar immunophenotype, and this time with a bit more confidence a more definitive diagnosis was made.

Diagnosis: Malignant meningioma, primary in the pleura.

Comments: The presence of meningiomas in the thoracic cavity is uncommon. During my time at the AFIP, we published a series of 10 cases of primary meningiomas of the lung. However, I am not aware of primary pleural meningiomas. I remember that in a past AMR a case of metastatic meningioma to the pleura was shared. However, in this case, we know for sure that the patient does not have past or present history of CNS tumor. Just wonder if other members of the Club have seen a similar case.

AMR Seminar #62

Case - 17

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

Clinical History: 78 year-old man with incidental finding of a 2.3 cm solid nodule in the lung on a routine chest x-ray. Radiologic evaluation suggests malignancy.

Macroscopic Findings: A 7 x 3.5 x 2.5 cm wedge biopsy was received from the operating room for a frozen section evaluation. A 2.3 cm white-tan nodule with a central cystic area was identified in the center of the lung parenchyma.

Microscopic Findings: The nodular area is formed by a mixed cell inflammatory infiltrate consisting of macrophages with a prominent eosinophilic cytoplasm with anthracotic pigment, multi-nucleated giant cells and abundant lymphocytes and plasma cells. The center of the nodular structure is cavitated and filled with abundant eosinophilic acellular material.

Immunohistochemical Stains:

S-100, pan-keratin: Negative.

CD138: Positive in plasma cells.

CD68, alpha1 anti-trypsin: Positive in macrophages.

Kappa-lambda: Faint mixed expression

Other Stains: Gram, Ziehl-Nielsen, Silver-methenamine: Negative for micro-organisms. Amyloid A: Negative.

Congo red: Red staining in central acellular material but no apple-green birefringency

Diagnosis: Light-chain disease involving the lung.

Comments: Light chain disease can show two different histological patterns, diffuse and nodular. The entity is rare in the lung and should warrant a thorough systemic examination for lympho-proliferative disorders, being associated with plasma cell dyscrasias and renal failure.. Of course, the differential diagnosis with amyloidosis and other necrotic lesions is basic to make the right diagnosis

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AMR SEMINAR #62

Case - 18

Contributed by: Dominic Spagnolo, M.D.

Clinical History: Male 47 with an asymptomatic mass in R thigh for 4 – 6 months, without antecedent trauma. Otherwise fit and well. On examination found to have a large non-tender mass inferior to inguinal ligament in the medial adductor compartment. No adenopathy. CXR normal. MRI revealed a mass completely within the adductor magnus muscle extending anteriorly and posteriorly around the proximal femur. The femur and hip joint were normal. The mass had an inhomogeneous appearance on T2-weighted sequences and enhanced extensively (digital image #1). Clinically and on imaging suspected of being a soft tissue sarcoma.

Image-guided core biopsy was performed (digital image #2), followed by open biopsy and finally marginal resection. There is no evidence of recurrence 18 months post-surgery.

Macroscopic Specimen: Large intramuscular yellow mass covered on some surfaces by fascia and skeletal muscle, approx 170 mm in max extent. Cut surface soft and yellow, with small fibrous septa producing slightly lobulated appearance. Areas of haemorrhage present (digital image #3).

Microscopy: The core biopsy was received by a colleague and proved problematic. A definite diagnosis was not rendered, though suspected; the core biopsy histology is shown in the image provided, with the inset demonstrating a myoinfiltrative pattern. The open biopsy and resection specimen showed a myoinfiltrative lesion including solid cellular areas, cystic foci, synovial-like papillary fronds and clefts. The cellular elements were polymorphous and heterogeneously distributed. They included sheets of mononuclear stromal cells, foamy histiocytes and Touton giant cells also often containing hemosiderin, and relatively few osteoclast-type giant cells. The mononuclear cells included smaller histiocyte-like cells with grooved nuclei, and larger cells sometimes containing clear intranuclear inclusions and eosinophilic cytoplasm with or without multiple peripheral vacuoles. Transitions between these cell types were evident. Hemosiderin deposits were prominent, as were areas of hyaline fibrosis, sometimes in narrow bands separating trabeculae of cells, sometimes diffuse and also forming giant rosette-like nodules. Clefts and papillary fronds were lined by epithelioid cells, focally displaying nuclear atypia, mitotic activity and including rare aberrant mitoses. However, there were no frankly sarcomatous changes. As these features may not all be equally represented in the 2 H&E's, please also see digital images 4 - 8.

The cells were immunoreactive for CD68 and CD163, podoplanin (especially those lining the spaces) and CD99. Only rare dendritic cells were desmin positive. The proliferation index was <1% (MIB-1). A wide range of other antibodies were applied on the original core biopsy, all negative.

The karyotype was 46,XY. By interphase FISH, there was trisomy 7 but no trisomy 5, nor losses or gains of 1p.

Diagnosis: Extra-articular diffuse-type tenosynovial giant cell tumour (extra-articular PVNS)

Discussion: The diagnosis is straightforward on the incisional biopsy and resection specimen, even given the purely intramuscular location. The original core biopsy was more problematic, particularly in light of the purely intramuscular location with infiltrative and destructive growth, and the imaging studies which were suggested a sarcoma. Typically, diffuse-type GCT (DT-GCT) exhibits low signal intensity on T1 and T2 weighted images, with contrast enhancement. In this case, the T2 images were inhomogeneous, with areas of high intensity and strands of low density (the latter due to hemosiderin deposits). The high intensity T2 images suggested sarcoma. Purely extra-articular DT-GCT/PVNS is rare. In a review of 50 cases of DT-GCT with extra-articular disease (defined as lesions presenting as

soft tissue masses, with or without articular involvement), 27 (54%) were purely extra-articular¹. This figure is almost certainly high because of the consultation bias. Of these, 12% involved the thigh as in this case, and 5 (9%) were entirely intramuscular. As a group, the DT- GCT's involved the extremities most often (the lower limb in 56% of cases) but there was a wide range of juxta-articular and extra-articular sites affected.

These lesions display clonal cytogenetic abnormalities, *CSF1* rearrangements (1p11-13) with one of a number of partners, *COL6A3* (2q35-37) being the most common. Trisomies 5 and 7 occur in some case, and aneuploidy in the the extra-articular forms of PVNS are common (GCT of tendon is diploid).

Extra-articular DT- GCT is an almost invariably benign, though locally aggressive lesion with a high rate of local recurrence and multiple relapses are common. Outcome data are relatively few, and are affected by the type of treatment (local excision *vs* piecemeal resection *vs* sarcoma-type surgery *vs* amputation). In Somerhausen and Fletcher's series¹ there was follow-up available for only 24 patients. Recurrence occurred in 33%, and multiple recurrences in 21%. Two cases were clinically malignant (almost certainly a high number because of selection bias) and developed nodal or pulmonary metastases. There was no correlation with tumour size and positive surgical margins were the only reliable predictor for recurrence.

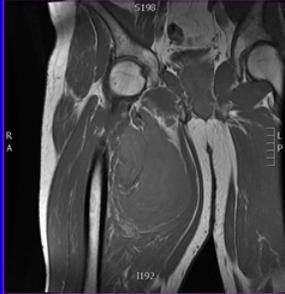
Malignancy in DT-GCT may be defined on histological and/or clinical criteria. According to the bible (Enzinger, Weiss, Goldblum) a case may be considered malignant if a conventional DT-GCT harbours frank sarcoma *ab initio*, or if it recurs as a sarcoma. Exceptionally rare are cases with typical histology but which behave in a clinically malignant fashion. In the Somerhausen and Fletcher series¹, 7 cases displayed atypical histologic features or contained frankly sarcomatous areas. Atypical features included any of: >20 mitoses/10hpf, necrosis, monomorphism and spindling of mononuclear cells, abundant eosinophilic cytoplasm in histiocytic cells, nucleomegaly and macronucleoli and stromal myxoid change. Of these 7 cases, 5 were typical DT-GCT with atypical histologic features (3) or frank sarcoma (2), 1 case recurred as a sarcoma and 1 case was a "benign" GCT which metastasised as such. No single atypical histological feature, in the absence of overt sarcomatous change was predictive of clinical malignancy. For practical purposes, malignancy defined in any way is exceptionally rare in this neoplasm.

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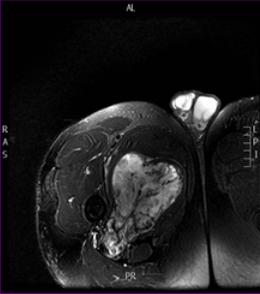
IMAGE 1

Coronal T1 non-contrast



Low signal intensity, slightly increased compared with muscle

Axial T2 non-contrast



High signal intensity, inhomogeneous; Strands of low intensity

IMAGE 2

Core biopsy

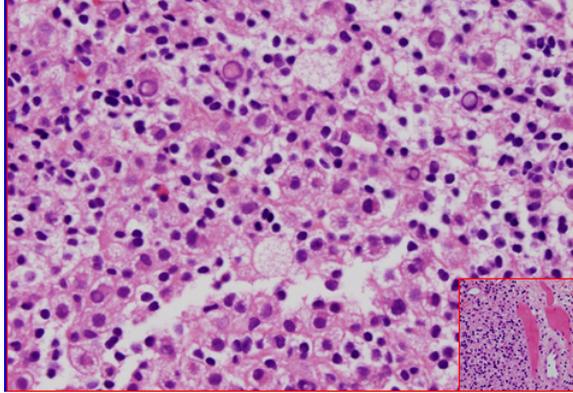


IMAGE 3



IMAGE 4

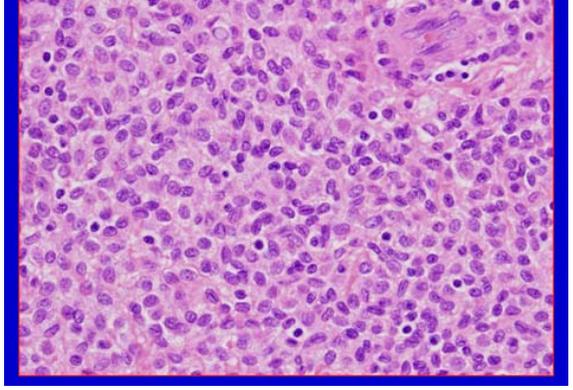


IMAGE 5

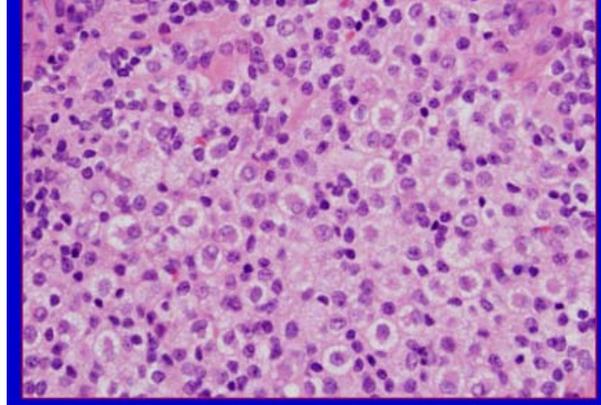


IMAGE 6

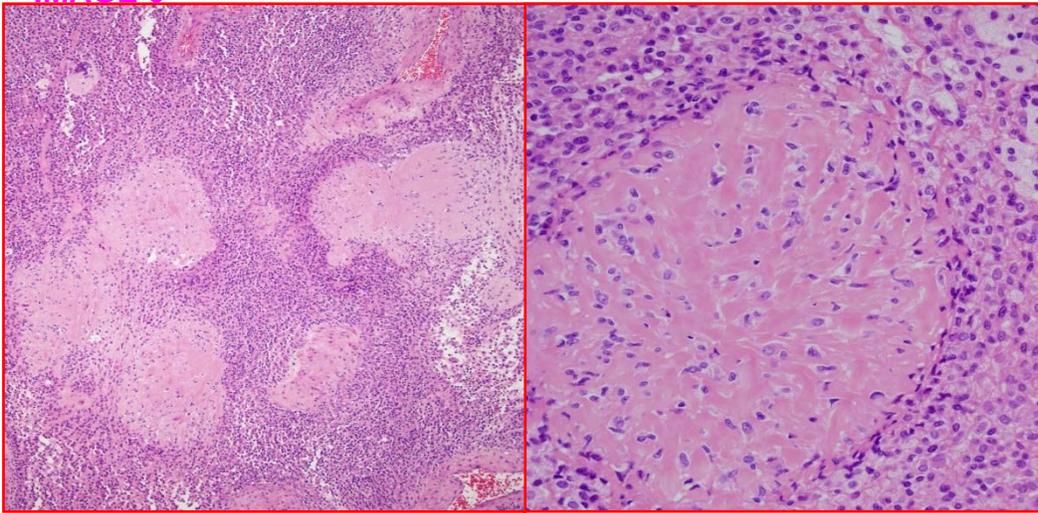
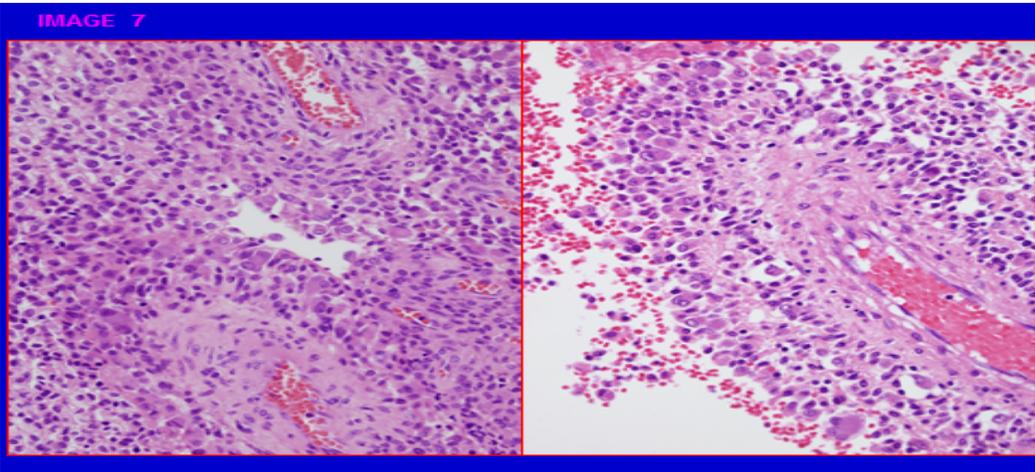
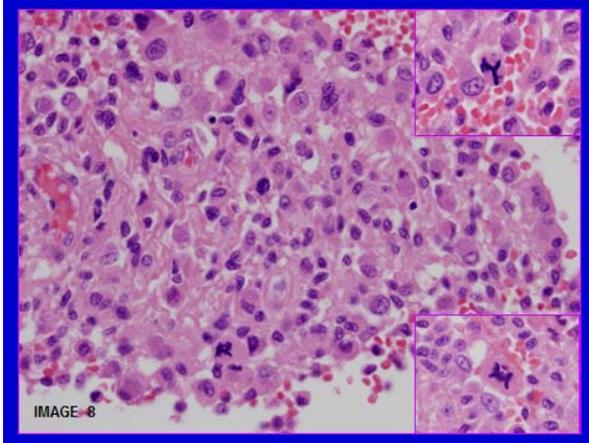


IMAGE 7





AMR SEMINAR #62

Case - 19

Contributed by: Paul E. Wakely, Jr., M.D.

History: A 37 year-old white male was admitted from an outside hospital with a diagnosis of MFH of scapular soft tissue. Suffering with a rash at the upper chest and face for two days, the patient was given a preoperative diagnosis of urticarial drug eruption vs gyrate erythema vs Sweet's syndrome. Core needle biopsies of a soft tissue mass (size unknown) at the scapular region, and of a supraclavicular lymph node were all performed at an outside hospital. After admission to our medical center, the patient had a bone marrow biopsy and partial colectomy due to severe transmural ischemic necrosis. He died within a week. No autopsy. The slide you have is from the lymph node; core needle biopsies of the soft tissue mass are identical, but too little tissue to make 45 slides for club members.

Pathology: Slides show a proliferation of epithelioid cells almost completely replacing this node accompanied by a concentrated infiltrate of eosinophils, and multinucleated/ multilobated tumor cells. Mitoses are easily identified. The soft tissue mass was originally diagnosed as undifferentiated pleomorphic sarcoma with metastasis to lymph node. Subsequent to the bone marrow biopsy (where mast cell granules were easily seen on Giemsa stain smears), additional staining of both scapular mass and lymph node for mastocytosis was done, and showed positive staining of these epithelioid cells with CD117, tryptase, CD43, and negative staining for myeloperoxidase, CD68, CD1a, CD2, CD3, CD5, CD8, CD20, CD45, and CD34. The diagnosis was amended to soft tissue and lymph node involvement by systemic mastocytosis.

Diagnosis: Systemic mastocytosis initially masquerading as undifferentiated pleomorphic sarcoma with metastasis to lymph node.

Comment: Core needle biopsies of scapular soft tissue and lymph node which were examined before a bone marrow biopsy were interpreted as undifferentiated pleomorphic sarcoma. Only after a subsequent bone marrow biopsy showed a diffuse mast cell infiltrate with positive staining for tryptase, CD117, and CD68 with negative staining for myeloperoxidase, CD20, CD3 and CD2 was the correct diagnosis recognized. Flow cytometry from the marrow demonstrated no immunophenotypic evidence of an abnormal population of B or T cells or myeloid blasts. However, 10% of leukocytes fell in the granulocyte region and expressed CD33, CD117, CD25 (moderate) and CD2 (dim).

The current WHO classification of mast cell disease is very convoluted with several major and minor criteria defining different subtypes. Suffice it to say that systemic mastocytosis (SM) requires multifocal, dense mast cell infiltrates in bone marrow or other extra-cutaneous organs. SM is subdivided into 6 variants according to the WHO with "B" and

"C" findings. The best I was able to do is place this patient into the category of "aggressive systemic mastocytosis"; he had no leukemic involvement of peripheral blood. Mast cell sarcoma (extremely rare) is defined as a unifocal mast cell tumor with high-grade cytology but without systemic mastocytosis (why the WHO would call it a variant of SM when the patient is not supposed to have SM is unclear to me).

A recent Mayo Clinic study of 41 patients with aggressive SM showed a median survival of 41 months.

References:

- Swerdlow SH, Campo E, Harris NL, Jaffe ES et al. (Eds.) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2008, p. 54-63.
- Pardanani A, Tefferi A. Systemic mastocytosis in adults: a review on prognosis and treatment based on 342 Mayo Clinic patients and current literature. *Curr Opin Hematol* 2010; 17:125.

AMR SEMINAR #62

Case - 20

Contributed by: Eduardo Zambrano, M.D.

Clinical History: This is a consult case received from abroad. The patient is a 29 year-old female who presented with a mobile mass in her left vulvar region 3 months prior to biopsy. The nodule was reportedly firm and painful on palpation. No history of weight loss. Abdominal CT, tumor markers, upper GI endoscopy and blood tests were all within normal limits. Upon excision, the 2.5 x 2 x 1.8 cm subcutaneous mass appeared soft, well-circumscribed, tan-yellow, with focal areas of hemorrhage.

Ancillary Studies: Immunohistochemical stains performed at our institution revealed focal EMA and CD10 expression, while CD31, CD34, CD117, AE1/AE3 and MDM2 were negative. Nuclear PR expression was noted in the majority of cells. Additional immunohistochemical stains received from the submitting institution included: vimentin (diffusely positive), whereas S100, SMA, MSA, desmin, bcl-2, HMB45, ER, CD21, CD45 and CD99 were all negative. Molecular studies by FISH were negative for EWS and INI-1 rearrangements/deletions.

Your help with this puzzling case is greatly appreciated.