AMR Seminar #74

Case – 1

Contributed by: Abbas Agaimy, M.D.

Clinical history: A 76-year-old man was diagnosed with a paraaortic intrathoracic mass initially thought to represent lung cancer (see imaging). Pleural effusion cytology failed to demonstrate any malignant cells. Surgical resection was performed. This is a recent case with no follow-up data.

Macroscopic features: The resection specimen (see illustration) revealed a 5.8 cm well circumscribed non-infiltrative mass with homogeneous tan to whitish soft cut-surface.

Histological & immunohistochemical findings: Histological examination revealed medium-sized to large epithelioid cells with copious cytoplasm disposed into diffuse sheets, macrotrabeculae and nests with prominent cytoplasmic vacuoles frequently resulting into double-barrel phenomena and cytoplasmic bridging with variable resemblance to adenomatoid tumors. Mild to moderate atypia and mitoses were present. IHC showed consistent expression of vimentin, pankeratin, CK5, calretinin, HMBE and podoplanin (representative images shown in the figure composite). Complete loss of BAP1 was evident in the neoplastic cells. Retrospective assessment of pleural cytology was negative for tumor cells. No other manifestations were detected at time of release from hospital.

Diagnosis: Localized malignant epithelioid mesothelioma, adenomatoid-like variant, BAP1-deficient.

Comments: Malignant mesothelioma may rarely present as a localized mass as in this case and thus represents a potential source of confusion regarding both histogenetic line and dignity of the lesion. I have not seen this variant in this presentation before and happy to hear the comments of the members of the club. A subset of mesotheliomas are known to harbor inactivating mutations in the BRCA-associated protein 1 (BAP1) which is illustrated by loss of BAP1 IHC. This is highly useful in effusions and on limited biopsy as los of this tumor suppressor is limited to malignant mesothelial proliferations and it has not been reported in reactive and benign lesions such as adenomatoid tumors. However, retained expression does not help in this distinction. Up to 50% of mesotheliomas are BAP1-lost with this being seen across all subtypes. However, there is evidence that BAP1-lost cases tend to show epithelioid morphology and bland-looking histology with or without adenomatoid features.

BAP1 inactivation may be either due to acquired (somatic) mutations or an indication of germline mutations (the latter has been referred to as "BAPomas" or BAP1 tumor syndrome. The spectrum of the hereditary BAP1-related diseases includes melanocytic tumors, malignant mesothelioma, uveal melanoma, cholangiocellular carcinoma, clear cell renal cell carcinoma, breast cancer and many other rare conditions. In the current case, I was unwilling to comment on possible heredity of the condition as the patient was 76 yo at time of diagnosis. However, at the post-op MDT meeting, I was surprised to hear that the patient underwent a tumor nephrectomy at age 28, but details of the histology was not available. Thus this is very likely a genetic disorder with unusual very long latency between his renal tumor (which was likely a ccRCC) and the current mesothelioma. Also, the possibility of a germline BAP1 defect would better explain this remarkably unusual presentation of malignant mesothelioma. I am sure whether this variant was overrepresented among previous series on localized malignant mesotheliomas or not.

It has been shown that patients with germline BAP1 defects and asbestos exposure developed mesotheliomas some 10 yrs earlier than control individuals. The current patient had no history of asbestos exposure.

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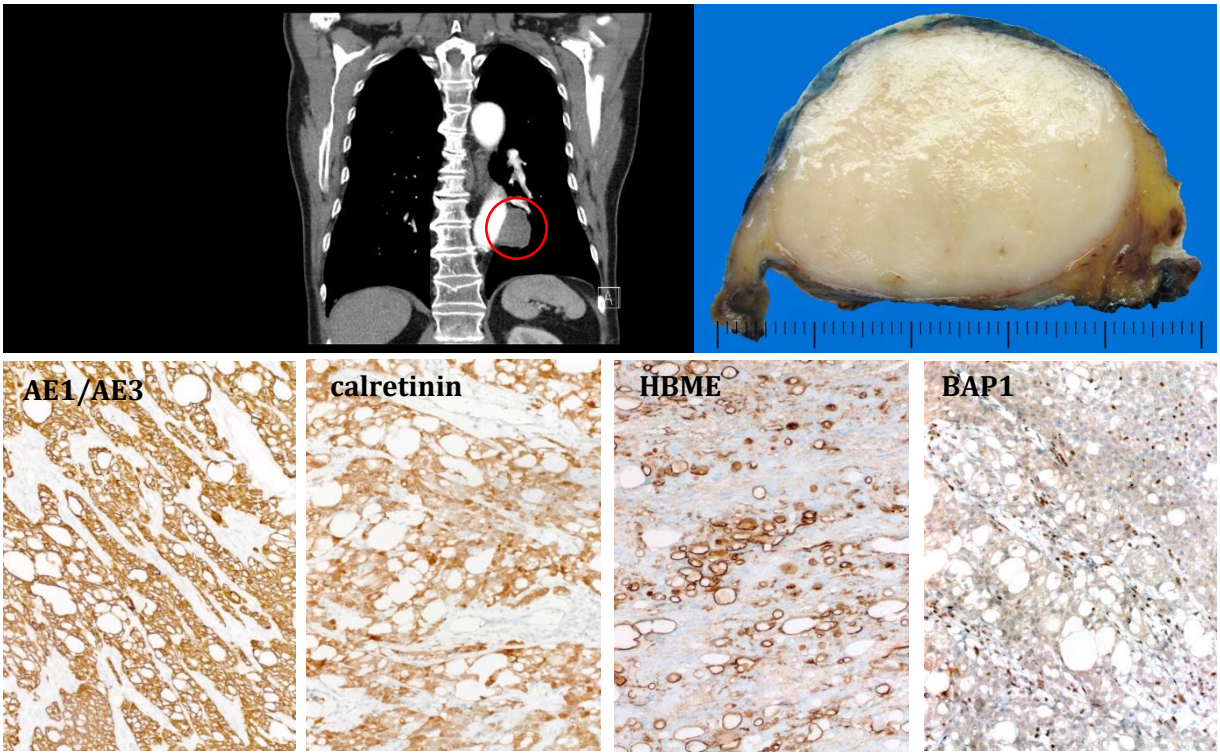
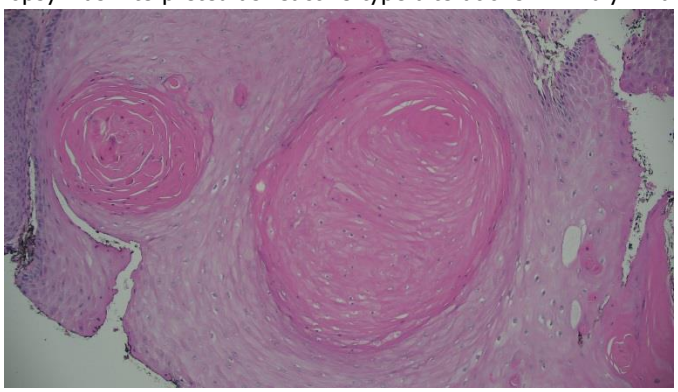


AMR Seminar #74

Case – 2

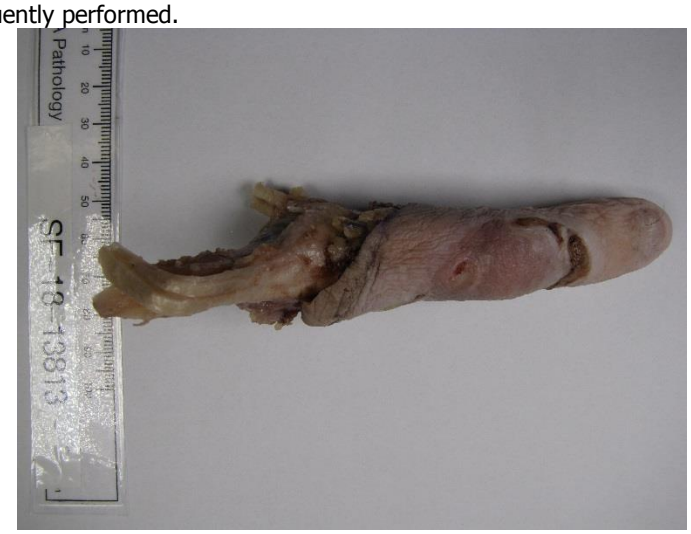
Contributed by: Phil Allen, M.D.

Clinical History: A farmer aged 49 presented on 5-4-18 with an eight-week history of swollen mass on his left index finger at the proximal interphalangeal joint, possibility related to a foreign body. He had been picking at the lesion with a needle and a knife. There was no foreign body visible on X-ray nor was there any evidence of osteomyelitis. The small biopsy was interpreted as reactive-type alterations in mildly inflamed skin.



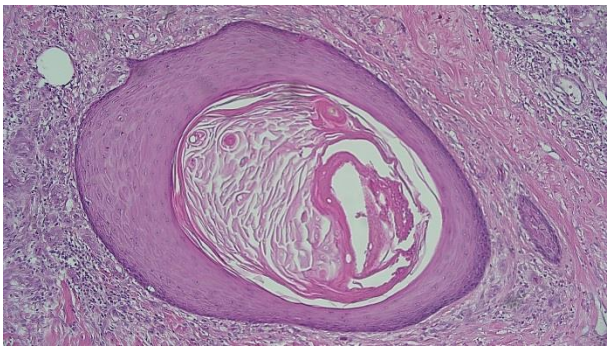
Here is a picture of that biopsy. I have not been able to get a clinical picture, but the clinicians said that the appearances were most unusual, particularly in a relatively young patient. They wondered about the viral disease "orf", which affects sheep farmers' hands.

The lesion continued to grow so an excision biopsy was attempted. A representative slide from the excision specimen is circulated to the club members. As the tumour extended to the deep margin, a ray amputation of the index finger was subsequently performed.



The scar marks the site of the previously excision biopsy.

Only a single small focus of completely excised tumour was found in the amputation specimen, as you can see below.



This is the only focus of the tumour I could find in the amputated finger.

The circulated sections from the attempted excision biopsy show what look like multiple small epidermoid cysts as well as the slightly atypical non-keratinised foci which indicate a diagnosis of well differentiated squamous carcinoma. The largest cyst-like structure could be described as a little burrow (cuniculus).

I think this is an example of the rare tumour usually occuring in acral sites which was originally described by the British surgeon, Ian Aird in 1954.

I usually refer to Kao's 1982 AFIP study of 46 cases. Those authors, who included the distinguished pathologists Graham and Helwig, implied in their title that carcinoma cuniculatum is a synonym for verrucous carcinoma but in their discussion, they say: "Although some researchers believe carcinoma cuniculatum is a variant of verrucous carcinoma….., the latter typically involves the mucous membranes of the oral cavity, larynx, nasal cavity or the external genitalia." They could have added that verrucous carcinoma is not characterised by deep burrows with normal overlying surface epithelium.

Those who believe that the two are essentially the same tumor may be right but the clinical appearance, the lack of verruciform exophytic growth, and the usual location on acral sites indicate that the two entities are at least clinically separate. I would be interested in the Club members' opinions. Interestingly, only one of Kao's 46 tumors involved the hand. I also saw one in the buttock in Hong Kong about 15 years ago.

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AMR Seminar #74

Case – 3

Contributed by: Gerald J. Berry, M.D.

Clinical History: This 70-year old man presented in 2016 with a large left atrial intra-luminal mass (see attached ECHO image). He underwent surgical resection at an outside institution. I spoke with his cardiac surgeon this past week and the patient is alive and thriving, without local recurrences or development of any other neoplasms.

Pathologic Findings: The specimen received as "atrial tumor" was spherical, tan-brown and smooth measuring 32.8 x 3.8 x 2.4 cm. A short 0.2 cm in length stalk was attached and measured 0.9 x 0.4 x0.2 cm. The cut surface e was uniformly tan-yellow and lacked necrosis or cystic changes.

The microscopic findings are fascinating. The interface between the atrial musculature and the cellular epithelial lesion is consistent with atrial myxoma (see attached image). The bulk of the lesion is composed of nests and trabeculae of uniform cells with oval nuclei, delicate chromatin and inconspicuous nucleoli. The cytoplasm varies from clear to pale amphophilic. Interspersed within the nests are scattered small lymphocytes. Pleomorphism and mitotic figures are absent.

I performed an array of immunostains and the only stain that was diffusely and strongly positive was calretinin. CD117, CD5, S100, desmin, synaptophysin, CD57, ERG, PAX8, P63 and CKMix were all negative. The small lymphocytes were CD45RB positive with scattered CD20+ B-cell clusters and numerous CD5+ T-cells. TdT and CD1a were both negative.

Diagnosis: Epithelial neoplasm most consistent with thymoma arising within a cardiac myxoma.

Comment: This is a fascinating neoplastic proliferation for which I don't have a perfect diagnostic label. At the time I was reviewing the case in consultation I came across the paper by Dylan Miller and Henry Tazelaar from the Mayo Clinic (see reference). I shared the case with Dylan at a meeting we were both attending around that time and he felt the lesion was identical to their 2 cases. Happy to entertain other diagnostic entities but importantly the lesion appears to be benign as it is now 3 years later without incident.

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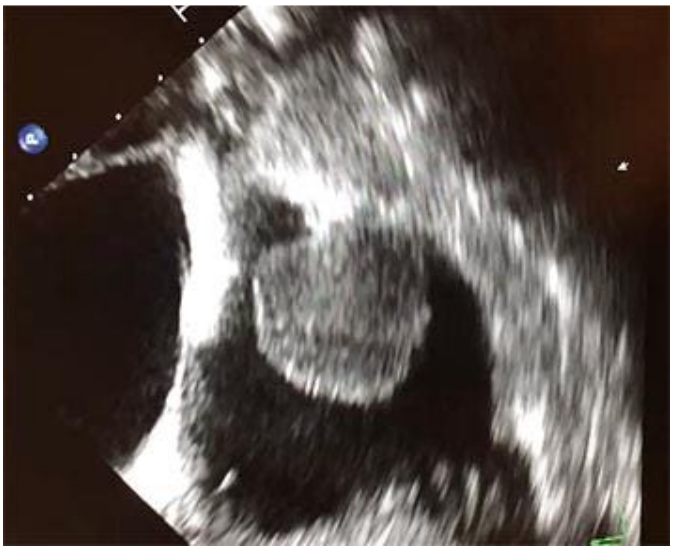
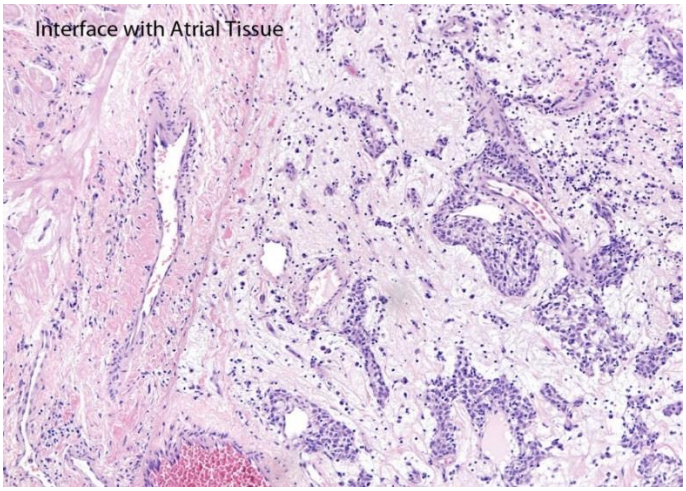
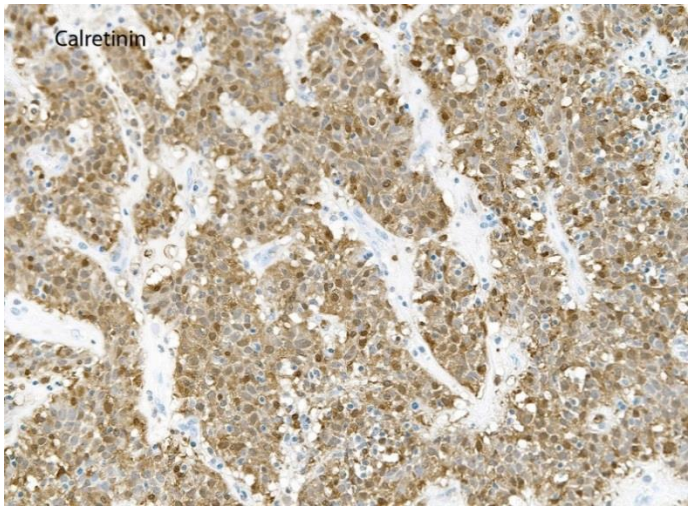



Interface with Atrial Tissue


Calretinin

AMR Seminar #74

Case – 4

Contributed by: Justin Bishop, M.D.

Clinical History: 69-year-old woman with a painless neck swelling, found to be centered in the right submandibular gland.

Macroscopic features: Well-circumscribed, firm, pale solid nodule measuring 2 cm.

Histological and Immunohistochemical Findings: The tumor is a well-circumscribed, seemingly encapsulated proliferation of haphazardly arranged epithelial elements separated by bands of fibrosis with focal myxoid change. The ducts range from small ductules to cystically dilated spaces, and most of them are lined by cells exhibiting apocrine cytoplasmic changes. Some of the dilated ducts contain secretory material and foamy macrophages. The apocrine ductal elements exhibit varying degrees of architectural and cellular atypia, reaching a level that in the breast might be regarded as atypical ductal hyperplasia or ductal carcinoma in situ. In addition to the predominant ductal tumor population, there is a minor population of myoepithelial cells surrounding these ducts, as well as occasional cells resembling serous acinar cells with brightly eosinophilic intracytoplasmic granules or hyaline globules.

By immunohistochemistry, the individual tumor cell elements stain as expected: the apocrine-appearing ducts are positive for androgen receptor, while intercalated ducts are positive for S100 and SOX10, and the myoepithelial cells are positive for p40, SMA, and calponin in a peripheral distribution. DOG1 is only weakly, focally positive in the acinar-like cells.

Diagnosis: Sclerosing polycystic adenosis/adenoma.

Discussion: Sclerosing polycystic adenosis is a rare salivary gland disorder first described in 1996, characterized by histologic similarities to fibrocystic changes of the breast. Approximately 60 cases of sclerosing polycystic adenosis have been reported. A majority of cases (approximately 70%) arise in the parotid gland, with occasional cases in the submandibular glands or oral cavity. Rare cases have been reported in the sinonasal tract or lacrimal glands. Sclerosing polycystic adenosis may occur in a wide age range (7 to 84 years), with a mean age of approximately 40 years. There is a slight female predominance (1.3:1).

Sclerosing polycystic adenosis presents clinically as a painless, slow-growing mass. Grossly, sclerosing polycystic adenosis consists of a well-circumscribed, firm, pale nodule ranging from 1 to 12 cm in size. Lesions often have a multicystic appearance.

At the microscopic level, this case was typical. Sclerosing polycystic adenosis is a well-circumscribed and sometimes encapsulated lobular proliferation of haphazardly arranged ducts, myoepithelial cells, and acini, often separated by bands of hyalinized fibrosis. Fatty stromal metaplasia is occasionally present and may be prominent. Lipomatous stromal changes may obscure the circumscribed nature of the lesion, giving the appearance of a more diffuse process. A characteristic feature is the presence of serous acinar cells with brightly eosinophilic intracytoplasmic granules or hyaline globules, possibly representing altered zymogen granules. Most cases harbor foci of apocrine intraductal neoplasia. The ductal proliferations range in their appearance from lesions resembling atypical ductal hyperplasia or low-grade ductal carcinoma in situ of the breast with monotonous cells arranged in rigid bridges, to high-grade intraductal carcinoma with necrosis and high mitotic rates, resembling intraductal salivary duct carcinoma. While atypical, these ductal proliferations are almost always completely intraductal; only a single case of invasive carcinoma has been reported to have arisen from sclerosing polycystic adenosis.

By immunohistochemistry, each cellular component (ductal cells, acinar cells, myoepithelial cells) of sclerosing polycystic adenosis demonstrates its expected immunophenotype. Myoepithelial cell markers may be helpful to highlight the intact myoepithelial cell layer surrounding atypical apocrine ductal proliferations, which in turn typically express androgen receptor. A single study reported X-chromosome inactivation using polymorphism of the human

androgen receptor (HUMARA), suggesting that sclerosing polycystic adenosis may be a neoplastic process. Indeed, some authors advocate the term "sclerosing polycystic adenoma."

Sclerosing polycystic adenosis may be confounding to pathologists unfamiliar with the diagnosis. The differential diagnosis is very broad, ranging from other non-neoplastic entities to benign or even malignant salivary gland neoplasms.

The ductal dilatation and fibrosis suggest the possibility of polycystic/dysgenetic disease or non-specific sialofibrosis with salivary duct cysts. The well-circumscribed nature and proliferative acinar and ductal elements of sclerosing polycystic adenosis are distinguishing features. Moreover, polycystic/dysgenetic disease is usually bilateral. As a well-circumscribed lesion of ducts and myoepithelial cells with prominent stroma, pleomorphic adenoma may be considered, but pleomorphic adenoma lacks acini and demonstrates at least some chondromyxoid stroma. The presence of disorganized serous acini within sclerosing polycystic adenosis raises the possibility of acinic cell carcinoma, but the other admixed epithelial components are not consistent with that diagnosis. In cases of sclerosing polycystic adenosis with a prominent lipomatous stroma, sialolipoma – a lipoma with entrapped salivary ducts, acini, and myoepithelial cells – is a consideration. Sialolipoma, however, lacks the proliferative epithelial elements of sclerosing polycystic adenosis. Finally, in cases of sclerosing polycystic adenosis with high-grade intraductal carcinoma, salivary duct carcinoma may be considered, but the intraductal elements of sclerosing polycystic adenosis are entirely surrounded by myoepithelial cells and are associated with other, benign ducts and acini.

Sclerosing polycystic adenosis is treated by surgical excision and recurs in approximately 10% of cases. A single case has transformed into invasive carcinoma following multiple recurrences over a period of decades. There have been no metastases or tumor-related deaths.

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8. Canas Marques R, Felix A. Invasive carcinoma arising from sclerosing polycystic adenosis of the salivary gland. Virchows Arch. 2014;464(5):621-625.

AMR Seminar #74

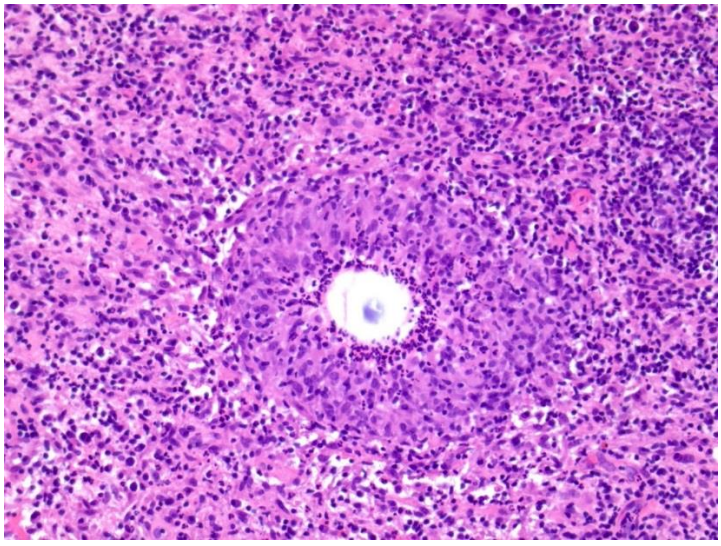
Case – 5

Contributed by: Ira Bleiweiss, M.D.

Short summary of case: 33-year-old female with a palpable well circumscribed partially solid, partially cystic mass. Core biopsies were performed.

Clinical History: 33-year-old female with a palpable well circumscribed partially solid, partially cystic mass, measuring 2.5 cm. Core biopsies were performed. Of note, the patient is not currently pregnant and does not have a history of recent lactation.

The slides show a localized mixed acute and chronic inflammatory infiltrate, essentially an organizing abscess. Most, but not all, of the slides show peculiar tiny microabscesses. Note that in these areas central neutrophils are surrounded by granulomatous reaction, ringing the microabscess like a doughnut. Gram stain was negative, as of course were AFB and GMS. Since not every slide shows the microabscesses at their best I'm including a photo of one at its most photogenic best.



Diagnosis: Cystic neutrophilic granulomatous mastitis.

I include this case not as a diagnostic challenge, but as a relatively newly recognized pattern of inflammation. There have been reports of gram-positive bacilli, such as corynebacterium, being identified only within the cystic spaces. These rods are difficult to find (our stain was negative), difficult to culture, and difficult to treat (several weeks of antibiotics such as tetracycline, doxycycline, vancomycin, etc. – you name it, they've tried it). They are just plain difficult!

I personally think these cases are distinct from the more typical abscesses associated with pregnancy and/or lactation and from idiopathic granulomatous mastitis. Pregnancy/lactation related abscesses often have occasional foreign body type giant cells but not these granulomata literally ringing the microabscesses. Idiopathic granulomatous mastitis is more of a diffuse process, not usually so well circumscribed as to make the radiologist consider abscess and the granulomata again are spotty and unrelated to neutrophils when they are even present

(usually they are not). Although almost all cases in the literature reportedly occurred in premenopausal women, they appear to be unrelated to pregnancy. One case was related to a nipple piercing.

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Troxell ML, Gordon NT, Doggett JS, Ballard M, Vetto JT, Pommier RF, Naik AM. Cystic Neutrophilic Granulomatous Mastitis: Association With Gram-Positive Bacilli and Corynebacterium. Am J Clin Pathol. 2016 May;145(5):635-45.

AMR Seminar #74

Case – 6

Contributed by: **Professor Fátima Carneiro**

Clinical history: 73-year-old male with previous history of high grade papillary urothelial carcinoma of the bladder, diabetes mellitus and ischaemic stroke. He had ponderal weight loss of 10kg in the last 6 months and anemia. Colonoscopy revealed polypoid lesion in the splenic flexure (12mm of largest dimension).

Pathologic features: Gross examination revealed a fungating mass in the splenic flexure, with diffuse infiltration of the colorectal wall. Histopathologic analysis showed the presence of adenocarcinoma, diffusely dissecting the colorectal wall (in a *linitis plastica* pattern) and perforating the peritoneum (pT4a stage), composed of "bona fide" signet ring cells throughout the entire tumor (>90%). Lymph node metastases were identified in five lymph nodes (pN2a stage). No peritoneal implants were detected.

By immunohistochemistry, the signet ring cells showed diffuse immunoreactivity for CDX2, MUC2 and MUC5AC. The expression of MUC6 was observed in rare signet ring cells. E-cadherin immunoreactivity was completely absent. The expression of mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) was retained.

Diagnosis: SIGNET RING CELL CARCINOMA (SRCC) OF THE COLON.

Comment: Primary SRCC of the colon and rectum (PSRCCR) is rare, with a reported incidence of less 1%. Signet ring-cell carcinomas are more common on the right side, present at a higher tumor stage, show a high rate of lymphatic invasion and have a propensity to peritoneal metastatic spread. In the present case there was no evidence of involvement of other organs, namely the stomach, fitting with a primary origin in the colon. For cancer in advanced stages, patients with a resectable colorectal SRCC have a poorer prognosis than those with conventional adenocarcinoma of the colon. Therefore, more intensive surveillance and closer observation should be offered to such patients. There is a high incidence of MSI in SRCC of the colon, which was not detected in the present case. The mucin profile observed in the case herein reported (MUC2, MUC5A and very low/absent expression of MUC6) is similar to the pattern described in the literature in colorectal SRCC and different from the typical pattern observed in the stomach, the latter characterized by high expression of MUC5AC and MUC6 and low expression of MUC2. These different expressions of these MUC apomucins in gastric and colorectal SRCC may be useful to determine the primary site of metastatic SRCC.

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AMR Seminar #74

Case – 7

Contributed by: Alberto Cavazza, M.D.

Clinical history: A 51-year-old smoking male, with an unremarkable past clinical history, presented with thoracic pain and a large bulla of the lower lobe of the left lung. A surgical bullectomy was performed.

Pathologic findings: We received a subpleural portion of lung tissue, 15 cm across, almost completely occupied by a poorly circumscribed cystic lesion. The cyst was mostly unilocular and unremarkable, but focally contained spongy tissue merging with a rim of surrounding lung. Your slide was taken from the spongy part of the lesion. At histology, the cyst was criss-crossed by fibrous septa forming papillary-like structures, covered by normal or mildly hyperpastic pneumocytes and with a fibro-inflammatory and vascularized core. Focal ossification was observed. A striking feature was the presence of bland, oval-to-spindle interstitial cells, with clear cytoplasm rich in glycogen, filling the stroma of the papillae. At immunohistochemistry, the interstitial cells expressed exclusively CD10 and (focally) vimentin, but were negative for many other markers including pan-cytokeratin, TTF1, chromogranin, HMB45, actin, CD68, S100, CD34 and CD117.

Diagnosis and comments: I think this is an example of **placental transmogrification (PT) of the lung**, an entity first reported in abstract form in 1979[1] and in two papers in 1995[2,3]. PT is an unusual, single cystic (occasionally solid) lesion of the lung, occurring preferentially in males at any age. It is benign and surgical excision is curative. Its name is due to a resemblance to placental tissue, both macroscopically and histologically: in reality it is composed of lung tissue and has nothing to do with placenta. Lipomatous metaplasia may occur[4,5].
The pathogenesis is unknown: it has been interpreted as a variant of emphysema, but this is in contrast with the localized nature of the lesion. My impression[6] is the interstitial clear cell proliferation likely represents the primary event, and the emphysema-like cystic change is just a secondary phenomenon: in the lung the same situation (interstitial mesenchymal cellular proliferation with secondary cystic dilatation of the alveolar spaces) may occur in other diseases, including cystic pleuropulmonary blastoma, lymphangioleiomyomatosis/PEC-omatosis and cystic metastases (particularly from endometrial stromal sarcoma, dermatofibrosarcoma protuberans/cellular dermatofibroma or uterine leiomyoma). In other words, in my opinion the defining feature of PT is not the resemblance to placental tissue (generally quite vague and superficial, like in this case, and which can be seen in the lung in different conditions[7] depending on the fantasy of the observer), but the presence of the peculiar interstitial clear cells. The latter are bland mensenchymal cells, without an evident line of differentiation. A colleague of mine is trying to better understand these cells, but we have just two cases in our Hospital: if some of you want to contribute with a case or with ideas, he/she is welcome on board!

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AMR Seminar #74

Case – 8

Contributed by: Göran Elmberger, M.D.

Clinical history: A 22-year-old man with hematuria. Cystoscopy reveal papillomatous bladder tumor.

Pathological Findings: Microscopy reveal a papillomatous tumor covered with reactive urothelium. In the stroma a solid growth of clear and eosinophilic polymorphous cells is seen. Occasional multinucleated giant cells noted. Plentiful of mitoses. Some neutrophilic micro abscesses. Focal stromal sclerosis. Dystrophic calcification.

Immunohistochemistry show CKAE1/AE3+, CK5-, CK8+, CKHMW+, EMA+, p63-/+, GATA3-, CD31-, CD34-, CD45-, s100-, SOX10-, Melan A-, HMB45-, Desmin-, D2-40-, NKX3.1-, ERG-, FLI-1-, INI-1-, Vimentin+, p53 wt, Ki-67 70%.

PAS+, PASD-.

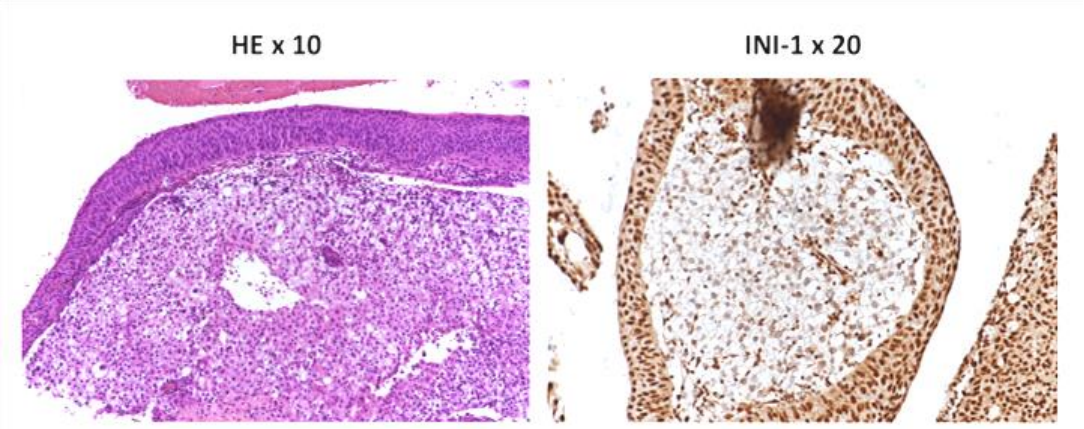


Fig.1

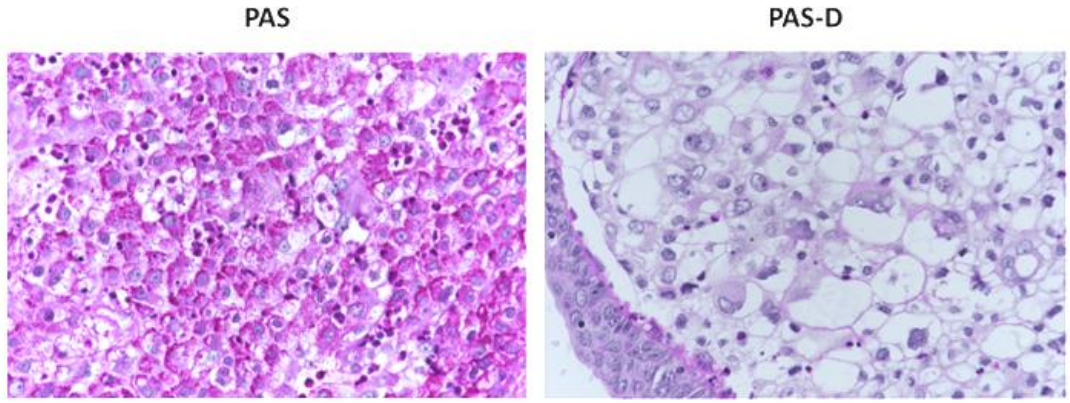


Fig.2

Interrogation of clinicians reveal patient was operated for epithelioid sarcoma left foot 3 years previously and suffered from locoregional recurrence, paraaortic metastases and pulmonary metastases.

Diagnosis: Bladder metastasis of conventional epithelioid sarcoma.

Discussion: Epithelioid sarcoma is a rare soft tissue sarcoma arising from mesenchymal tissue and characterized by epithelioid-like features. It accounts for less than 1% of all soft tissue sarcomas. It was first clearly characterized by F.M. Enzinger in 1970. It commonly presents itself in the distal limbs (fingers, hands, forearms, or feet) of young adults as a small, soft mass or a series of bumps. A proximal version has also been described, frequently occurring in the upper extremities. Rare cases have been reported in the pelvis, vulva, penis, spine, orbita, tongue, chest wall and pleura. A brief literature search with Google/PUBMED could not reveal any described cases of primary bladder ES or metastasis of ES to bladder.

Histologically, epithelioid sarcoma forms nodules with central necrosis surrounded by bland, polygonal cells with eosinophilic cytoplasm and peripheral spindling.

Epithelioid sarcomas typically express vimentin, cytokeratins, epithelial membrane antigen, and CD34, whereas they are usually negative for S100, desmin, and FLI-1. They typically stain positive for CA125. Loss of INI is a characteristic feature.

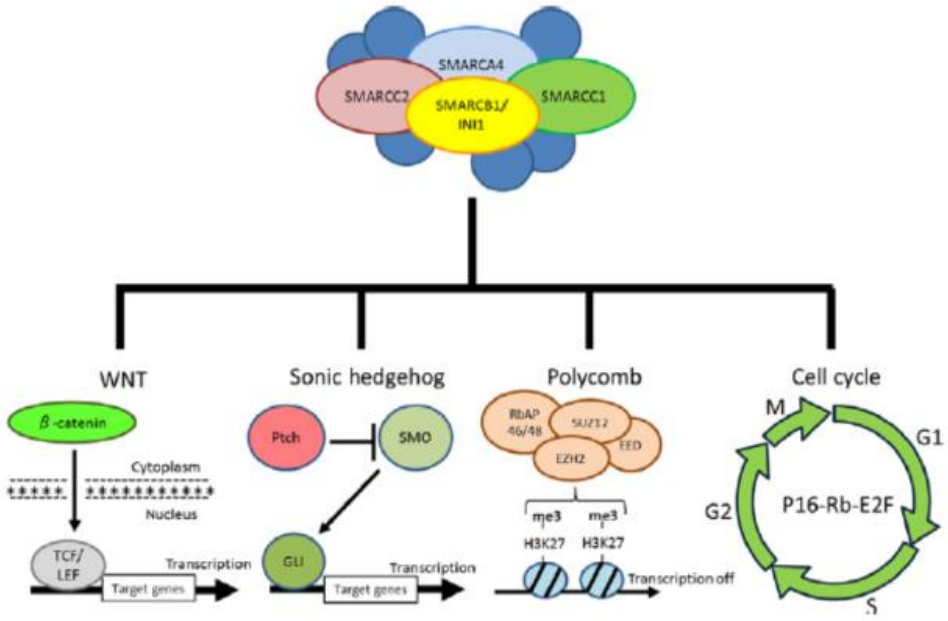
Epithelioid sarcoma most commonly strikes young adults, yet no age group is immune. The disease tends to develop local recurrences and metastasis thereafter to regional lymph nodes, lung, bone, brain, and other locations, including the scalp. Epithelioid sarcoma has a high rate of relapse after initial treatment and tends to recur locally. Epithelioid sarcoma also demonstrates lymphatic spread (in 22-48% of cases), and metastasis (in 21-63% of cases). These events, as well as advanced stage and grade, are predictive of an overall worse outcome. The overall five-year survival rate for epithelioid sarcoma is anywhere from 25 to 78%. Importantly, the 10-year and 15-year survival rate drops off significantly. Associated with a more positive outcome are younger age, female vs. male sex, distal vs. proximal location, smaller tumor size, and negative margins upon tumor resection.

Genetics

The most common genetic mutation (found in 80-90% of epithelioid sarcomas) is the inactivation of the SMARCB1 gene, or the loss of INI-1 function which is thought to be a major contributor to disease progression. Epithelioid sarcoma typically contains chromosome 22q11.2 mutations or deletions and 8q gains, particularly. Aberrations of 18q and 8q, as well as recurrent gains at 11q13, have also been observed. Complete loss of SMARCB1/INI1 expression is found in 76–100% cases of proximal-type and 81–93% cases of conventional-type epithelioid sarcoma. The ratio of gene alteration at either the DNA or RNA level causing SMARCB1/INI1 protein inactivation varies widely between 0% and 58% in conventional-type or between 19% and 100% in proximal-type cases. In addition, it is suggested that microRNAs such as miR193a-5p, miR-206, miR-381 and miR-671-5p may have the potential to inhibit SMARCB1 mRNA in epithelioid sarcoma.

The SMARCB1 gene is located on chromosome 22q11.2 and codes for a member of the SWI/SNF chromatin remodeling complex. Loss of SMARCB1 function is the most common genetic mutation observed in epithelioid sarcoma, and this dysfunction is likely a major driver of disease progression. SMARCB1 is a core protein subunit of the 15 subunit SWI/SNF complex involved in regulating the nucleosome architecture of our genome and has been shown to be a potent tumor suppressor gene meaning that its primary role is to control cell division and to even halt division under appropriate circumstances (i.e. signals to over-replicate). As this tumor suppressor is commonly inactivated in epithelioid sarcoma, cell division can fail to appropriately halt, resulting in unregulated cellular growth and the formation of cancer tumors.

Fig. 3. Oncogenic pathways activated by SMARCB1/INI



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SMARCB1/INI1 plays an important role in various interwoven factors in several pathways, and different cancers show different aberrant expression patterns of its protein. Although the several pathways related to mechanisms of tumorigenesis and tumor proliferation are intertwined in complex ways, the clarification of these mechanisms may contribute

to therapeutic strategies in SMARCB1/INI1-deficient tumors. Several research teams are currently developing techniques to reverse this loss of genetic function characteristic of epithelioid sarcoma.

SWI/SNF is a multi-subunit chromatin remodeling complex that performs fundamental roles in gene regulation, cell lineage specification, and organismal development. Mutations that inactivate SWI/SNF subunits are found in nearly 20% of human cancers, which indicates that the proper functioning of this complex is necessary to prevent tumor formation in diverse tissues. Recent studies show that SWI/SNF-mutant cancers depend on residual SWI/SNF complexes for their aberrant growth, thus revealing synthetic lethal interactions that could be exploited for therapeutic purposes.

Differential diagnosis of clear cell tumors in bladder:

- Primary clear cell tumors in urinary bladder:
- Nephrogenic metaplasia
- Urothelial carcinoma with clear cell cytoplasm
- Clear cell carcinoma Mullerian type
- Diffuse large B-cell lymphoma
- Leukemias
- PECOMA
- Paraganglioma
- Melanoma

Secondary clear cell tumors in urinary bladder

- Clear cell carcinoma with the primary originating elsewhere; renal or GYN
- Melanoma
- Sarcoma
  - Epithelioid sarcoma
  - Clear cell sarcoma
  - Myoepithelial carcinoma of soft tissues
  - Metastases to bladder with clear cells

Secondary cancers to the bladder are rare. They are often categorized as direct extension of tumor from surrounding organs or systemic metastasis. The most common sites of spread to the bladder are prostate, colorectal, or cervical sites. Breast, lung, and skin primaries are less common sources.

In present case history, morphology and results of ancillary stains are consistent with metastasis from ES.

Conclusions:

- Differential diagnosis of bladder clear cell tumors is wide and sometimes challenging
- Never fail to interrogate patient history
- Don't forget rare possibility of metastasis
- Rare events do occur
- Correct diagnosis can open for experimental targeted therapy

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AMR Seminar #74

Case – 9

Contributed by: Franco Fedeli, M.D.

Clinical History: A 74-year-old male presented with a history of right flank pain, microhematuria. A CT scan revealed a 3,5 cm renal mass within the collecting system. The patient had no other primary malignancies.

Macroscopic Findings: The patient underwent laparoscopic radical right nephrectomy. Examination of the specimen revealed a 3,2x3x2,5 cm endophytic, ill defined, grey-yellowish friable mass attached to the renal pelvis.

Microscopic Findings: Histologically, the tumor was composed of complex papillary structures lined by neoplastic cells with frequent hobnail appearance, clear cytoplasm, and large irregular and round nuclei containing small nucleoli. Mitosis were rarely found. The papillary cores contained a variable amount of hyalinized stroma. The neoplasm seemed to reside entirely within the renal pelvis with focal involvement of the renal medulla. Intravascular extension in renal pelvic subepithelial connective tissue was present.
No invasive or in situ component of conventional urothelial carcinoma was identified in the adiacent tissue.

Immunohistochemical Findings: The neoplastic cells were positive for PAX-8, Ck7. The immunohistochemical stains for Cd10, GATA-3, Ck5/Ck6, p63, Ck20 and CDX2 were neagtive.

Diagnosis: Clear cell adenocarcinoma, Mullerian type of the renal pelvis.

Comments: Clear cell adenocarcinoma of Mullerian origin most commonly associates with the neoplasms of the female genital tract. However clear cell adenocarcinoma can occur in urinary tract and rarely is seen in male patient like as happened in our case. This tumor is morphologically identical to its counterpart in the gynecologic tract. It is usually papillary in architecture and ~~is~~ characterized microscopically by a mixture of tubular glands, papillae and cysts. A distinctive characteristic of this tumor is the presence of hobnail cells and abundant cytoplasmic glycogen. Clear cell adenocarcinoma of the female genital tract and of the urinary tract shows typical immunoexpressions of CK7, PAX8 and HNF (Hepatocyte Nuclear Factor-1-beta) and negativity for Gata-3 and CK20. This type of positivity helps to exclude urothelial carcinoma.

It is noteworthy not to mistake these tumors with nephrogenic adenoma which is a lesion that lacks the nuclear atypia and mitotic activity.

Clear cell adenocarcinoma can metastasize to lymh nodes and distal organs, but the prognosis is not well studied due to rarity of cases. Our case has only 4 month of follow up and no recurrence was present.

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AMR Seminar #74

Case – 10

Contributed by: Maria Pia Foschini, M.D.

Short clinical information: 54-year-old man, presenting a huge extra-axial mass located in the right temporo-orbital region.

Case history: A 54-year-old man presented with a huge extra-axial mass, located in the right temporo-orbital region. The adjacent bone presents osteolytic features. On frozen section the lesion was interpreted as possible meningioma.

Macroscopy: A total surgical resection of the lesion was achieved, and the specimen consisted of multiple fragments measuring 7 cm in total. Fragments of soft and whitish tissue were intermingled with bone fragments.

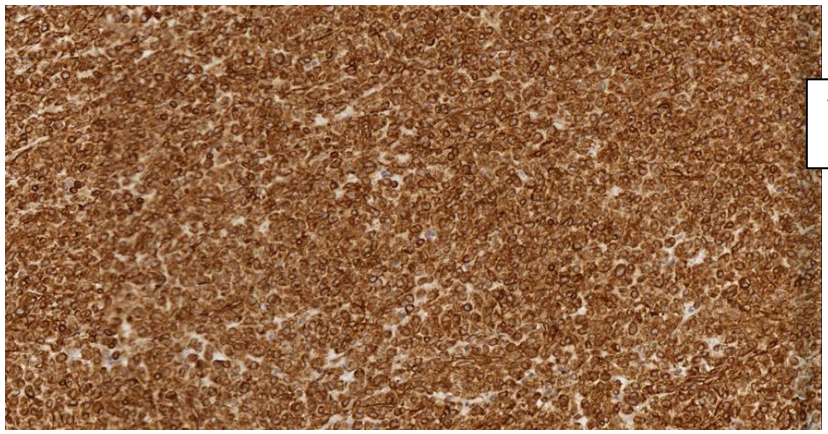
All the surgical tissue was embedded to paraffin for histology.

All the sections obtained presented similar features.

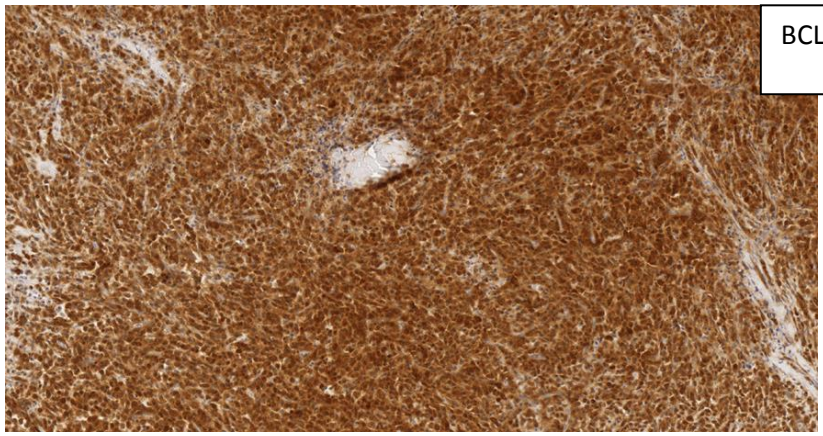
On histology, the lesion was moderately cellular, composed of epithelioid cells, sometimes binucleated, with nuclear atypia. Atypical mitotic figures were frequent, necrosis was focally present.

On immunohistochemistry the following results were obtained:

Positive	**Negative**
Vimentin	Progesterone receptor
CD56	CD34
BCL2	STAT 6
CD138	CD99
EMA focal positivity	CD45, CD20, CD3, CD21, CD23
CD79a	S-100
	MART 1
	HMB45
	GFAP
	Cytokeratins (high and low molecular weight)
	CD68
	Smooth muscle actin

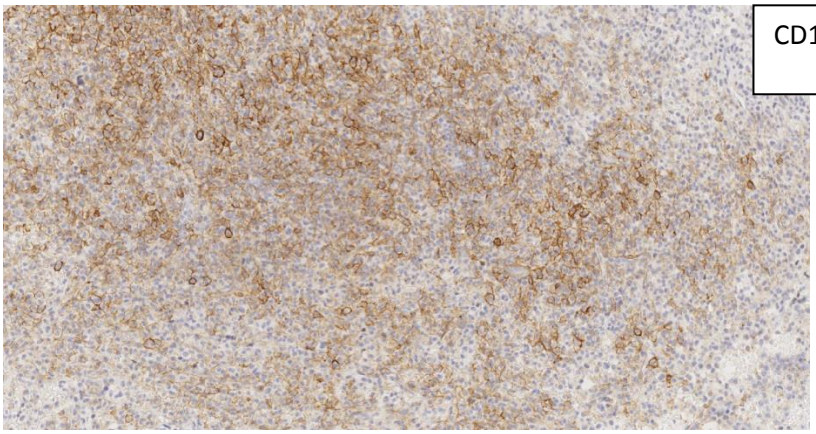


Vimentin



BCL2

CD56



CD138

In addition K chain restriction was observed.

Diagnosis: Anaplastic plasmocytoma.

Comment: Meninges can be site of metastatic tumours, most frequently being of mammary or pulmonary origin.

Therefore, in the present case, a possible secondary meningeal involvement was suggested.

After the diagnosis of anaplastic plasmocytoma, the patient was referred to the Haematology Department and staging was performed. There was no evidence of any other organ involvement. Bone marrow biopsy was within normal limits.

Extramedullary plasmocytomas constitute about 10% of all plasmacellular tumours. In the present case, the lesion was extended to the adjacent bone, therefore it is not easy to define exactly the site of origin. Nevertheless, the majority of the lesion involved the meninges. Therefore, the lesion was considered a primary meningeal anaplastic plasmocytoma.

Meningeal involvement by plasmacell tumour is a rare event. It can occur in patients with multiple myeloma, presenting neurologic symptoms. Even more rarely, extramedullary plasmocytomas can arise primarily in the meninges. Primary meningeal plasmocytomas can present as diffuse leptomeningeal disease or as localized mass. This latter presentation can simulate meningioma. Sometimes the adjacent brain parenchyma can be involved.

Most of the reported cases of meningeal plasmocytoma are classical type. One case only has been reported of blastic plasmacytoid dendritic cell tumour. At the best of our knowledge no cases of anaplastic plasmocytoma affecting the meninges have been reported to date.

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AMR Seminar #74

Case – 11

Contributed by: Masaharu Fukunaga, M.D.

Clinical history: A 57-year-old female was admitted because of lower abdominal pain.

Her past history was uneventful. Image analyses indicated right side paratubal cyst. A laparoscopic excision of the lesion was performed. It attached the broad ligament.

Macroscopic findings: The lesion measuring 50x45x33mm was yellowish, mucinous, solid and cystic.

Immunohistochemical findings: It was positive for calretinin, D2-40, vimentin, AE1/AE3, collagen type IV and negative for ER, PgR. Mib-1 index was less than 1%.

It was positive for alcian blue and was digested by hyaluronidase.

Microscopic findings: This solitary lesion, which was well demarcated with thin fibrous capsule, was characterize by glands, anastomosing gland-like, and slit-like spaces lined by flattened or cuboidal cells that contain cytoplasmic vacuoles. Large cystic spaces were observed in the peripheral area. The lesional cells contain bland, round to oval, mitotically inactive nuclei with no or rare mitotic figures. The stroma was fibrous.

Diagnosis: Adenomatoid tumor of the broad ligament.

Comments: This symptomatic case has been submitted for an educational material. Diagnosis is histologically very straightforward, and it is the most impressive case I have ever seen. However, I could not make a macroscopic diagnosis.

Differential diagnoses include well differentiated papillary mesothelioma and malignant mesothelioma. It is easily distinguished form them because the present tumor lacked papillary pattern and cytological atypia.

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AMR Seminar #74

Case – 12

Contributed by: Thomas Krausz, M.D.

Clinical History: 62-year-old female with history of postmenopausal bleeding and endometrial biopsy diagnosed as grade 3 endometrioid carcinoma. Patient was referred to University of Chicago. Hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node sampling performed. A representative section of the hysterectomy specimen with tumor is submitted for this seminar.

Pathology: Grossly, the hysterectomy specimen contained a partly necrotic tumor (6.7 cm), filling the entire endometrial cavity and invading the full thickness of the myometrium (the submitted slide is histologically representative, but shows less myometrial invasion). Histologically it demonstrates various components, including areas of endometrioid FIGO grade 1 carcinoma and endometrioid FIGO grade 3 carcinoma. Focally, however, it shows areas of undifferentiated carcinoma with discohesive growth pattern. Rhabdoid phenotype is limited to rare tumor cells. The histologic differential diagnosis is between FIGO grade 3 endometrioid carcinoma and dedifferentiated carcinoma of the endometrium.

In order to characterize the neoplasm further, **immunohistochemical study** was performed. The gland-forming differentiated areas express epithelial markers (Cam 5.2, AE1/AE3, EMA) strongly and diffusely, while there is decrease in staining intensity of the undifferentiated areas. All the tumor cells are positive for PAX-8 but ER and PR are entirely negative. p53 is wild type and p16 staining is patchy. There is retained nuclear expression of SMARCB1(INI1) throughout the tumor, but loss of nuclear expression of SMARCA4(BRG1) can be observed in the undifferentiated component. The overall morphologic features together with the loss of BRG1 expression are consistent with the diagnosis of dedifferentiated endometrial carcinoma. Additional stains for mismatch repair proteins demonstrate heterogenous expression of all 4 proteins.
Ovaries, tubes, omentum and lymph nodes were free of tumor.

Diagnosis: Dedifferentiated endometrioid carcinoma with SMARCA4 (BRG1) loss.

Discussion: Undifferentiated carcinoma of the endometrium is defined in the WHO 2014 classification as "a malignant epithelial neoplasm with no differentiation" and is composed of a monotonous population f epithelioid tumor cells with a discohesive pattern. Dedifferentiated endometrial carcinoma, initially described by Silva et al, 2006 (1,2) is a neoplasm of low-grade endometrioid adenocarcinoma juxtaposed with an undifferentiated carcinoma. In such cases, the undifferentiated carcinoma component is thought to be derived from the differentiated endometrioid component. Undifferentiated carcinoma may also occur in a pure form. In the initial study by Silva et al, dedifferentiated/undifferentiated endometrial carcinoma exhibited rhabdoid morphology in 24% of cases.

The majority of undifferentiated carcinomas and the undifferentiated component of dedifferentiated carcinomas lack expression of PAX8, ER and PR but up to 20% of tumors may show focal staining with these markers. The submitted case, in contrast, is PAX-8 positive. PAX-8 was lost in 83% of cases in the series published by Ramalingham et al 2015. Intense immunoreactivity of epithelial markers (EMA, cytokeratin especially cytokeratin 18) in undifferentiated carcinomas is limited to small proportion of the tumor cells in more than 80% of cases. Diffuse expression of EMA and cytokeratins is not typically found but can occur (Murali et al, 2018). In the submitted case there was marked decrease in staining intensity of the undifferentiated component of the tumor compared to the differentiated areas.

The SWItch/Sucrose non-fermentable (SWI/SNF) complex is a highly organized complex comprising >20 proteins encoded by different genes mapped to different chromosomes. The complex is evolutionary highly conserved and is universally expressed in developing and mature human cell types. The SWI/SNF complex is composed of several core subunits including SMARCB1 (INI1) and two catalytic subunits SMARCA4 (BRG1) and SMARCA2 (BRM) which through chromatin remodelling, determines which genes are to be expressed (7,8). Abnormalities of SMARCB1

(INI1) are found in various neoplasms with rhabdoid morphology (7,9). SMARCA4 (BRG1) is mutated in almost all small-cell carcinomas of the ovary, hypercalcemic type with loss of IHC staining for BRG1. Germline mutations in SMARCB1 result in rhabdoid tumor predisposition syndrome-1, and SMARCA4 mutations result in rhabdoid predisposition syndrome-2. A few studies have shown loss of expression of SMARCA4 (BRG1), SMARCB1 (INI1) and SMARCA2 (BRM) in a proportion of dedifferentiated/undifferentiated endometrial carcinomas (3,4,5,6). Ramalingham et al, 2017 (11) found that 32.5% of endometrial dedifferentiated/undifferentiated endometrial carcinomas (40 cases analyzed) were associated with SMARCA4 (BRG1) loss, but only a subset had rhabdoid morphology. Most, but not all, of the SMARCA4 (BRG1)-deficient cases showed concomitant SMARCA2 (BRM) loss. SMARCB1 (INI1) was lost only in 4% of the cases.

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AMR Seminar #74

Case – 13

Contributed by: Alberto Marchevsky, M.D.

Clinical History: The patient is an 80-year-old man with lung adenocarcinoma. There is no diagnostic problem and the slides are sent to illustrate and review the current controversial topic of Spread Through Air Spaces (STAS) in cases of lung cancer. The slides will hopefully show the presence of a few detached tumor cells, singly and in small groups, that were present in airspaces away from the main tumor mass. It will be interesting to hear the opinion of AMR members whether this finding represents an artifact of cases or a recently recognized mode of spread of lung cancer.

AMR Seminar #74

Case – 14

Contributed by: Thomas Mentzel, M.D.

Clinical History: A 69-year-old male patient developed a large retroperitoneal neoplasm with infiltration of the right kidney. Grossly, a 30 cm measuring 5 kg multinodular lesion with areas of necrosis and myxoid changes has been described (see enclosed pictures).

Pathological Findings: Histologically, a variable cellular neoplasm was seen composed of atypical spindle-shaped tumour cells containing enlarged and also hyperchromatic nuclei and scattered multinucleated tumour giant cells were present in hypercellular areas. Tumour cells were set in a myxoid stroma containing numerous narrow vessels and band-like areas of necrobiosis and necrosis were present. Immunohistochemically, neoplastic cells stained positively for CD34, EMA and MUC4, whereas STAT6, pancytokeratin, TLE1, S-100 protein, MDM2 and CDK4 were all negative.

Diagnosis: "low-grade" fibromyxoid sarcoma with morphological signs of progression

Comments: Low-grade fibromyxoid sarcoma represents a well-known and characteristic soft tissues neoplasm of usually bland cytomorphology with a significant potential for local recurrences and metastases especially in long time follow-up studies. The well-circumscribed neoplasms have firm and homogenous cut surfaces without necrosis or areas of haemorrhage and are composed of bland spindled fibroblastic tumour cells set in an alternating myxoid and fibrous stroma with arcades of vessels. In a number of cases giant rosettes are observed surrounded by rather round and epithelioid cells. Occasional cases contain areas with features of sclerosing epithelioid fibrosarcoma. Immunohistochemically, tumour cells stain positively for MUC4, what is very helpful in the distinction of a number of benign and malignant mesenchymale neoplasms, and often for EMA and CD34, whereas cytokeratins, S-100 and desmin are usually negative. Low-grade fibromyxoid sarcoma represents a translocation-associated sarcoma showing t(7;16) (q34;p11) and t(11;16) (p11;p11) which juxtaposes the FUS gene either with the CREB3L2 or with the CREB3L1 genes. Rarely, cases with increased cellularity, increase nuclear atypia and pleomorphism have been reported. The shown case represents an example of low-grade fibromyxoid sarcoma arising in the retroperitoneum and given the anatomic location the neoplasm grew to a considerable size (as cases of atypical lipomatous tumour and dedifferentiated liposarcoma). The morphological progression with increased cellulary, atypia, pleormorphism and the presence of necrosis is a time-dependent phenomenon (as dedifferentiation in lipogenic neoplasms).

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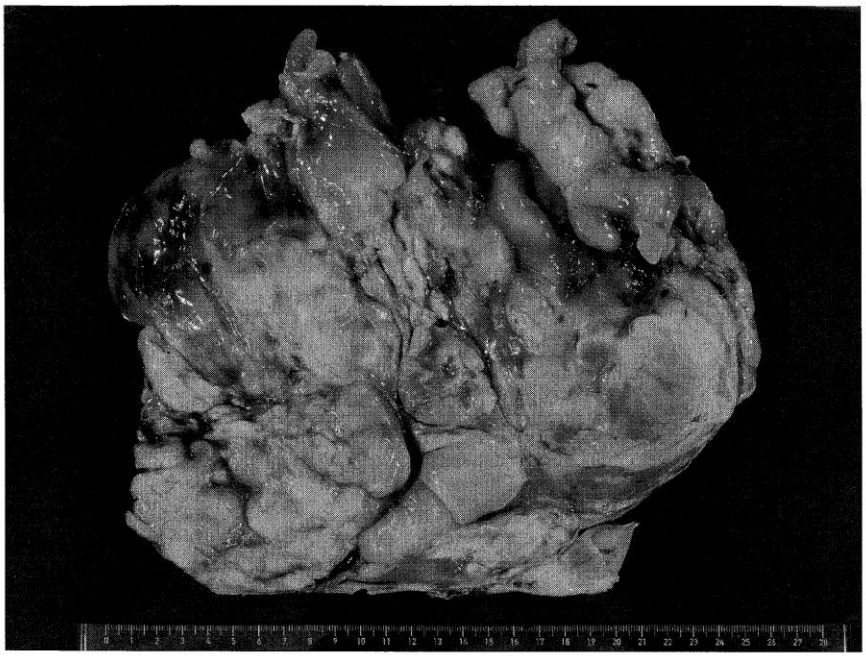

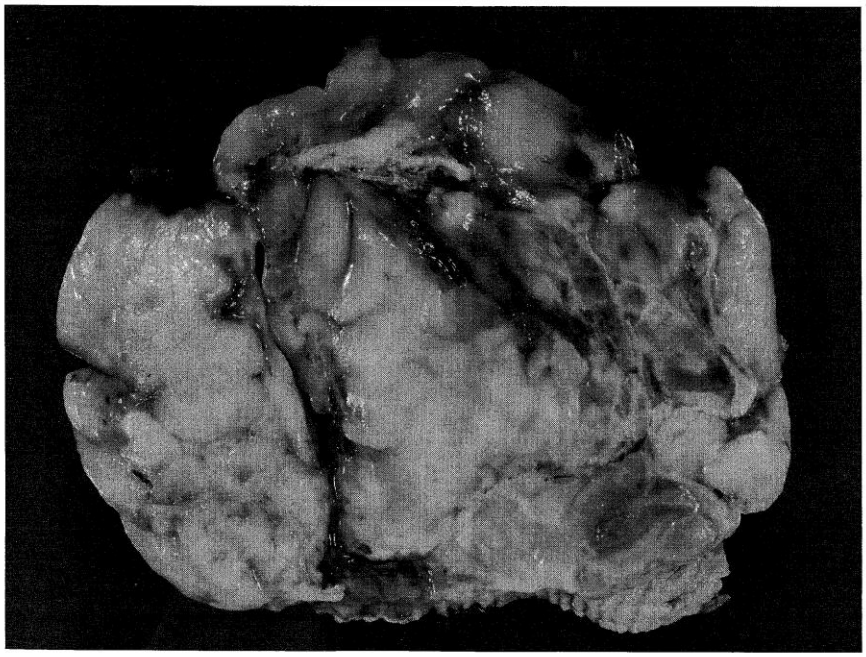

AMR Seminar #74

Case – 15

Contributed by: Michal Michal, M.D.

Clinical History: Male, 57 years of age, had a lipomatous tumor on the shoulder measuring 11x10x5 cm. The lesion was well delimited by a thin fibrous layer.

The tumor has conspicuous variability in the fat cell size, with occasional, mildly atypical hyperchromatic nuclei. Some of the nuclei are microvacuolated (Lochkern change). A subset of the adipocyte nuclei stains with p53 antibody. There is no spindle cell stroma present, some cells show lipoblast-like features. There are also rare cells with single cell fat necrosis and foam cell reaction. The tumor does not have MDM2 amplification by FISH but shows heterozygous gene deletion of RB1 gene. No mutation of TP53 gene is present.

Diagnosis: Dysplastic lipoma (1), also called anisometric cell lipoma (2,3).

Comment. We have several cases of this tumor that occurred in patients with history of retinoblastoma. It is the only lipomatous tumor we have seen in association with this ocular neoplasm and it is possible that most, or perhaps all lipomatous neoplasms developing in these patients are dysplastic lipomas.

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AMR Seminar #74

Case – 16

Contributed by: Michal Michal, M.D.

Clinical History: 17-year-old female patient with multiple tumors and neurofibromatosis had an excision of a subcutaneous lesion on the back.

The tumor is typical plexiform neurofibroma. Inside of the tumor there are few clear cell-looking myxoid neoplastic nodules. On high power, virtually hundreds of multivacuolated amoeba-like cell can be seen inside of these nodules. These cells stained positively with CD34 and Glut1 antibodies.

Diagnosis: Plexiform neurofibroma with multivacuolated mucin-filled cells

Comment: These multivacuolated amoeba-like cell were seen in 10% of plexiform neurofibromas (in 11 out of 109 cases) in our study **(1)** and seem to be characteristic of these tumors. They could be of diagnostic help especially in fine needle biopsies of soft tissues. Morphologically similar multivacuolated cells can be seen in inflammatory fibroblastic sarcomas.

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AMR Seminar #74

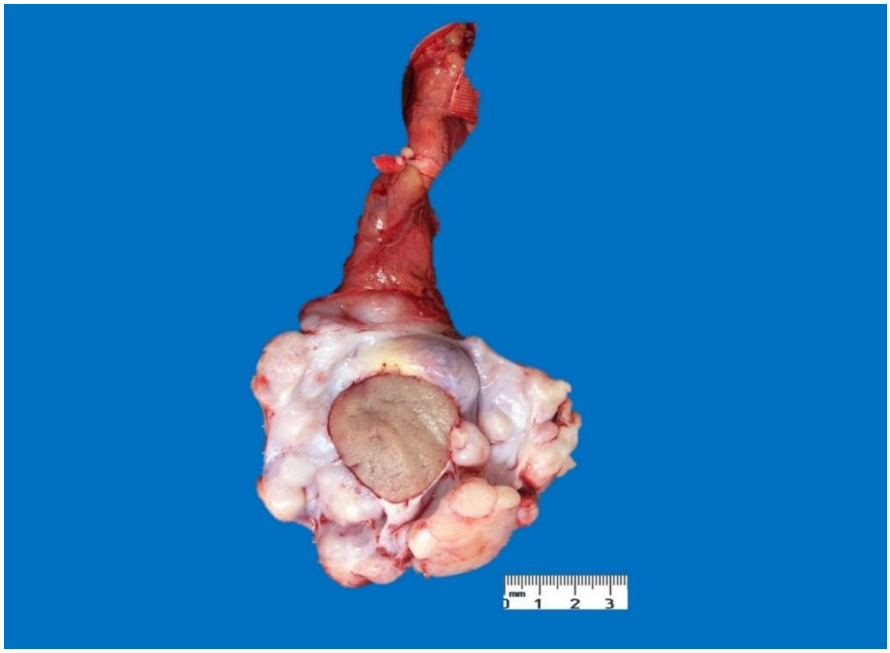
Case – 17

Contributed by: Delia Perez-Montiel, M.D.

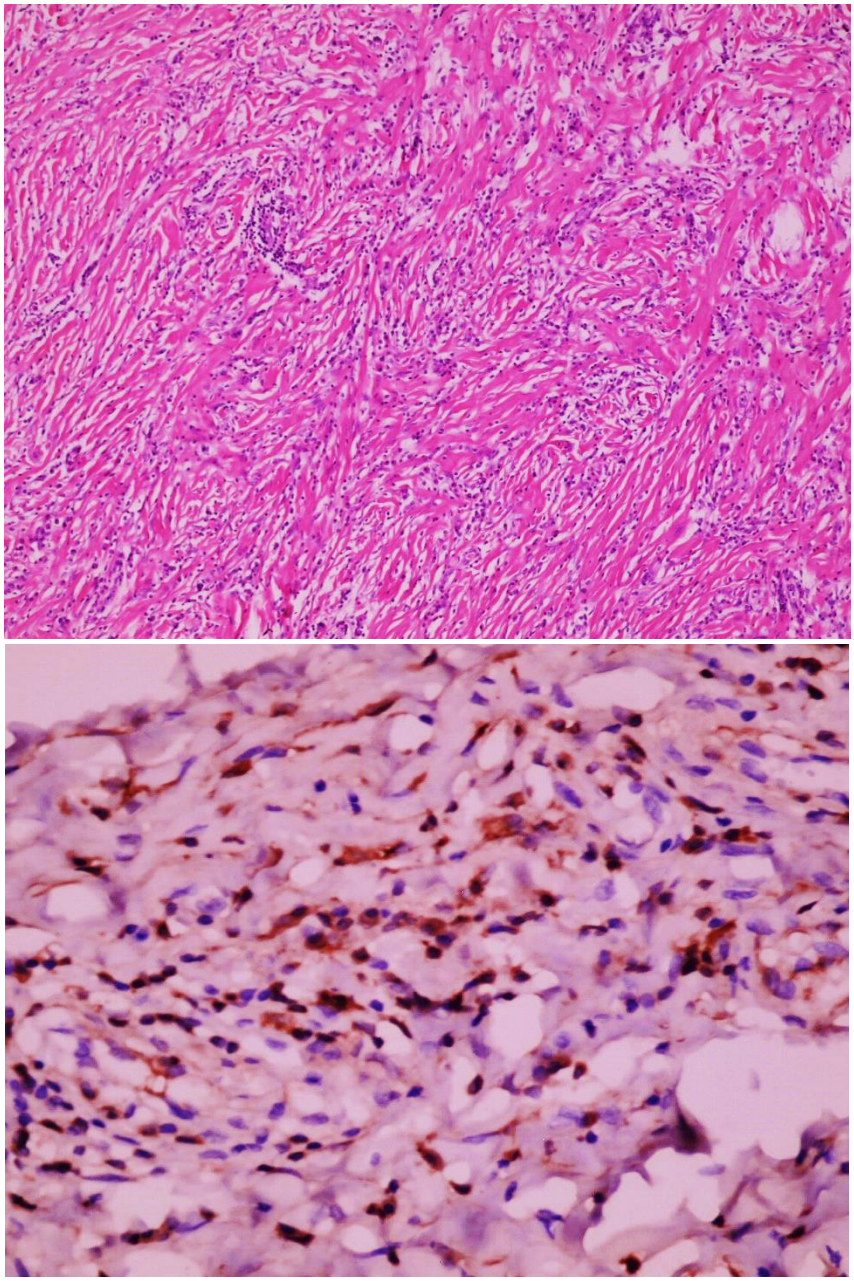
Clinical History: A 20-year-old male with slow testicular growing of 6 months. Serum tumor markers negatives.

Pathology findings: A radical orchiectomy was received. External surface was not remarkable. Cut surface shows multiple nodules on tunica vaginalis. These nodules were white, firm, with leiomyomatous appearance. Testicular parenchyma was not affected.

Microscopically a densely arranged myofibroblastic proliferation with cellular and hypocellular areas with dense collagen was identified. Other areas show a whorled pattern with similar myofibroblastic cells. Mixed in the tumor, inflammatory cells were identified with predominant plasma cells and less number of lymphocytes. The lesion has a well delimited borders with focally invasive appearance. No mitosis was seen. Testicular parenchyma with not alteration.



Immunohistochemistry stains: Stromal cells were positive to vimentin, negative to CD34, Actin, PS100 and STAT6. Inflammatory cells were positive diffuse to CD138 and IgG4 predominance.



IgG4 immunostain

Diagnosis: Paratesticular fibrous pseudotumor associated to IgG4 related disease.

Comment: Paratesticular fibrous pseudotumor is a benign tumor-like lesion confined to intrascrotal, paratesticular areas. It is believing that represent a reactive process affecting mostly the tunica vaginalis and less commonly in the epididymis, spermatic cord, or tunica albuginea. Although the lesion is often associated with a history of hydrocele, trauma, or infection, it clinically mimics a testicular malignancy, which may result in radical surgery as our case. Its pathogenesis remains controversial and numerous designations have thus been used for the lesions. These include "fibrous pseudotumor," "nodular and diffuse fibrous

proliferation," "chronic proliferative periorchitis," "inflammatory pseudotumor," and "nodular periorchitis," among others. Less than 200 cases have been reported to date.

Recently, because of the similarities between this lesion and chronic fibroinflammatory processes associated to IgG4 related sclerosing disease in other organs, has been postulated than paratesticular fibrous pseudotumor is a part of the spectrum of so-called immunoglobulin G4-related diseases (IgG4-RD). Some cases in this location has been reports associated to high serum concertation of IgG4 and isotype distribution.

After the diagnosis, the patient was sent to the clinical laboratory and high serum concentration of IgG4 was demonstrated. MIR was negative for another lesion in the rest of the organs.

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AMR Seminar #74

Case – 18

Contributed by: Cesar Moran, M.D.

Clinical History: 47-year-old man with a pleural tumor. Imaging showed the presence of a large pleural based mass.

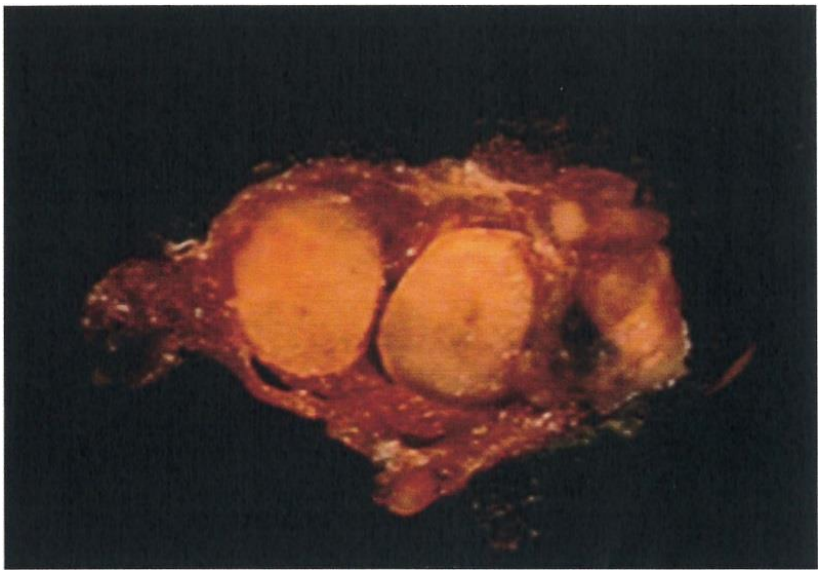
AMR Seminar #74

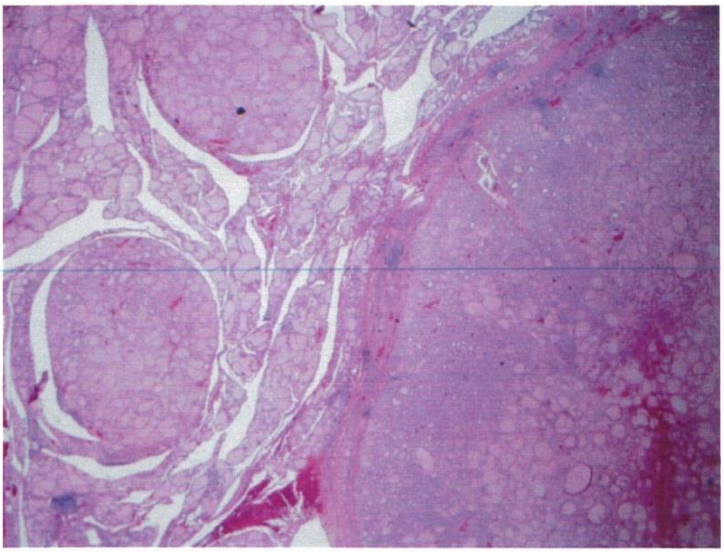
Case – 19

Contributed by: Vania Nose, M.D.

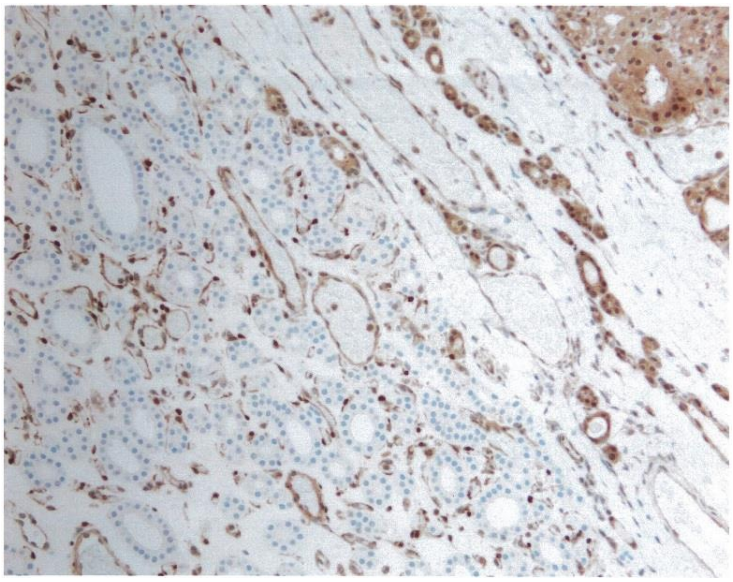
Clinical History: 23-year-old woman with slowly enlarging thyroid followed for several years; now somewhat symptomatic; no h/o radiation to her neck. Mother had a subtotal thyroidectomy at the age of 16.

Submitted to total thyroidectomy





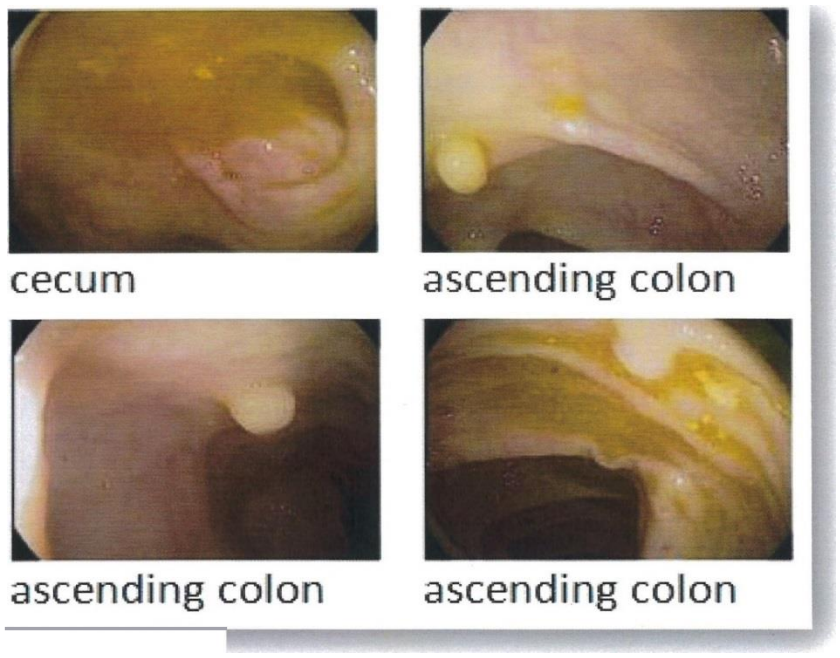
Diagnosis: Multiple Adenomatous Nodules and Lymphocytic Thyroiditis and Follicular Thyroid Carcinoma, Minimally Invasive, with focal capsular invasion right lobe, two foci: superior pole (0.5 em) and mid pole (1.2 em).



PTEN loss by immunohistochemistry. Endotelial cells and adjacent thyroid with preserved PTEN immunoexpression.

Patient suggested to get *PTEN* mutation analysis and was found to have germ line mutation of *PTENgene.*

Colonoscopy showed numerous polyps.



PTEN Hamartoma Tumor Syndrome (PHTS)

PTEN hamartoma tumor syndrome (PHTS) is the molecular diagnostic term describing patients with diverse syndromes. It is an autosomal dominant disorder caused by a germline mutation in *PTEN (phosphatase and tensin homolog, deleted on chromosome 10).* PTEN Hamartoma Tumor Syndrome includes Cowden syndrome (CS), Bannayan-Riley Ruvalcaba syndrome (BRRS), Proteus syndrome (PS), and Proteus-like syndrome. First described in 1963 (named after the family in which it was described).

CS is the most common syndrome and characterized by the development of multiple hamartomas and with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s.

BRRS is a congenital disorder characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis.

PS is a complex, highly variable disorder involving congenital malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

Etiology: The diagnosis of PHTS is made only when a *PTEN* pathogenic variant is identified. When accrued from tertiary referral centers, up to 85°/o of individuals who meet the diagnostic criteria for CS and 65°/o of individuals with a clinical diagnosis of BRRS have a detectable *PTEN* pathogenic variant. However, in prospective accrual series, from both academic and community clinical settings, approximately 25°/o of individuals who meet the clinical diagnostic criteria for CS have a germline *PTEN* pathogenic variant. Preliminary data also suggest that up to 50°/o of individuals with a Proteus-like syndrome and up to 20°/o of individuals who meet the clinical diagnostic criteria of Proteus syndrome have an identifiable *PTEN* pathogenic variant.

Epidemiology: Although CS has a reported incidence of 1 in 200,000, it is likely that it is actual more common and that cases are overlooked because of the complex clinical criteria for CS, the fact that many of the manifestations of CS are common in the general population, and the finding that only about half of the patients with CS have a known family history. However, a diagnosis of CS is important because it confers a significant risk for cancer. Once a diagnosis of CS is made, there are screening and genetic counseling guidelines outlined by the NCCN. Thus, recognition of CS is important so that cancer screening and genetic counseling can be initiated.

Genetic susceptibility: Germline mutations in *PTEN* were first described in patients with CS in 1997. *PTEN* is a tumor suppressor gene that maps to 1Oq23.3 and encodes a 403 amino acid dual-specificity (lipid and protein) phosphatase. While most cases are inherited in a family for generations, following an autosomal dominant pattern, at least 10°/o and perhaps as many as 44°/o of cases are due to a new (de novo) mutation. Approximately 85°/o of patients with CS harbor intragenic mutations of *PTEN* or mutations in the promoter region.

Clinical features: Clinical presentations can vary dramatically from patient to patient, even among those in the same family. Features-of this ceAeition that may assist in-diagnosis-prior to cancer development can be subtle and difficult to recognize. Clinical criteria for CS based on guidelines put forth by the International Cowden Consortium have been delineated by the National Comprehensive Cancer Network (NCCN) and include pathognomonic, major, and minor criteria.

Adult Lhermitte-Duclos disease (LDD), autism spectrum disorder with macrocephaly, and 2 biopsy-proven trichilemmomas are all pathognomonic for CS.

The major criteria include breast cancer, mucocutaneous lesions (trichilemmomas, multiple palma-plantar keratoses, multifocal or extensive oral mucosal papillomatosis, multiple cutaneous facial papules, and macular pigmentation of the glans penis), endometrial cancer, nonmedullary thyroid cancer, macrocephaly, and multiple gastrointestinal hamartomas or ganglioneuromas.

The minor criteria include mental retardation, autism spectrum disorder, fibrocystic disease of the breast, other thyroid lesions (adenomas and nodular hyperplasia), lipomas, fibromas, renal cell carcinoma, and uterine fibroids.

CS is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, and endometrium. Affected individuals usually have macrocephaly, trichilemmomas, and papillomatous papules, and present by the late 20s. The lifetime risk of developing breast cancer is 85o/o. Moreover, the average age at diagnosis is between 38 and 46 years, younger than patients with sporadic breast cancer. The lifetime risk for thyroid cancer (usually follicular, rarely papillary, but never medullary thyroid cancer) is approximately 35°/o. The risk for endometrial cancer, although not well defined, may approach 28o/o. Although breast, endometrial, and thyroid malignancies are the most frequent cancers in CS patients, patients with CS also appear to be at increased risk for developing renal cell carcinoma, melanoma, and glial tumors.

BRRS is characterized by macrocephaly, intestinal hamartomatous polyposis, lipomas, and pigmented macules of the glans penis.

PS is a disorder involving malformations and hamartomatous overgrowth of multiple tissues, as well as connective tissue nevi, epidermal nevi, and hyperostoses.

Proteus-like syndrome is undefined but refers to individuals with significant clinical features of PS who do not meet the diagnostic criteria for PS.

Pathognomonic lesions	**Major criteria**	**Minor criteria**
1. Any single pathognomonic criteria: trichilemmomas, acral keratosis, papillomatous papules or adult Lhermitte-Duclos disease (cerebellar gangliocytomas):	Macrocephaly (>97th percentile)	Mental retardation
- 6 or more facial papules of which 3 or more trichilemmoma	Breast carcinoma (25-50% of females)	Fibromas or lipomas; soft tissue tumors
- Facial papules and oral mucosa papillomatosis	Thyroid carcinoma (3-10%)	Thyroid hyperplastic nodules, and multiple adenomatous nodules
- Oral mucosal papillomatosis and acral keratosis	Endometrial carcinoma (5-10%)	Urogenital tumors, renal cell carcinoma
- 6 or more acral keratoses		
3. One major or three or more minor criteria		
4. Four or over four minor criteria		
5. Adult Lhermitte-Duclos disease (cerebellar gangliocytomas)		

Macroscopy: Thyroid pathologic findings in patients with PHTS that normally affect the follicular cells include multinodular goiter, multiple adenomatous nodules (MAN), follicular adenoma, follicular carcinoma, and less frequently papillary carcinoma. Follicular carcinoma is an important feature in CS and BRRS. Per the diagnostic criteria for CS, follicular carcinoma is a major criterion, and multinodular goiter, adenomatous nodules, and follicular adenomas are minor criteria, with a frequency of 50°/o to 67°/o.

In a recent study evaluating thyroidectomy specimens from patients with CS and Bannayan-Riley Ruvalcaba syndrome, Laury et al found that multiple adenomatous nodules were the most common finding (present in 75°/o), followed by papillary thyroid carcinoma (PTC; 60°/o), lymphocytic thyroiditis (55°/o), C-cell hyperplasia (55°/o), follicular carcinomas (45°/o), follicular adenomas (25°/o), and nodular hyperplasia (25°/o).

Multiple adenomatous nodules are characteristic findings in these syndromes, and present grossly as multiple firm yellow-tan well-circumscribed nodules. These nodules are multicentric, bilateral, well-circumscribed unencapsulated features like follicular adenomas. These tumors are more frequently multicentric. Most carcinomas arise in a background of MAN. Although cancer risk in BRRS was expected to be like the general population, Laury et al found 4 cases of follicular thyroid carcinoma (67°/o), showing that this type of carcinoma was more frequent in the pediatric population; we believe that these patients should follow the same management guidelines as CS. Immunohistochemistry for PTEN shows loss of staining of the follicular cells.

MerluUary thyroid carcinoma (MTC) is not considered part of the spectrum of PHIS however, earlier studies, including two studies by us, have identified C-cell hyperplasia (CCH) in individuals affected with this syndrome.

Careful phenotyping gives further support for the suggestion that BRRS and CS are actually one condition, presenting at different stages.

Histopathology: The most common histologic findings in patients with CS are the presence of multiple adenomatous nodules (100°/o), follicular adenomas (38°/o), nodular hyperplasia (50°/o), lymphocytic thyroiditis (50°/o), follicular carcinoma (25°/o), and PTC (63°/o).

Distinctive and characteristic findings in PHTS include multiple unique adenomatous nodules in a background of LT, and C-cell hyperplasia. The constellation of histologic findings in thyroidectomy specimens from CS is unusual, and although non-specific for CS, raises the possibility of a diagnosis of CS.

There were no morphologic differences between the thyroid findings in CS and BRRS. Also, there was no correlation between specific *PTEN* germline mutations and pathologic findings.

From Laury et al, 2011	Total Cases (20)	CD (14)	BRRS (6)
Age at diagnosis	33.7 (9-76) y	41.7 (13-76) y	15 (9-23) y
Multiple Adenomatous Nodules	75°/o (15)	85o/o (12)	50°/o (3)

Follicular Carcinoma	45°/o (9)	35 °/o (5)	66°/o (4)
Follicular Adenoma	25 °/o (5)	35 0/0 (5)	0
Lymphocytic Thyroiditis	55°/o (11)	43 °/o (6)	83o/o (5)
Papillary Thyroid Carcinoma	60°/o (12)	64°/o (9)	50°/o (3)
C-cell Hyperplasia	55°/o (11)	43°/o (6)	83°/o (5)
Nodular Hyperplasia	25°/o (5)	28°/o (4)	17°/o (1)

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AMR Seminar #74

Case – 20

Contributed by: Brian Rubin, M.D.

Brief Clinical History: 37-year-old woman with an abdominal wall mass involving the soft tissues of the abdominal wall and measuring 5 cm in greatest dimension.

Clinical History: The patient is a 37-year old woman with no significant past medical history who presented 2 months prior to resection with a painless "lump" involving the right side of her abdominal wall. The lesion was getting progressively bigger so she sought medical attention. MRI showed a 4.2cm enhancing mass in the right abdominal wall musculature. The mass was partially mobile. The patient underwent core needle biopsy which was inconclusive and signed out as "low-grade mesenchymal neoplasm with myoid differentiation". 2 months after presenting to her physician, she underwent a wide local excision with primary closure and had an uneventful post-operative course.

Gross Pathology: The gross specimen consisted of an ellipse of skin overlying soft tissue. On sectioning, there was a well-circumscribed mass measuring 5. 0 x 4. 8 x 3.8 cm. The mass was not described any further. The prosector did however paint the margins five different colors.

Histology: The lesion is well circumscribed and partially encapsulated and surrounded by fascia and skeletal muscle. The lesion is variably cellular and consists of fascicles of benign/low-grade appearing spindle cells set in a variably collagenous and myxoid stroma and admixed with numerous small, unremarkable blood vessels and occasional lymphocytes. The lesional cells have elongated nuclei with finely stippled chromatin and small nucleoli, and inconspicuous cytoplasm. There is no mitotic activity, cytologic pleomorphism or necrosis.

Immunohistochemistry: Immunohistochemical studies revealed about 75% of lesional cells to be positive for desmin in a myofibroblastic pattern with filamentous staining (in contrast to the homogenous staining of tumor cells showing smooth muscle differentiation). Smooth muscle actin, ALK, MUC4, CD34, beta catenin, STAT6, ER, S-100, AE1/AE3, cathepsin-K, CD31, ERG, HMB-45, and MDM2 were negative. The large amount of IHC performed is reflective of the reality that I did not have a good handle on the diagnosis.

Molecular Diagnostics: *AHRR-NCOA2* gene fusion demonstrated by next generation sequencing/modified Archer gene fusion panel.

Diagnosis: Angiofibroma of Soft Tissue

Discussion: Angiofibroma of soft tissue was first described as an entity in 2012 in a series of 37 cases by Adrian Marino-Enriquez and Chris Fletcher (1). There were 25 female and 12 male patients, 6-86 years of age (median, 49y). Most tumors arose as slowly growing, painless masses involving the soft tissues of the extremities, most commonly the lower extremity, and often close to joints or involving fibrotendinous tissue around joints. Other, less common sites included shoulder, back, pelvic cavity, trunk (paraspinal), pectoralis major, inguinal region, breast, and abdominal wall (as with the case presented here). Most lesions were circumscribed and ranged in size from 1.2 to 12 cm (median, 3.5 cm). The histological appearance was described as "remarkably consistent" and "characterized by two components: a relatively uniform proliferation of bland, spindle-shaped cells with inconspicuous cytoplasm and ovoid-to-tapering nuclei set in a variably collagenous or myxoid stroma and a prominent vascular network composed of numerous small, branching, thin-walled blood vessels, often accompanied by medium-sized round or irregular and ectatic vessels". Low level mitotic activity (1-4/10 hpf) was seen in 9 cases and mild "degenerative" nuclear atypia was found in only 5 cases. IHC revealed epithelial membrane antigen, at least focally, in 44%, CD34 and SMA in 14%, and desmin 11%; none expressed S-100. Treatment consisted of simple excision (29 cases), which I interpret as marginal excision, wide excision (6 cases), or amputation (1 case). Follow-up information was available for 28 patients with a mean of 51.9 months. Most patients were alive with no evidence of disease, irrespective of margin status. Four patients developed local recurrences at 9, 12, 36, and 120 months and one of these cases was associated with extensively positive surgical margins. No patient developed metastasis.

Marino-Enriquez and Fletcher also noted the presence of a balanced, t(5;8) reciprocal translocation in 5 of 6 cases tested by cytogenetics. Their report was quickly follow-up by a report by Jin and colleagues (Fred Mertens senior author) identifying an in-frame gene fusion involving *AHRR* and *NCOA2* genes, corresponding to the t(5;8) in 7 of 14 cases (50%)(2). This gene fusion has not been identified in other neoplasms so it appears to be specific to angiofibroma of soft tissue. *AHRR* and *NCOA2* both encode transcription factors. *AHRR* encodes the aryl hydrocarbon receptor repressor, a key regulator of the aryl hydrocarbon receptor. *NCOA2* encodes nuclear receptor coactivator 2, which is a coactivator of nuclear hormone receptors. *AHRR* has been implicated as a tumor suppressor while the carboxy terminus of *NCOA2* is involved in several fusions involving leukemias and sarcomas (e.g. *HEY1-NCOA2* in mesenchymal chondrosarcoma and *PAX3-NCOA2* in alveolar rhabdomyosarcoma). The pathogenetic mechanisms by which AHRR-NCOA2 fusion protein leads to cancer has not been elucidated and will require further study.

The clinical, histological, and immunohistochemical features of angiofibroma of soft tissue are not very distinctive, essentially consisting of a bland fibroblastic proliferation associated with a prominent vascular component. The differential diagnosis therefore includes cellular angiofibroma, solitary fibrous tumor, low-grade fibromyxoid sarcoma, and myxoid liposarcoma. Cellular angiofibroma arises in the perineal region so is unlikely to cause confusion with angiofibroma of soft tissue very often. It is also positive for estrogen receptor by IHC which I find helpful. The other lesions in the differential diagnosis arise more broadly and may present diagnostic problems more often. However, most cases should be able to be sorted out using classical histological features. For morphologically difficult cases, the following tests might be helpful. STAT6 IHC positivity or demonstration of *NAB2-STAT6* gene fusion is helpful in diagnosing solitary fibrous tumor. MUC4 IHC positivity and/or *EWSR1* gene region rearrangement, and/or presence of *EWSR1-CREB3L1* or *EWSR1-CREB3L2* gene fusion is helpful in diagnosing low-grade fibromyxoid sarcoma. The presence of either *FUS-DDIT3* or *EWSR1-DDIT3* gene fusion or *DDIT3* gene region reagent is helpful in diagnosing myxoid liposarcoma. Of course, demonstrating the presence of *AHRR-NCOA2* gene fusion appears to be unique to angiofibroma of soft tissue so if this fusion can be demonstrated then it's pretty much a slam dunk.

Follow-up: No recurrences or metastasis 5 months post-resection.

Summary: Angiofibroma of soft tissue is a recently described benign soft tissue tumor with a female predominance that typically arises in the extremities. It has limited potential for local recurrence but no metastatic potential. The histological and immunohistochemical features are non-specific – a benign appearing fibroblastic/myofibroblastic neoplasm with prominent blood vessels. However, *AHRR-NCOA2* gene fusion appears to be unique and diagnostic of angiofibroma of soft tissue. In the absence of *AHRR-NCOA2* gene fusion (approximately 50% of cases), classical histological features and the exclusion of other neoplasms in the differential diagnosis is required.

References:

1. Marino-Enriquez A, Fletcher CDM. Angiofibroma of soft tissue: clinicopathologic characterization of a distinctive benign fibrovascular neoplasm in a series of 37 cases. Am J Surg Pathol 2012;36;500-508.
2. Jin Y, Moller E, Nord KH, et al. Fusion of the *AHRR* and *NCOA2* genes through a recurrent translocation t(5;8)(p15;q13) in soft tissue angiofibroma results in upregulation of aryl hydrocarbon receptor target genes. Genes Chromosomes Cancer. 2012;51:510-520.

AMR Seminar #74

Case – 21

Contributed by: Niels Rupp, M.D.

Clinical History: Female, 70-years-old. Swelling of the left parotid gland.

Localization: Left parotid gland.

Tumor size: 1.9 cm diameter.

Histopathology: relatively circumscribed / virtually encapsulated cellular salivary gland neoplasm with epithelial-myoepithelial differentiation. The stroma is fibrous, and in some places, reminiscent of a jigsaw pattern. The cells are medium large and show some atypia (solid / apocrine touch). Focally there are tumor complexes in association with blood vessels in the capsule (status post fnp is known). Focal calcifications and intraluminal secretions.

Immunohistochemistry: MIB-1 worrisome. SOX10 diffusely positive, biphasic population in p63 - / EMA / CD117; PLAG-1 negative, beta- catenin (nuclear negative), ARID1A (partial loss)

Next Generation Sequencing (two populations): *HRAS*-Mutation
(p.Q61R) in both populations; ARID1A loss (terminating mutation) in only one population;
No *HMGA2* or *PLAG1* rearrangement

Diagnosis: (Low-grade) Epithelial-myoepithelial carcinoma, corroborated by *HRAS*-Mutation with additional heterogeneous terminating *ARID1A*- Mutation.

Comment: To the best of my knowledge, a heterogeneous terminating *ARID1A* mutation has not been described in epithelial-myoepithelial carcinoma of the salivary gland in the literature so far. If there is a potential association with this uncommon morphology can only be presumed.

References:

1. Sebastiao APM, Pareja F, Kumar R, et al. Genomic analysis of recurrences and high-grade forms of polymorphous adenocarcinomas. *Histopathology.* 2019.

2. El Hallani S, Udager AM, Bell D, et al. Epithelial-Myoepithelial Carcinoma: Frequent Morphologic and Molecular Evidence of Preexisting Pleomorphic Adenoma, Common HRAS Mutations in PLAG1-intact and HMGA2-intact Cases, and Occasional TP53, FBXW7, and SMARCB1 Alterations in High-grade Cases. *Am J Surg Pathol.* 2018;42:18-27.

3. Chiosea SI, Miller M, Seethala RR. HRAS mutations in epithelial- myoepithelial carcinoma. *Head Neck Pathol.* 2014;8:146-150.

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AMR Seminar #74

Case – 22

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

Clinical History: A 53-year-old HIV+ man presented with fever, as well as pain and swelling of his posterior hard palate. Although born in Mexico, he has been a resident of the United States for > 20 years. At the time of presentation he was found to be hypotensive and tachycardic. A 5-6 cm ulcerated irregular mass was seen involving the hard palate, buccal mucosa and extending to the gingiva on the upper and lower bridge. The patient had no anterior or posterior cervical lymphadenopathy.

CT revealed a L maxillary sinuses mass that had eroded the medial wall. Chest X-ray revealed mediastinal, axillary, and perihilar lymphadenopathy. Biopsies of the palate and maxilla were obtained and your slide is from the hard palate. No flow cytometry was performed.

Pathologic Findings: A dense, solid population of mitotically active medium to large cells is present just below the epithelial surface. Cells have rounded nuclei with smooth contours, coarsely clumped chromatin, and variably present macronucleoli. Most have a moderate amount of amphophilic cytoplasm. Many nuclei are eccentrically placed within the cells, but features of mature plasma cells are rare. A perinuclear clear zone (hof) is absent. Individual cell necrosis is present, but a so-called starry sky pattern is not seen. Multinucleated cells are largely absent. Immunohistology results:

● positive: CD138, VS38c, vimentin, EBV-EBER by in-situ hybridization

● negative: CD3, CD20, CD56, cytokeratin AE1/3, CD10, bcl-1, bcl-2, CD5, bcl-6, CD23, CD99, actin, desmin, cytokeratin 7, CD30, S-100, HMB-45, CD79a.

Diagnosis: Plasmablastic Lymphoma [PL] of the Oral Cavity.

Comments: Plasmablastic Lymphoma is one of the known AIDS-associated non-Hodgkin lymphomas. The others include: a.) diffuse large B-cell lymphoma (DLBL), b.) Burkitt Lymphoma, c.) Primary Effusion Lymphoma and d.) Plasmablastic Lymphoma Associated with Multicentric Castleman's disease. The most recent WHO classification (2017) lists plasmablastic lymphoma (PL) as an aggressive mature B-cell neoplasm with a negative CD20 phenotype. The relative risk of B-cell NHL among HIV positive individuals is markedly increased (reported as 80-100 times greater) compared to the non-HIV population. It may occur in patients with other causes of immunodeficiency.

The initial report of this neoplasm and its association with HIV was recognized by Delecluse et al. over 20 years ago when they presented 16 patients with a lymphoma of the oral cavity, and called it PLOC (plasmablastic lymphoma of the oral cavity). Only 2 of their patients had bone marrow involvement, and unlike multiple myeloma none had a serum monoclonal protein. Cells PL are essentially monomorphic with little variation in nuclear or cytoplasmic appearance. Most have immunoblastic morphology with coarse chromatin, a distinct nucleolus, and a plasma cell immunophenotype. Some examples show multinucleation and binucleation. Cells with features of maturing plasma cells are present, but often inconspicuous. Giemsa staining reportedly will allow one to see a paranuclear cytoplasmic hof. Unlike plasma cell myeloma PL is rapidly growing with a high mitotic index with some authors reporting a "starry sky" pattern in most cases, while others report it to be an infrequent finding.

A large series by Dong et al. (13 patients; median = 41 yrs.; M:F =5.5:1) showed all with extramedullary disease, and 85% with extranodal tumor at time of presentation with the oral cavity being the most common site

(46%) followed by bone/soft tissue (31%), and GI tract (23%). All patients with follow-up died of disease (DOD) within 3 years. The initial report of Delecluse showed an even more aggressive behavior with 82% of patients DOD in 1 year. The typical immunophenotype is negative staining for CD3, CD20, PAX-5, and bcl-6, variable staining with CD45, CD79a, and EBV (60-75% +), and almost universal expression of plasma cell markers CD138, and VS38c, IRF4/MUM1. Ki-67 index usually > 90%.

Differential diagnosis includes: undifferentiated carcinoma, diffuse large B-cell lymphoma (DLBL) – immunoblastic type, anaplastic plasmacytoma (plasmablastic myeloma), Burkitt lymphoma with plasmacytoid differentiation, and possibly even melanoma. Carcinoma can be excluded with keratin staining. DLBL has less of a plasmacytic appearance than PL, and is consistently CD20+. Extramedullary large cell transformation of myeloma with plasmablastic morphology usually occurs after a prolonged interval as multiple myeloma. These tumors typically arise in immunocompetent rather immune suppressed individuals. Plasmablastic myeloma (PM) shows only a minor number of plasmablasts with nuclei that are often more pleomorphic than those encountered in PL. Also, PM is consistently negative for EBV. Burkitt lymphoma is typically negative for plasma cell markers, and CD20/bcl-6 +. Rarely, patients with primary effusion lymphoma (an HHV-8 + lymphoma) may develop a tissue mass, or present with a tissue mass and later develop a cavitary lymphomatous effusion. HHV-8 staining should exclude these cases from diagnostic consideration.

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AMR Seminar #74

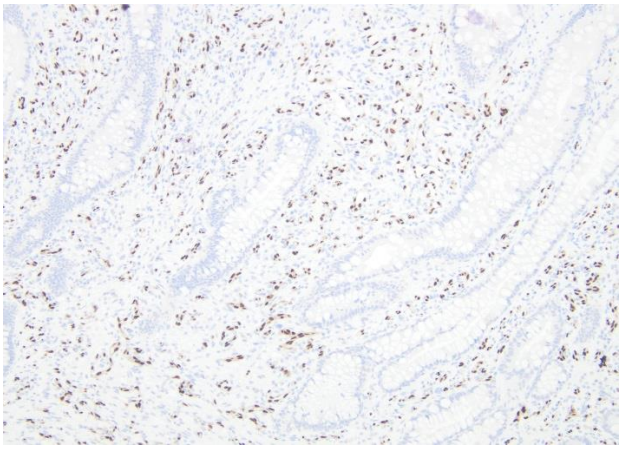
Case – 23

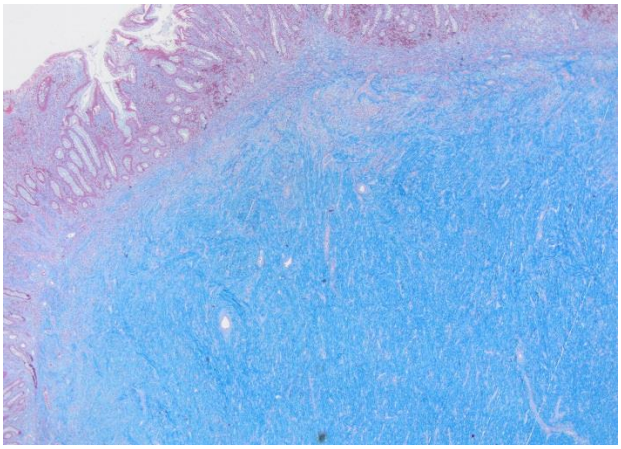
Contributed by: **Paul E. Wakely, Jr. (Courtesy of Martha Yearsley, M.D.)**

Clinical History: A 21 y/o HIV-negative woman presented with acute onset abdominal pain, vomiting, and diarrhea. A month earlier an initial CT scan showed ileoileal intussusception which resolved with contrast CT the next day. She has an extensive family history of Crohn's disease. However, because of repeated bouts of abdominal pain over the next 3 weeks, and concern for peritonitis, she finally underwent exploratory laparotomy. A long segment of ileocolic intussusception with the intussusceptum extending to the level of the hepatic flexure was found with no evidence of bowel ischemia. Since the intussusception could not be reduced, a right hemicolectomy with ileocolic anastomosis was performed. She had no other lesions. The patient is doing well 3 months later.

Pathologic Findings and Diagnosis: Gross examination showed a 3.0 cm red-tan, pedunculated, polypoid lesion as the leading edge of the intussusception. The remainder of the bowel was normal. On cut surface, the lesion was tan-white, firm, and nodular. The case was signed out as a pedunculated submucosal fibroma.

Comment: This case was brought to me by one of our GI pathologists, Dr. Yearsley, who asked me if I had ever seen this type of florid vascular proliferation restricted to the mucosa overlying a fibroma in a case of intussusception. I told her it appeared to be a form of mucosal angiomatosis, but I had no formal name for this vascular change. I told her I was aware of a paper by Bavikatty et al. from the U. of Michigan on vascular change in intussusception mimicking angiosarcoma, but that paper described vascular changes that were extensive within the bowel wall and not limited to the mucosa as in this case. I told her I would send slides to the Club to see if any of you had encountered this before, and if you have a formal 'name' for this. I have included an image of the trichrome and ERG stain.





Reference:

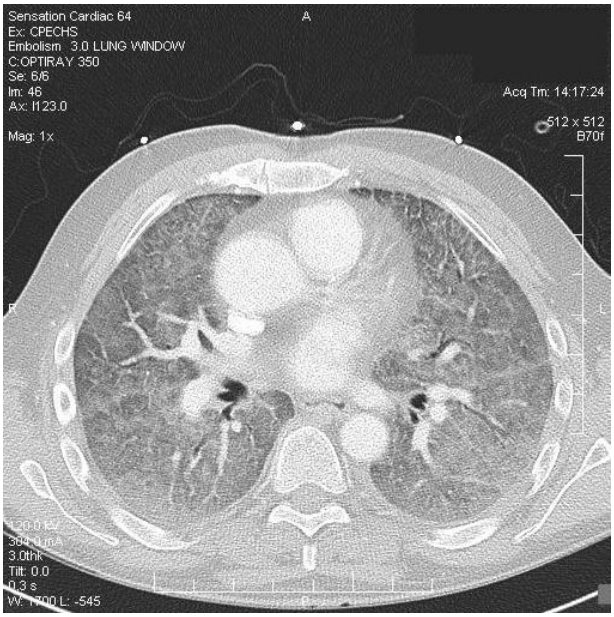
Bavikatty NR, Goldblum JR, Abdul-Karim FW, et al. Florid vascular proliferation of the colon related to intussusception and mucosal prolapse: potential diagnostic confusion with angiosarcoma. Mod Pathol. 2001; 14(11):1114-8.

AMR Seminar #74

Case – 24

Contributed by: Brandon Larsen, M.D., Ph.D.

Clinical History: A 55-year-old man presented with a 3-month history of progressive shortness of breath, cough, fatigue, and diaphoresis. He also had a history of asthma and hypertension and a 10 pack-year history of smoking, but quit smoking 4 years prior to presentation. Imaging studies showed diffuse bilateral ground glass opacities with focal peripheral reticulation and upper lobe consolidation (see representative image from the CT scan, below). No masses, pleural disease, or pleural effusions were seen. Clinically, a fibrotic interstitial lung disease was favored, possibly progressing to acute respiratory distress syndrome (ARDS). Surgical wedge biopsies were obtained from multiple lobes to characterize his interstitial lung disease.



Pathology: The sections show diffuse alveolar filling by a monotonous epithelioid neoplasm, which in many areas shows dyshesive or micropapillary growth that closely resembles the desquamative interstitial pneumonia (DIP) pattern. In some sections, other growth patterns are seen including solid, lepidic, acinar, and adenomatoid growth. Focal minimal pleural involvement is present in some sections, but this is a minor feature.

Immunohistochemistry: Calretinin, CK5/6, WT-1, D2-40, and pankeratin are positive in the lesional cells; TTF-1, polyclonal CEA, B72.3, CD15, EMA, and p63 are negative.

Diagnosis: Diffuse intrapulmonary malignant mesothelioma, epithelioid type, clinically simulating interstitial lung disease

Comment: Diffuse intrapulmonary malignant mesothelioma is a rare variant of mesothelioma that remains poorly understood. Tom Colby (former AMR member) and I published two papers on this topic in the last few years, which included this case, and I thought the group might enjoy seeing an example of this peculiar phenomenon.

In our experience, this diagnosis is never suspected by the clinicians or radiologists before the biopsy, which is not surprising given the clinical presentation and imaging findings. Often, there is no known history of asbestos exposure or clinical or imaging evidence of pleural disease or effusions, as in this patient. Also not surprising is the fact that this diagnosis can stump pathologists, as the tumor can simulate adenocarcinoma and other non-neoplastic lung diseases histologically (e.g. DIP, as in this case, or organizing pneumonia, Langerhans cell histiocytosis, and even silicotic nodules). Thankfully the tumors stain like straight-forward conventional mesotheliomas, but biphasic lesions can sometimes occur which makes the diagnosis harder. Although not required to confirm their malignant nature (as they clearly are invading the lung), BAP1 expression is usually lost in these tumors, and *CDKN2A* (p16) gene deletions can also occur, which can be detected by FISH. If you perform electron microscopy on these cases, they show classic ultrastructural features of mesothelial differentiation (long sinuous microvilli, etc.), but this is probably also unnecessary for primary diagnosis.

References:

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2. Larsen BT, Smith ML, Roden AC, Sukov WR, Hornychová H, Thirumala S, Colby TV, Tazelaar HD. Molecular and ultrastructural features of diffuse intrapulmonary malignant mesothelioma. Am J Surg Pathol. 2019 Jan;43(1);147-50.

AMR Seminar #74

QUIZ CASE No.1

Contributed by: Saul Suster, M.D.

Clinical history: A 15-year-old girl was seen for a palpable soft tissue nodule in her left groin region. The tumor was resected.