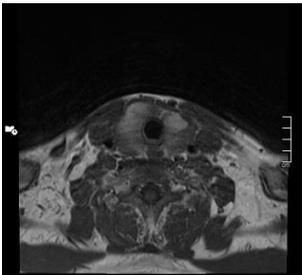


# AMR Seminar #71

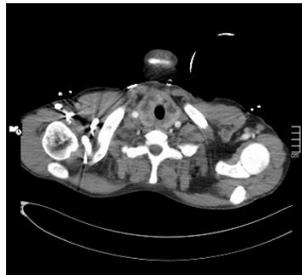
## Case – 1

Contributed by: Abbas Agaimy, M.D.

**Clinical History:** A 29-year-old man with a histologically verified secondary amyloidosis due to familial Mediterranean fever presented with progressive bilateral thyroid enlargement over several months. Imaging revealed diffuse and vaguely nodular thyroid enlargement with signal intensity comparable to that of normal subcutaneous fat on MRI (Fig. 1A) and CT scan (Fig. 1B). He underwent total thyroidectomy.



1A



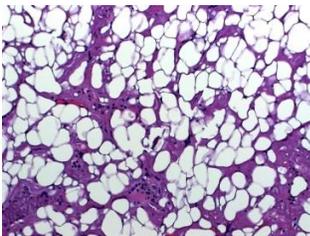
1B

**Macroscopic features:** The resection specimen weighed 64 grams and measured 7.5 x 4 x 1 cm (right lobe), 7 x 4 x 1.5 cm (left lobe) and 3.5 x 3 x 1.5 cm (isthmus). The cut-surface showed diffuse yellowish discoloration with vague lobulation/nodularity but no colloid nodules were seen (Fig. 2A).

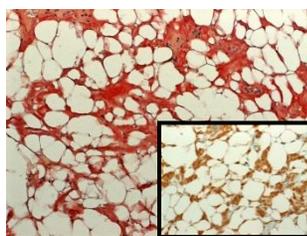


2A

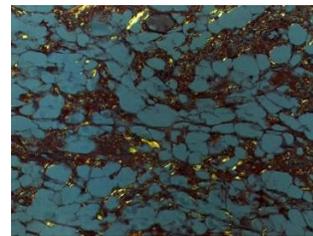
**Histological and Immunohistochemical Findings:** Histological examination revealed extensive replacement of the thyroid by diffusely distributed mature adipose tissue entrapping native follicles making >60% of the thyroid. In the background, hyaline glossy material entrapping adipocytes and small blood vessels was seen (Fig. 2B) which showed congophilia (Fig. 2C), reacted with the antibody against amyloid A (Fig. 2C, inset) and displayed characteristic apple-green birefringence under polarized light microscopy indicating amyloid (2D).



2B



2C



2D

**Diagnosis:** Amyloid goiter (secondary amyloidosis due to familial Mediterranean fever) associated with diffuse lipomatosis of the thyroid.

**Discussion:** Amyloid goiter (AG) is a rare manifestation of primary and systemic amyloidosis associated with a variety of chronic inflammatory and neoplastic diseases. Although the term AG was initially used in a rather loosely defined and vague manner, strict criteria have been applied in more recent studies (see the paper on the largest series from the AFIP by Bruce Wenig and the review by Pinto & Nosé). AG presents as diffuse usually rapid bilateral enlargement of the thyroid frequently causing compression symptoms (dyspnea, dysphagia or dysphonia). Due to the rapid enlargement of the gland, anaplastic carcinoma and lymphoma are among the clinical differential diagnoses. As per definition, AG is distinct from amyloid deposits incidentally found in thyroid specimens from patients with systemic amyloidosis and in specimens harboring medullary carcinoma. Histology of AG shows diffuse amyloid deposition throughout the thyroid entrapping the thyroid follicles in the background. An unexplained diffuse lipomatosis of varying degree seems to be a constant feature in majority of cases and can be as extensive as to be visualized or recognized on imaging studies as illustrated in this case and in a few cases in the literature. Looking at the literature, the term "thyroid lipomatosis" and "thyrolipomatosis" is used in around 60 reports. In most of these however, the presence of amyloid was confirmed histologically while in some others it was denied, although some of the patients had rheumatoid arthritis and renal failure making secondary amyloidosis very likely. Taken together, the presence of diffuse thyroid lipomatosis should alert to the possibility of "amyloid struma" even if the patient was not known to have systemic amyloidosis as rare cases have presented initially with AG prior to diagnosis of systemic amyloidosis. A recent report (Lau et al) described loss of SDHB and a *SDHB* deletion mutation in case of thyroid lipomatosis not associated with amyloidosis, so it seems that rare cases of diffuse lipomatosis of the thyroid are related to other conditions other than AG.

Thyroidectomy is the treatment of choice for AG to relieve pressure symptoms. Rare reports described different types of thyroid carcinomas (including insular) arising on a background of AG but this might represent a mere coincidence. I would be glad to hear the comments of our thyroid specialists in particular regarding the pathogenesis of the lipomatosis in this setting.

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# AMR Seminar #71

## Case – 2

**Contributed by: Ofer Ben-Izhak, M.D.**

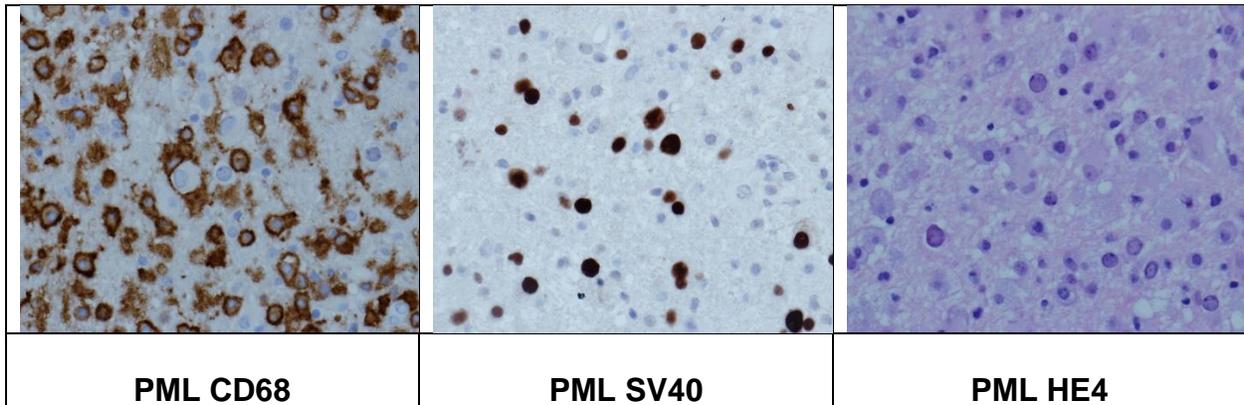
**Clinical History:** A 61 y.o. woman was diagnosed with low-grade B cell lymphoma in 2009. She presented then with lymphadenopathy and lymphoma cells in bone-marrow biopsy. She was treated with 6 courses of Rituximab and CVP, which resulted in complete remission.

Recurrent lymphoma in 2010 was treated with FCR, leading again to complete remission. Following the second series of treatment she developed splenomegaly, pancytopenias and recurrent infections.

In early 2013 splenectomy resulted in improved blood counts and disappearance of significant infections. The spleen weight was 578 gm. and showed small T cells in the red pulp with negative TCR rearrangement. Stains for CD20, CD79a and PAX5 showed severe depletion of B cells.

In mid 2013 she presented with dysarthria and left perioral paresthesias. Brain CT showed hypodense lesions in cerebellum (bilateral), rt. frontal and lt. thalamic areas, with fine enhancement following contrast medium. The differential diagnosis included inflammatory, infectious or tumoral masses. Brain biopsy was performed.

**Pathologic Features:** Tiny fragments of brain tissue were received. The histology showed brain tissue with abundant macrophages (Figure PML CD68), few perivascular lymphocytes, and many cells with viral nuclear inclusion bodies. The inclusion bodies show ground-glass enlarged nuclei with marginated chromatin. The inclusion bodies showed strong immunostain for SV40 large T antigen (which cross reacts with JC and BK polyomaviruses . Fig. PML SV40). Stain for myelin (LFB) showed marked decrease of myelin in the tissue.



**Diagnosis:** Progressive Multifocal Leukoencephalopathy (PML) due to JC virus.

The diagnosis was confirmed by positive JC virus PCR in CSF.

**Clinical Course:** The patient was treated with mirtazapine (antiviral drug) and IV-IG. Blood PCR for JC virus progressively decreased from 23,000 copies/ml at the diagnosis to 0 during 2.5 months, and remains 0 until now. The

patient is asymptomatic and remains in complete remission for both the hematologic malignancy and the neurologic viral infection.

**Comment:**

1. PML was first described in 1958 in patients with hematologic malignancies. It is caused by JC virus (one of the human polyomaviruses. JC are the two initials of the patient John Cunningham). The virus infects the majority of the general population (40-90% in various series) and remains latent in lymphatic tissue, in renal tubular epithelial cells and probably in glial cells. Following reactivation during immunosuppression it causes lytic infection and destruction of oligodendrocytes, resulting in clinical PML.
2. The clinical presentation maybe cognitive impairment, motor/sensory losses, ataxia, vision disorders, convulsions. MRI shows multiple lesions in the white matter. The diagnosis is made by finding JC virus DNA in spinal fluid and/or by typical biopsy with IHC or ISH confirmation of JC virus, in patients with typical clinical and MRI changes.
3. Immunosuppression: Although most common in patients with HIV1 infection, PML occurs in various other immunosuppressed patients. The latter include transplant recipients , patients with hematologic malignancies and autoimmune diseases, and especially patients treated with biological therapies which depress the immune system. Our patient was treated with Rituximab (and other chemotherapeutic drugs). PML following Rituximab (in HIV negative patients) was reported in 2009 (Carson et al; Blood 113:4834, 2009). The publication reports 57 cases of PML which developed 0.3 to 66 months following cessation of treatment , with high mortality rates (of 89%). A boxed warning for the drug includes association of Rituximab with PML and death. The same warning is present for Natalizumab (Tysbary, drug for multiple sclerosis patients), Brentoximab vedotin ("anti CD30" drug) and other immunoregulatory and immunosuppressive drugs.
4. The disease, which was described as "usually fatal" has a current mortality rate of 30-50%, while those who survive can be left with varying degrees of neurologic disabilities. The main treatment strategy for PML is to reverse the immune deficiency by stopping the immunosuppressive drug or starting highly active antiretroviral therapy for HIV patients. The rapid, complete recovery of our patient is unusual.

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# AMR Seminar #71

## Case – 3

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

**Case History:** The patient is an 87-year old man who presented with a mediastinal mass. He underwent surgical excision that yielded a 24gm. Specimen measuring 7.5 x 4.0 x 2.5 cm. Upon sectioning, a multiloculated red-brown hemorrhagic lobular mass with a distinct white fibrous capsule was observed.

**Microscopic Findings:** Sections display an encapsulated lesion composed of large epithelioid cells with prominent nucleoli and conspicuous intranuclear inclusions. Areas of degenerative changes and inflammation are present but tumor cell necrosis and mitotic activity are absent or infrequent.

**Immunohistochemical staining showed the following profile:** CK5/6 positive, CD5 negative, CD117 negative, TTF-1 negative, thyroglobulin negative and S110 negative.

**Diagnosis:** Atypical thymoma (WHO Type B3)

**Comment:** I was struck by the frequency of intranuclear inclusions in the otherwise classic B3 thymoma. I asked Saul his experience with intranuclear inclusions in thymoma and he reported occasionally finding them. Since he was impressed with the number of inclusions in this case, I thought I would share it with the group!

# AMR Seminar #71

## Case – 4

**Contributed by:** Hugo Dominguez Malagón, M.D.

**Clinical History:** A 55 year-old female was first seen in June 2016 because a tumor in her left breast . -----The tumor was irregular in shape, hard in consistency, adherent to deep planes and measured 11 cm. It was resected and the histopathological study was informed as musculo-aponeurotic fibromatosis. In January 2017 was admitted for a recurrent tumor involving 60% of the breast, a biopsy was done and diagnosed as consistent with sarcoma. Radical mastectomy was performed.

**Pathological Findings:** The tumor is composed of spindled and plump cells with occasional nuclear atypia surrounded by dense keloid-like collagen fibers resembling fibromatosis.

Immunohistochemistry was positive for –CK 5-6, CD10, Vimentin (in the stroma), smooth muscle actin (tram track pattern in stromal cells), Ki67 in 20% of the cells. Negative for CK7 ,P63, Calponin.

**Diagnosis:** Fibromatosis-like metaplastic carcinoma of the breast.

**Comment:** Metaplastic carcinoma is a heterogeneous group of lesions, they include squamous cell carcinoma, metaplastic carcinoma with mesenchymal (heterologous) differentiation, low-grade adenosquamous carcinoma, spindle cell carcinoma and fibromatosis-like metaplastic carcinoma.

This late type is often confused with fibromatosis and is important to be aware of the entity. The submitted slides show enough atypia to suspect the entity, it is not a real challenge for diagnosis, I just submitted it as a nice example for non-breast pathologists.

# AMR Seminar #71

## Case – 5

**Contributed by:** Cyril Fisher, M.D.

**Clinical history:** A 26 year-old female presented during pregnancy with a pelvic mass. All tumor markers including germ cell markers were within the normal range. She delivered a healthy baby at 28 weeks. Post partum MRI scan showed a large, lobulated soft tissue mass filling the pelvis and infiltrating the left obturator internus. The tumor abutted the anterior vaginal wall and was in close proximity to the urinary bladder, but did not infiltrate normal structures, including the uterus, cervix, fallopian tubes and ovaries, right ureter or urethra. This was initially deemed inoperable, and she was treated with conventional chemotherapy. She was then transferred to our center where the tumor was marginally but completely excised. However, two months after surgery a repeat CT scan showed new pulmonary metastases. The patient died of progressive disease 20 months after initial diagnosis.

**Pathologic Features:** This is a cellular neoplasm composed of sheets and fascicles of markedly pleomorphic polygonal and spindle cells in fibrous or myxoid stroma. The cells have highly pleomorphic nuclei with prominent nucleoli and eosinophilic cytoplasm. Multinucleated tumor cells are present focally. The striking feature is the presence in many areas of variably sized pleomorphic lipoblasts, which show hyperchromatic, scalloped nuclei. The mitotic index is up to 4 per 10 hpf, and there is extensive tumor necrosis. Areas of fibrosis, hyalinization and patchy chronic inflammation with hemosiderin-laden macrophages are present, consistent with changes secondary to previous chemotherapy. No conclusive well-differentiated liposarcoma is seen.

The tumor shows diffuse and strong immunohistochemical expression of p16 and CDK4 in both the spindle cell component and the pleomorphic lipoblasts (images). There is focal nuclear expression of S100 protein (including in lipoblasts) and focal smooth muscle actin (SMA) expression, but desmin, h-caldesmon, AE1/AE3, CD31, CD34, CD117, DOG1, MUC4 and estrogen and progesterone receptors are negative. FISH shows high-level *MDM2* gene amplification (image).

**Diagnosis:** Dedifferentiated liposarcoma with 'homologous' (pleomorphic liposarcoma-like) lipoblastic differentiation.

**Comment:** 5-10% of dedifferentiated liposarcoma (DDL) can exhibit heterologous differentiation, including myoid or osteo/chondrosarcomatous lineage. Homologous differentiation in DDL is, however, a recently recognized concept, whereby the undifferentiated pleomorphic or spindle cell sarcomatous areas of DDL show variable numbers of interspersed or adjacent multi-vacuolated lipoblasts. As these areas are essentially morphologically identical to pleomorphic liposarcoma they can cause diagnostic confusion in tumors without an identifiable component of well-differentiated liposarcoma (WDL).

This case is unusual for dedifferentiated liposarcoma in being pelvic rather than retroperitoneal. It also lacks a component of well-differentiated liposarcoma (atypical lipomatous tumor). *MDM2* amplification can also be found in other tumor types including some sarcomas and carcinomas. However, most pleomorphic sarcomas in retroperitoneum with *MDM2* amplification are currently regarded as representing dedifferentiated liposarcoma even without a well-differentiated liposarcomatous component.

Dedifferentiated liposarcoma with homologous lipoblastic differentiation shows similar genetic features to classical DDL, with the vast majority showing high-level *MDM2* amplification with FISH and diffuse and strong expression of MDM2, CDK4 and p16 immunohistochemically. Low-level *MDM2* amplification is also rarely noted. Although it has also been postulated that the presence of homologous lipoblastic differentiation reflects a transitional step in the progression of WDL to classical DDL, this remains to be proven, and homologous lipoblastic differentiation may conceivably simply represent randomly divergent differentiation in DDLs undergoing tumor progression. In this case, the effect of chemotherapy on the differentiation might be a factor.

The differential diagnosis is principally from pleomorphic liposarcoma. This is a high-grade pleomorphic neoplasm with variable amounts of lipoblastic differentiation that occurs most frequently on the limbs of older adults, but very rarely arises intra-abdominally. It is a complex karyotypic tumor that lacks amplification of *MDM2* and *CDK4*. It is important to distinguish pleomorphic liposarcoma from DDL as it is typically more aggressive and is generally resistant to current treatment modalities while DDL generally behaves less aggressively than other pleomorphic sarcomas. The treatment for these neoplasms might also differ significantly due to the potential for targeted therapies towards gene products associated with chromosomal 12q13-15 abnormalities, such as CDK4 inhibitors that may be effective in combination with cytotoxic drugs.

Heterologous liposarcomatous differentiation also occurs very rarely in both MPNST and carcinosarcoma of the genital tract (MMMT) but additional features of these are lacking here. All these tumors should also lack adjacent WDL, and typically lack expression of CDK4 or MDM2 amplification (though this is sometimes found in MPNST).

NB This case was presented by my colleague Dr Khin Thway at the bone/soft tissue evening specialty conference at USCAP this year.

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# AMR Seminar #71

## Case – 6a & 6b

**Contributed by:** Jerónimo Forteza, M.D.

**Case History:** 77 year old male.

History of prostate adenocarcinoma in 2014.

Bone metastasis (Blastic in S1 Right ischiopubial branch) and lungs.

Mesenteric mass (present in 2014)

**Diagnosis:** Large B cell lymphoma (possibly arising in MALT lymphoma). Retractive sclerosing mesenteritis.

**Comment:** This case has the typical B cell large cell lymphoma morphology, with positivity for CD20, bcl2 and bcl6. The arrangement is monoclonal for IgH. The question in this case, is the lymphoma affecting the colon? This last B cell lymphoma is developed around mucosa-associated lymphoid tissue. The mucosa has disappeared from the lymphoma invasion.

Another interesting question in this case is the clinical debut in the patient. The patient has retroperitoneal disease similar to retroperitoneal fibrosis. This is the disease related in most cases to IG4, but in this case immunohistochemistry with IG4 antibody is negative, but in the histological image of the fibrosis and non-tumoural areas the intensive fibrosis is evident and minor fibrosis is also evident in the lymphoma areas. The question is what is the mechanism for fibrosis in this case? It's possible it's in the relationship with B proliferation.

The better strategy for this fibrosis is possibly intensive therapy against the lymphoma.

# AMR Seminar #71

## Case – 7

**Contributed by: Ondřej Hes, M.D., Ph.D.**

M27117/17 (case sent for second opinion by Dr. Boris Pospihajl, Slovenj Gradec, Slovenia)

**Clinical History:** 86-year-old Caucasian female underwent radical nephrectomy for centrally located tumor. On gross section, tumor was whitish with dark areas. Grossly visible angioinvasion into renal vein was documented.

**Histology:** Tumor was arranged in solid pattern, focally with prominent papillary structures. Neoplastic population was formed by mostly clear cell elements, focally with more eosinophilic cytoplasm. Substantial part of neoplastic cells displayed subnucleolar distinct vacuole, the whole tissue resembled endometrial glands in secretory phase. Coarse calcification and psammoma bodies were disclosed within the tumor.

Immunoprofile was interesting: Tumor was focally positive for TFE3, cathepsin K, AMACR, and vimentin. Neoplastic cells were negative for CK 7.

Because morphology was, despite the age of the patient suggestive from possible translocation origin, tumor was further examined by fluorescence *in situ* (FISH). Break of *TFE3* gene and break of *NONO* gene were disclosed.

**Diagnosis:** Xp11 translocation renal cell carcinoma with established *TFE3-NONO*.

**Comments:** Very nice study written by Argani et al: "TFE3-Fusion variant analysis defines specific clinicopathologic associations among Xp11 translocation cancers" has been published in June 2016 (1). Authors described, among others, 5 cases with NONO-TFE3 RCC and characterized their morphologic features. Tumors were characterized mostly by papillary architecture, clear to weakly eosinophilic cells with subnuclear vacuoles leading to distinctive nuclear palisading.

Actually, we believe, that Xp11 translocation RCCs are the most common translocation RCCs in adult population. Besides typical Xp11.2 RCC with papillary architecture, mostly clear cells and frequent psammoma bodies, there are several other morphologic variants as well as tumors with different TFE3 fusion partners (2-4).

However, not only papillary tumors with clear cells and psammoma bodies are Xp11 translocation renal cell carcinomas. Also tumors, closely resembling urothelial lesion has been described. Such tumors can be arranged in tubulopapillary architecture and neoplastic cells are more eosinophilic. Even palisading pattern was documented in such cases (5,6).

Differential diagnosis is apparently more complicated, because from above mentioned data is evident, that morphologic spectrum of Xp11 translocation renal cell carcinomas (and of NONO-TFE3 RCC among them) is much broader, than was originally estimated. It is evident, that not only children and adolescents can be affected by this tumor, but also elderly patients are diagnosed with translocation RCCs. Immunohistochemical profile is relative variable and antibodies against TFE3 protein and cathepsin K are not specific. It has been shown, that diagnosis of translocation Xp11 RCCs should be supported at least by genetic analysis of *TFE3* gene.

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# AMR Seminar #71

## Case – 8

**Contributed by: Jason Hornick, M.D., Ph.D.**

**Case History:** A 46-year-old man presented with nasal obstruction. A mass filling the right nasal cavity and nasopharynx was resected.

**Pathologic Features:** The tumor is composed of nests of uniform large epithelioid cells with voluminous clear cytoplasm and central nuclei with small nucleoli. In other areas, the tumor shows a trabecular architecture, and the tumor cells contain granular eosinophilic cytoplasm. By immunohistochemistry, the tumor cells are positive for HMB-45, melan A, and TFE3, whereas SMA, desmin, keratins AE1/AE3, and PAX8 are negative. FISH was positive for *TFE3* gene rearrangement

**Diagnosis:** PEComa (with *TFE3* gene rearrangement).

**Comments:** Although PEComas are often defined by co-expression of melanocytic and smooth muscle markers, a small subset of PEComas (mostly epithelioid examples with clear cytoplasm) are negative for SMA and desmin. Recent studies have shown that PEComas fall into two main genetic groups: those with *TSC2* gene mutations/deletions and those with *TFE3* gene rearrangements (the latter much less common).

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# AMR Seminar #71

## Case – 9

**Contributed by: Michal Michal, M.D.**  
**M28104/15**

**Clinical History:** A 32-year-old man noticed a tumor adhering closely to the right testis. The tumor measured 4.8 cm in the largest dimension and on cut section presented as a lobulated mass with focal hemorrhagic spots. Thorough clinical check-up did not reveal any tumor elsewhere in the body. One year after the excision, the patient was without any signs of recurrence or metastasis.

**Histological Findings:** Microscopically, the tumor was composed of two distinct components, both of low grade appearance. The major part of the tumor volume was represented by population of signet ring cells. This component merged with solid, non–signet ring cell areas. The solid component was occasionally arranged in trabecular fashion. Focally, periodic acid–Schiff–positive hyaline globules were detected throughout the tumor. In the septa of the neoplasm, there were deposits of hemosiderin, Gandy-Gamna bodies, and foci of foamy macrophages as remnants of old hemorrhage. Adjacent testis was devoid of any pathological changes including germ cell neoplasia in situ. Immunoprofile showed distinct diffuse intranuclear positivity with antibodies to  $\beta$ -catenin and cyclin D1. The neoplastic cells further reacted with CD10, vimentin, galectin-3, S-100, androgen receptors,  $\alpha$ -antitrypsin, Fli-1 and neuron-specific enolase (NSE), and were focally positive with synaptophysin, CD56, E-cadherin, AE1/3 and progesterone receptors antibody. The tumor showed no reactivity with inhibin, calretinin, FOXL2, SF-1, chromogranin, serotonin, AFP, GFAP, NANOG, SALL4, LIN28, CD57, GATA3 and placental alkaline phosphatase. Mutational analysis revealed mutation c.101GNT (p.Gly34Val) in exon 3 of the *CTNNB1* gene encoding  $\beta$ -catenin.

**Diagnosis:** Pancreatic analogue solid pseudopapillary neoplasm arising in the paratesticular location (PA-SPN).

**Comments:** Pancreatic solid pseudopapillary neoplasm (SPN) is a rare tumor with uncertain histogenesis traditionally encountered in the pancreas; 7 cases have been also described in the ovary (1-5). The solid component of the herein presented tumor is histologically indistinguishable from the pancreatic SPN which prompted us to investigate this case using immunohistochemical (IHC) antibodies and mutational analysis of exon 3 of the *CTNNB1* gene ( $\beta$ -catenin) which is characteristic for pancreatic SPN (6) and to compare both neoplasms. As a result, both IHC testing and molecular analysis revealed identical results as would be expected in pancreatic SPN. This allowed us to postulate that these tumors represent the same entity (7). When comparing the morphological appearance of our paratesticular tumor with the classical features of pancreatic SPN, the most striking difference was the signet ring cell component in the paratesticular neoplasm, which is not considered as a typical feature of pancreatic SPN. However, after meticulous review of a set of pancreatic tumors from our files, we were able to detect occasional signet ring cells in the vast majority of pancreatic SPNs (19/22 cases) indicating that signet ring cells are constantly present in pancreatic SPN as well. Owing to the very pronounced signet ring cell component in the pancreatic analogue solid pseudopapillary neoplasm of the paratestis (PA-SPN), we came to the idea that the previously published primary signet ring stromal tumor of the testis (PSRSTT) might belong into the same category (8). For this purpose, we have collected 13 cases of PSRSTTs and while 7 cases were composed of signet ring cells only, the remaining 6 cases were more similar to PA-SPN as they contained both signet ring and solid component. Not surprisingly, the IHC and molecular genetic results precisely correlated with PA-SPN (and indeed pancreatic SPN). On the basis of these results (unpublished data), we assume that SPN of the pancreas, ovary, PA-SPN and PSRSTT probably represent the same entity occurring in different organs. We consider the pure signet ring stromal tumor as an incipient growth phase of SPN. All the 13 PSRSTTs were small (up to 2 cm) in comparison with the typically bulky pancreatic SPN. Currently presented PA-SPN further supports this hypothesis, as its size (nearly 5 cm) was significantly larger than PSRSTTs and the solid, SPN-like component was here very well developed.

This concept was further strengthened by a recently published letter to the editor by Mengoli et al (9,10). The authors reported another 2 identical cases with the same results and conclusion.

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# AMR Seminar #71

## Case – 10

**Contributed by: Michal Michal, M.D.**  
**M64082/15**

**Case Report:** The patient was a 56-year-old, HIV positive man who presented with a painless, bleeding, non-itching, erosive solitary lesion, measuring 25 mm, involving the inner foreskin and the glans of the penis. The clinical differential diagnostic considerations included erosive balanitis, precancerous lesion or penile carcinoma. After the initial histological diagnosis of EMPD, the patient was treated with Aldara, Efudix and 7 rounds of photodynamic therapy. Due to persistence of the lesion (Fig. 1), repeated biopsies were taken 32 and 34 month later.

**Histopathologica and immunohistochemical findings:** The initial biopsy of the tumor showed focally atypical, basaloid surface epithelium containing numerous goblet cells filled with PAS-positive, alcian blue-positive mucin, some of which resembled signet ring cells. Immunohistochemically, they were positive for CK7. The second biopsy performed 32 months later revealed only a minor surface epithelial component with appearances similar to those seen in the original biopsy, and, in addition, there were a few tiny gland-like structures in the dermis contained mucin-filled goblet cells. Focally, destruction of these structures and extrusion of the mucus into the corium has resulted in mucin pools.

Two months later, a large specimen was sampled, revealing microscopically an invasive process, with variably sized solid nodules and gland-like structures composed of atypical squamous and/or basaloid cells intermixed with numerous goblet cells, filled with mucus (Fig. 4 A, B, C). Both components expressed CK7 and p16 protein

### **HPV genotyping**

HPV genotyping was performed using the following primer systems: CPSGB, GP5+/GP6+, and type specific primers for HPV 16, 18, 31, 33, 35, 45, as described elsewhere. HPV type 16 was detected in the last biopsy specimen and, retrospectively, in the original specimen. The lesion was thus reclassified as the penile analogue of cervical SMILE with an invasive component of both squamous and glandular phenotype.

**Diagnosis:** Penile analogue of stratified mucin-producing intraepithelial lesion (SMILE) of the cervix.

*Michal M., Michal M., Hercogová J., Skopalikova B.: The penile analogue of stratified mucin-producing intraepithelial lesion (SMILE) of the cervix: the first described case. A diagnostic pitfall. American Journal of Dermatopathology, 38, e64-e67, 2016*

# AMR Seminar #71

## Case – 11

**Contributed by:** Markku Miettinen, M.D.

**Clinical History:** 45 F, 13 cm intramuscular proximal thigh mass.

**Diagnosis:** Myxoid liposarcoma with extensive necrosis, possible treatment effect.

**Comment:** This is an extensively necrotic myxoid liposarcoma with vascular thrombosis. Such necrosis is not uncommon for large myxoid liposarcomas and it could also be part of treatment effect. In this case, there is no specific information on treatment.

Uniform ovoid cells are typical of myxoid liposarcoma. While prominent vessels are typical of untreated tumor, radiated tumors lose vascular density and may undergo extensive hyaline fibrosis. Sometimes increased lipomatous differentiation also follows radiation treatment.

Liposarcomas with prominent myxoid matrix in the abdominal cavity are usually well-differentiated liposarcomas, mostly only metastatic myxoid liposarcomas are seen in the retroperitoneum. Well-differentiated liposarcomas with myxoid matrix usually contain variable cellular components, including atypical fat cells and cellular septa. While myxoid liposarcoma is typically CD34-negative, well-differentiated liposarcomas are usually positive. If needed, MDM2 amplification studies would support well-differentiated liposarcoma and FUS or DDIT3 gene rearrangements a myxoid liposarcoma.

# AMR Seminar #71

## Case – 12

**Contributed by: Cesar A. Moran, M.D.**  
**S02-42917**

**Clinical History:** 38-year-old man presents with a right upper lung mass. The original biopsy was interpreted in an outside institution as “carcinoid tumor.” Lobectomy was performed and referred to my opinion as to the grade of this carcinoid tumor.

**Diagnosis:** Myxopapillary Ependymoma, primary site undetermined

**Comments:** I know that this tumor has been reported as a primary lung neoplasm, however, in this case I am not sure how to interpret this tumor. I personally believe that it is metastatic from somewhere else but I did not get any additional clinical information.

# AMR Seminar #71

## Case – 13

**Contributed by:** Kyle Perry, M.D.

**Clinical History:** The patient is a 61 y/o male who had a history of liposarcoma of the lower extremity and prostatic adenocarcinoma. After presenting with numbness and loosening of the teeth, he was found to have a mandibular mass. The outside biopsy of this mandibular lesion showed a mast cell neoplasm. A bone marrow biopsy was found to be negative for evidence of systemic disease. After receiving a course of radiation therapy, the tumor was resected at Mayo Clinic.

**Pathologic findings:** Sections of the resected tumor demonstrated sheets of tumor cells with eosinophilic cytoplasm with intermediate to large nuclei. Scattered cells show conspicuous nucleoli or multiple nucleoli (Fig. 1a-1d). Immunohistochemical stains revealed the cells to be positive for CD117, mast cell tryptase and CD33 and negative for CD68, OSCAR cytokeratin, CD45RA, MUM1 and S-100 (Fig. 2a-2c). A PCR assay showed the tumor cells to be negative for the KIT Asp816Val mutation.

**Diagnosis:** Mast cell sarcoma.

**Comment:** Mast cell sarcoma is an extraordinarily rare type of mast cell neoplasm that has only been reported in a handful of cases. The tumors arise as a unifocal destructive lesion and can be found both in pediatric and adult patients. Histologically, mast cell sarcomas are comprised of intermediate sized epithelioid like cells with atypical, enlarged and irregular nuclei. Conspicuous nucleoli and multinucleation can be seen. Although these tumors typically have associated eosinophils, these cells were not identified in our particular case. Mast cell sarcomas are typically positive for mast cell markers such as tryptase, CD117, and CD33. Additionally, tumors have been found to be positive for CD68, CD2, CD25, CD43 and MITF. Unlike other mast cell neoplasms, mast cell sarcomas are typically negative for the frequent D816V mutation found in the KIT gene.

The differential diagnosis includes other pleomorphic malignancies such as undifferentiated high-grade pleomorphic sarcoma, poorly differentiated carcinoma as well as Langerhans cell histiocytosis, and lymphoma or myeloid neoplasms. Poorly differentiated carcinomas will typically exhibit at least some keratin staining while high-grade pleomorphic sarcoma will lack any particular immunophenotypic differentiation. The cells in Langerhans cell histiocytosis are positive for CD1a and S-100. Myeloid tumors can be positive for CD117 but usually show other granulocytic markers while lacking tryptase staining. Lymphomas usually exhibit other B or T lymphocyte markers.

Mast cell sarcomas have not been found to respond well to radiation or conventional chemotherapy. The prognosis is typically poor. This particular patient was alive and without disease for three years, after which, he was lost to follow-up.

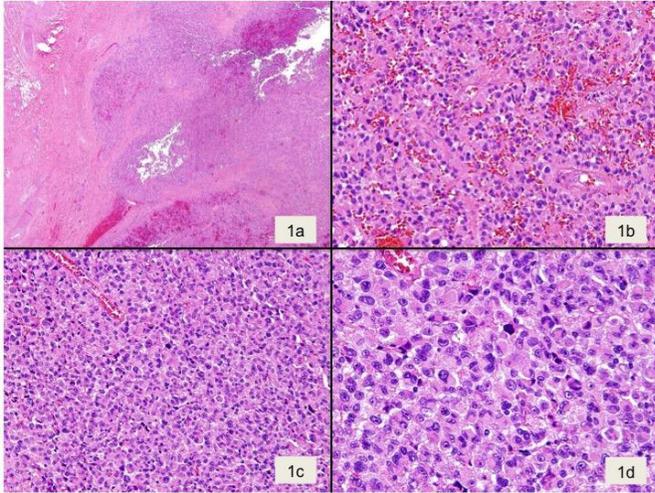


Figure 1a-d. Tumor cells of this mast cell sarcoma show pleomorphic epithelioid cells with enlarged nuclei, conspicuous nucleoli and nuclear irregularity. Occasional multinucleated tumor cells are present.

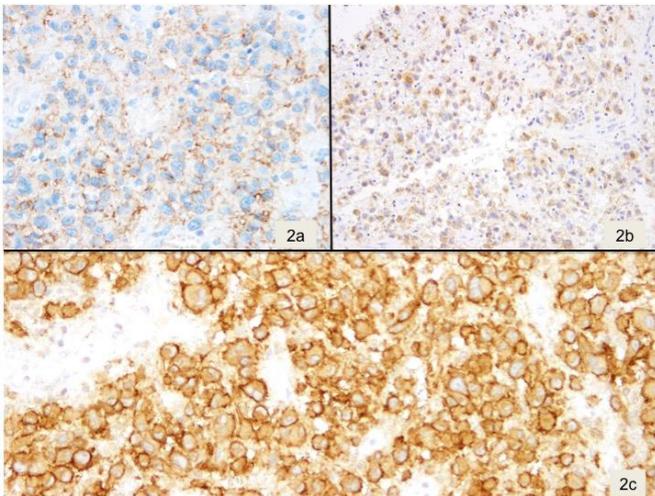


Figure 2. The tumor cells are positive for CD117 (a), mast cell tryptase (b), and CD33 (c).

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# AMR Seminar #71

## Case – 14

**Contributed by: Fredrik Petersson, M.D.**

**Clinical History and Gross Feature:** The patient is an otherwise healthy 17 year old girl with a 2 months history of an intramuscular lump in the deltoid. This was confirmed on MRI (solitary enhancing lesion suspicious for sarcoma). After core biopsies, the lesion was excised together with the surrounding triceps muscle. Cut sections of the resected specimen showed an intramuscular, rather circumscribed fleshy firm tumor measuring 2.0 x 1.5 x 1.5 cm.

**Histology:** The tumor has infiltrative margins, invading the adjacent skeletal muscle fibers. Scattered atrophic skeletal muscle fibers and nerves are seen trapped within the tumor. Lymphocytic infiltrates are present at the periphery of the tumor. The tumor is characterized by fascicular and sheet-like arrangement of plump spindle to epithelioid cells. Many of the tumor cells have abundant brightly or 'glassy' eosinophilic cytoplasm, mimicking rhabdomyoblasts. The tumor cells contain vesicular nuclei with prominent, inclusion-like nucleoli. Mitotic figures are easily identified. No necrosis is present

**Immunohistochemistry:** Tumor cells diffusely and strongly express cytokeratins (AE1/3, CK7). There is focal expression of EMA. There was variable expression for vascular markers (ERG and CD31 expressed in many tumor cells, albeit quite weak; Factor VIII was focally expressed, but again not super convincing). Focal expression for CAM5.2 and SMA is also seen. There is no expression of CD34, S100, HMB45, myogenin, MyoD1, ALK1 or CD30. INI-1 is retained in the tumor cells.

**Diagnostic considerations and comments:** To me this is a low-grade malignant epithelioid, cytokeratin positive sarcomatous neoplasm. A pseudosarcomatous tumor (e.g. fasciitis and its variants) was also considered but this tumor lacks 'zonation' and background regenerative-type / fasciitis-like stroma, and displays cellular atypia and a sclerotic stroma. Initially, given the weak (and, admittedly, in retrospect not very convincing), expression of vascular markers, the possibility of an "epithelioid sarcoma-like hemangioendothelioma/ pseudomyogenic hemangioendothelioma", was high on my list of differentials. After the broad range of diagnostic possibilities provided by 4 different soft tissue experts (vide infra), I am a bit puzzled, but I favor an epithelioid sarcoma ("pseudomyogenic hemangioendothelioma-like ???!).

**Discussion:** I am sharing this case with the members of the club (1) because I am interested in your take on the diagnosis and (2) to get a better understanding on the members' perception of the nosological relationship between epithelioid sarcoma-like hemangioendothelioma and pseudomyogenic hemangioendothelioma.

In general, for cytokeratin positive sarcoma the differential diagnoses are multiple (e.g. epithelioid sarcoma, sclerosing epithelioid fibrosarcoma, malignant rhabdoid tumor or epithelioid malignant vascular tumors, e.g. epithelioid hemangioendothelioma and epithelioid angiosarcoma, epithelioid variants of liposarcoma, leiomyosarcoma, rhabdomyosarcoma and epithelioid MPNST). The morphology does not fit with synovial sarcoma even for a poorly differentiated type and for most of the epithelioid variants of other types of specific sarcomas the cytokeratin expression is weak and/or focal, which is in contrast to this case.

As mentioned above, due to the unusual appearance and rarity of this tumor, this case was sent to four soft tissue tumor pathologists. One concurred with our diagnosis based on H&E sections alone (no IHC done). The other three performed IHC and could not detect any expression of vascular markers and hence did not think the tumor represents PMEHE/ES-likeEHE. However, all three had conflicting opinions on the nature of this case. One perceived the best fit to be epithelioid sarcoma, one as a diffusely cytokeratin positive proliferative myositis and the third as a an "atypical epithelioid and spindle cell neoplasm with uncertain malignant potential".

The patient has been followed up for 2 years (serial MRIs of the arm and chest x-rays) with no evidence of recurrence or metastatic disease.

Coming back to the relationship between PMEHE and ES-like EHE, the interested can get an amusing and educational read in the February issue of AJSP 2011 where the “entity/concept” of PMEHE was launched.<sup>1</sup> However, ES-like EHE had been up and running since 2003 <sup>2</sup> (sic!) and the authors of the 2003 paper (who claim that these two entities are identical), responded in a letter to editor<sup>3</sup>, with a rebuttal by the “PMEHE-authors” in the same issue. Again, interesting read.

Genetically, the recurrent  $t(1;3)(p36.23;q25.1)$  – leading to fusion of *CAMTA1* on 1p36.23 to *WWTR1* on 3q25.1 which is present in most conventional EHEs of different anatomic locations, is to the best of my understanding not detected in PMEHE/ES-like EHE.

From my reading, I have noted cases of PMEHE/ES-like EHE with different genetic changes, such as balanced translocation of  $t(7;19)(q22;q13)$  [most common] and an unbalanced translocation of  $der(7)t(7;19)(q22;q13)$ . Perhaps the soft tissue experts of the club can enlighten us further on this matter.

**Figures:**



Fig. 1. Well circumscribed, unencapsulated intramuscular tumor.



Fig. 2. Well circumscribed, unencapsulated intramuscular tumor.

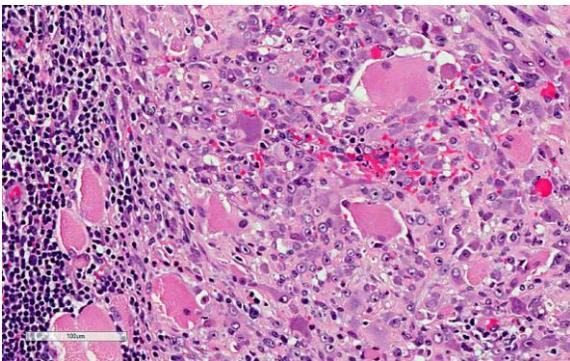


Fig. 3. At the periphery, focal aggregates of lymphocytes are present and neoplastic cells infiltrate among striated muscle cells.

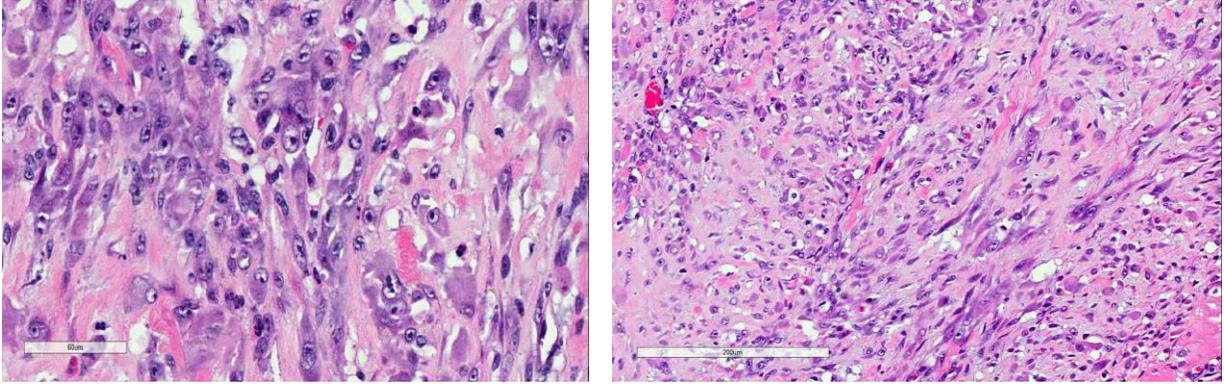


Fig. 4A, B. The tumour was composed of plump spindle to epithelioid cells. Many of the tumor cells have abundant brightly or 'glassy' eosinophilic cytoplasm, mimicking rhabdomyoblasts. The tumor cells contain vesicular nuclei with prominent, inclusion-like nucleoli. Mitotic figures are easily identified.

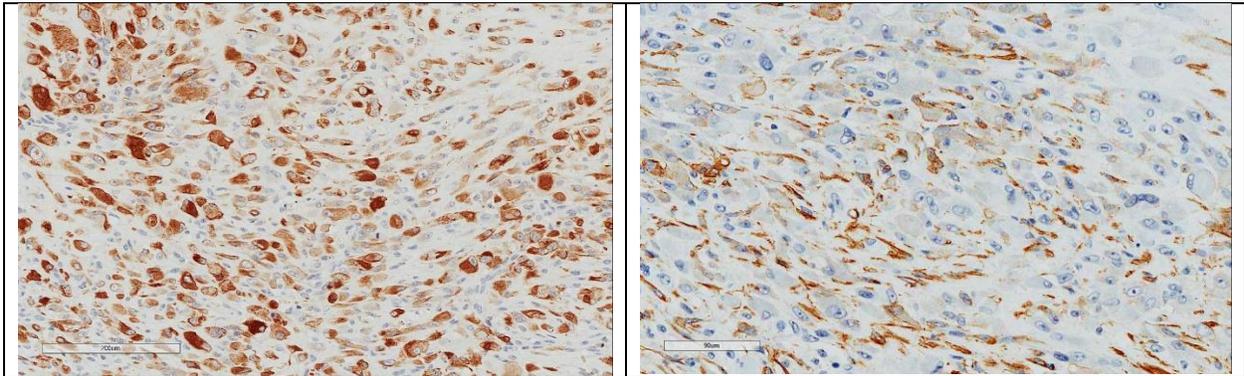


Fig. 5A,B. The neoplastic cells showed strong and widespread expression of CK7 and very focal and relatively weak expression of SMA.

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Billings SD, Folpe AL, Weiss SW: Epithelioid Sarcoma-like hemangioendothelioma (pseudomyogenic hemangioendothelioma). *The American journal of surgical pathology* 2011, 35:1088; author reply -9.

# AMR Seminar #71

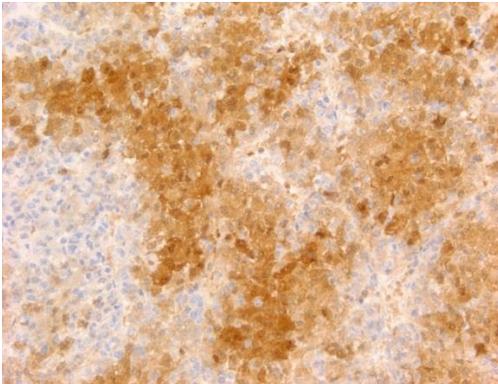
## Case – 15

**Contributed by: Murray Resnick, M.D.**

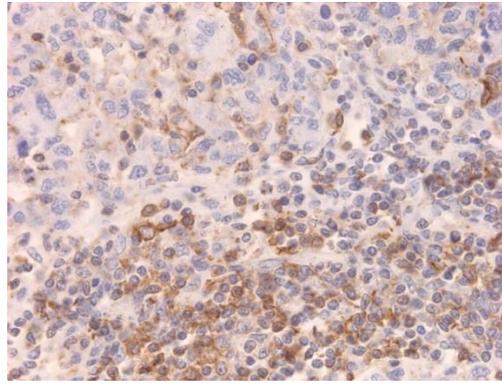
**Clinical History:** This 12 cm liver mass was resected from a 66 year old female with no previous chronic liver disease. The surrounding liver tissue showed no evidence of cirrhosis or significant fibrosis.

**Diagnosis:** Hepatocellular carcinoma, lymphoepithelioma like variant.

**Comment:** The tumor is composed of pleomorphic malignant cells with bizarre nuclear atypia and surrounding dense lymphoid stroma. The lymphoid cells are Cd3 and CD8 positive. Tumor cells are positive for Hepar-1 and arginase (Figure 1). These features are consistent with lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC). The WHO has recently recognized LEL-HCC or inflammatory HCC as a variant of HCC. While lymphoepithelioma-like carcinomas from other sites are associated with EBV infection, in hepatocellular carcinoma EBV has been found only rarely. In this case EBER in-situ was negative.



Arginase



PDL-1

A minority of these tumors are MSI-H, however, the percentage of MSI-H tumors of this variant does not differ from that of conventional HCC. Certain studies have found that LEL-HCC is associated with overall better prognosis. As one would expect with this dense lymphoid infiltrate the tumor stroma and to a lesser degree the tumor itself is PDL-1 positive (Figure 2). The majority of reports do not describe background cirrhosis although cirrhosis was detected in 40% of cases in the study by Chan et al.

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1. Bosman FT, Carneiro F et al eds. WHO Classification of Tumors 3<sup>rd</sup> ed Lyon, France, IARC Press, 2010.
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# AMR Seminar #71

## Case – 16

**Contributed by: Ady Yosepovich, M.D.**

**Clinical History:** A breast mass in a 3 y/o child. I was acquainted with this lesion seven years ago during my breast observership in Mount Sinai.

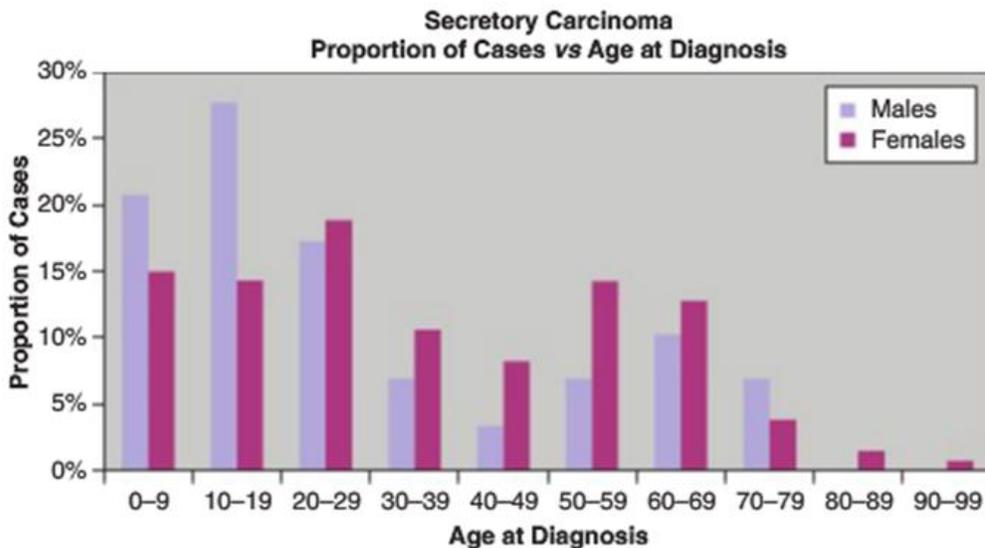
My mentor, teacher and friend, Ira Bleiweiss showed me a peculiar breast lesion in a 9 y/o girl. I could have never guessed that I will see this again 5 years later in my own breast consultation practice in a 3 y/o boy. This case sent by the primary pathologist with a preliminary working diagnosis of a very peculiar lesion "hamartoma / florid hyperplasia, but the IHC does not fit". The family addressed to the pediatric surgeon after the father discovered a lump in the left breast of his 3 y/o son. The child had unremarkable medical history with normal laboratory exams. On clinical examination, a well circumscribed mass was found. The boy underwent excisional biopsy under general anesthesia. The resected mass was oval, firm grey-white, solid with lobulated aspect on cut section and measured 1.5 cm in diameter.

Microscopically, the cells were arranged in solid and microcytic patterns with abundant granular eosinophilic cytoplasm. The nuclei were small ovoid/round with minimal pleomorphism and small nucleoli and showed rare mitotic activity. Eosinophilic secretion was present intracytoplasmic and in the extracellular material. On immunostains the cells were negative for ER, PR, Her2. Calponin and P63 were negative for myoepithelial cells, and the secretory eosinophilic material was positive for PAS and Alcian blue stain. The margins were involved. CK5/6 and mammoglobin were positive.

**Diagnosis:** The diagnosis was concluded as secretory breast carcinoma.

A FISH study was performed and showed that 70% of the tumor cells had rearrangement of the ETV6 gene. I had only one block so I spliced and re-embedded the tissue so I could have enough sections for you all. Each one of you will receive half of the lesion seen below, I believe that the essential histological feature are present in all slides.

Secretory breast carcinoma is a rare type of breast malignancy, representing 0,15% of all breast carcinomas. It is a triple negative carcinoma with an exceptional favorable prognosis.



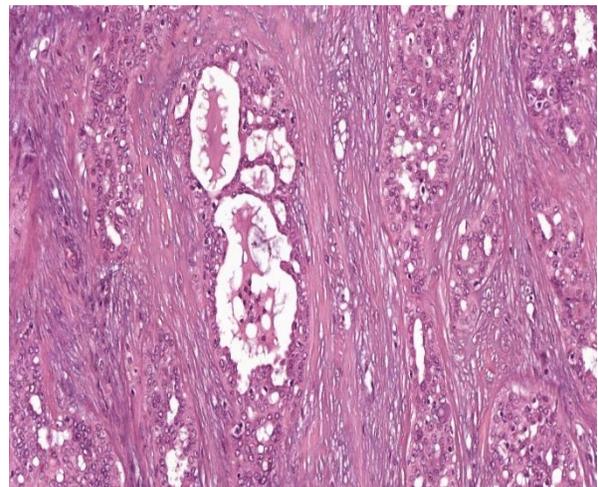
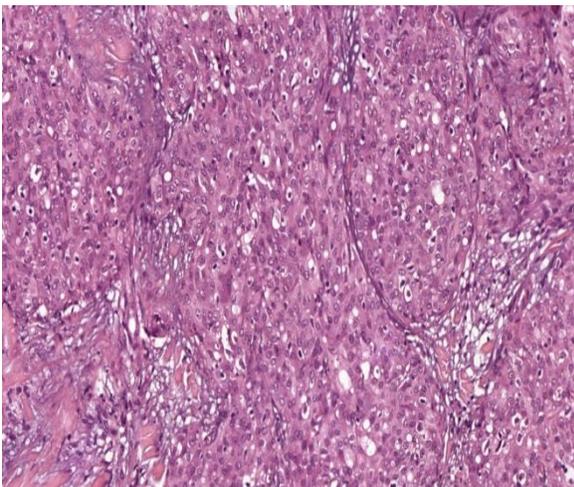
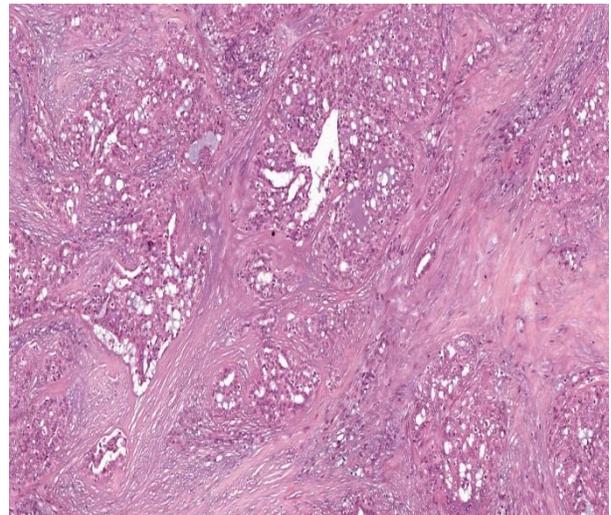
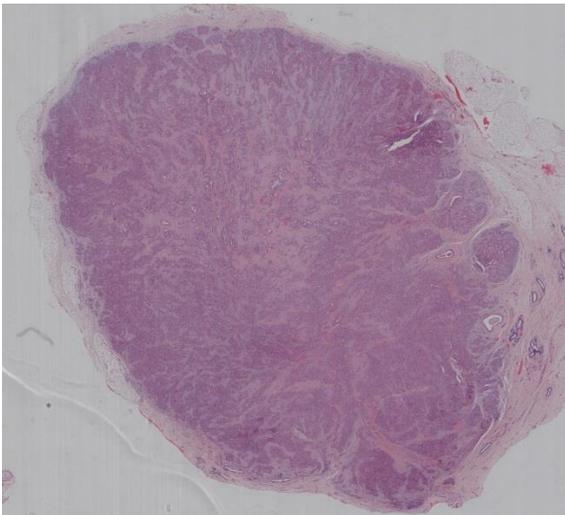
The tumor can occur in all ages, in the age group under 20 is more frequent in males. It has indolent clinical course, with exceptional favorable prognosis. The treatment is lumpectomy and SLNB, in males – mastectomy is the treatment of choice.

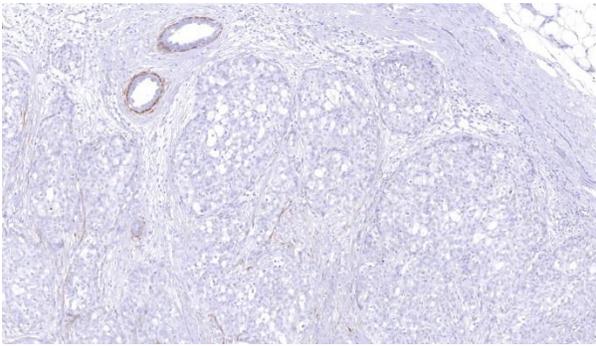
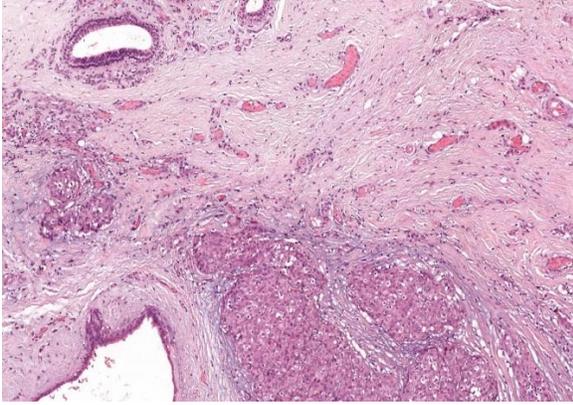
Recurrences may occur many years after initial treatment (>10 years), most are local and occur in the scar. Systemic metastasis are rare. ~30% of patients have ALN metastasis, usually < 3 nodes are involved. Nodal metastasis do not predict poor outcome.

As the margins were involved, one month later a mastectomy and SLNB were performed. Microscopic examination revealed few microscopic foci of secretory carcinoma in the scar region. The resection margins were free. SLNB was free of tumor.

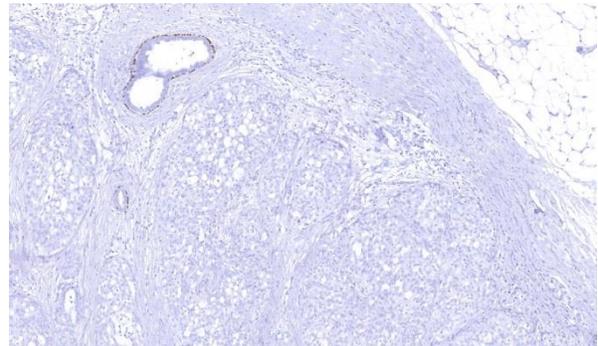
The patient did not receive adjuvant therapy and is currently disease free.

I believe that the take home message is for the clinicians to perform diagnostic core needle biopsy (CNB) to breast lesions, no matter patient's age and gender, before an excisional biopsy. This can avoid the unnecessary second trip to the operating room.





Calponin



P63

# AMR Seminar #71

## Case – 17

**Contributed by: Barbara Gazić, M.D., Ph.D.**

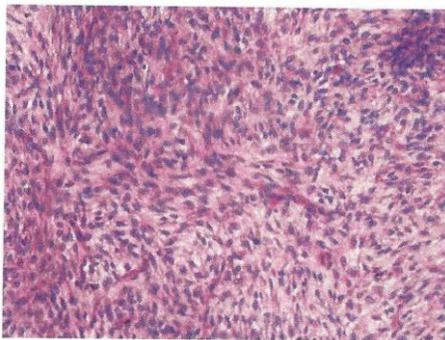
(Case Courtesy: Jerca Blazina, M.D.)

**Clinical History:** A 10-month-old girl presented with a rapidly growing subcutaneous tumor in the para-spinal region of the back.

**Pathologic Features:** The tumor is well demarcated but not encapsulated. It is composed of relatively uniform spindle-shaped cells in a loose myxoid matrix with prominent delicate thin-walled vessels. The tumor cells have mildly atypical nuclei, mitoses are not numerous (4/10 HPF) and there is no necrosis. Tumor cells are positive for CD99, Bcl-6 and cyclin-D1 and negative for CD34, S-100, desmin, Myogenin, MyoD1, EMA, Stat6 and MUC4. Molecular testing was negative for NTRK3/ETV6 gene fusion. We sent the case in consultation and got the information that tumor cells are also positive for BCOR.

**Diagnosis:** Primitive myxoid mesenchymal tumor of infancy.

**Comment:** Primitive myxoid mesenchymal tumor of infancy (PMMTI) is a rare tumor and less than 20 cases were reported to date (Cramer SL. Et al, 2017). It was first described by Allagio in 2006 as a primitive spindle, polygonal or round cell tumor with myxoid background, immunohistochemically only positive for vimentin and negative for SMA, desmin, Myogenin and S-100. It is a soft tissue sarcoma occurring almost exclusively in the trunk, extremities and neck of infants, histologically composed of sheets of primitive round to spindle cells, a delicate vascular network and a variably myxoid background (Allagio et al, 2006). Until recently, there were no known specific immunohistochemical markers or molecular alternations to distinguish PMMTI from its histologic mimics, and the diagnosis was based on morphologic features and the absence of the ETV6-NTRK3 gene fusion that is typically present in congenital infantile fibrosarcoma (Santiago et al, 2017). Recently PMMTI's have been found to harbor BCOR internal tandem duplication (ITD), the same genetic alternation detected in clear cell sarcoma of the kidney (Kao et al., 2016). In the same study, undifferentiated round cell sarcomas (URCS) were also tested and BCOR ITD was found in half of the cases. This overlapping between PMMTI, infantile URCS and CCSK suggests that PMMTI and a subset of URCS might represent the soft tissue counterpart of CCSK.



PMMTI, HE 20x

**References:**

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Santiago T, Et. Al. Recurrent BCOR internal tandem duplication and BCOR or BCL6 expression distinguish primitive myxoid mesenchymal tumor of infancy from congenital infantile fibrosarcoma. *Mod Pathol* 2017;30:884-891.

Kay YC, et al. Recurrent BCOR internal tandem duplication and YWHAE-NUTM2B fusions in soft tissue undifferentiated round cell sarcoma of infancy – overlapping genetic features with clear cell sarcoma of kidney. *Am J Surg Pathol* 2016;40:1009-1020.

# AMR Seminar #71

## Case – 18

**Contributed by: Saul Suster, M.D.**

**Clinical History:** A 56 year old woman was seen for uterine bleeding and an enlarged uterus. A biopsy was diagnosed as endometrioid adenocarcinoma, and a total hysterectomy and bilateral salpingo-oophorectomy was performed. The uterus contained a tumor that was diagnosed as a non-invasive endometrioid adenocarcinoma of endometrium, FIGO Grade 1. There were additionally a few small uterine myomas. The ovaries were within normal limits, except for a 2 cm. nodule in the right ovary that was diagnosed as a fibrothecoma (see attached slides).

**Diagnosis:** Unusual sclerosing ovarian stromal tumor.

**Comments:** I've never seen a lesion like this before in the ovary and I'm hoping our GYN experts can illuminate me and take me out of my misery. Our immunohistochemistry showed strong positivity of the tumor cells for vimentin and CD10. Stains for CD117, HBME-1, OCT4, S100, SOX10, cytokeratin AE1/AE3, calretinin, CK7, chromogranin, synaptophysin, NUT and SMA were negative. A stain for PAX8 showed strong cytoplasmic staining and faint nuclear staining. The histology is quite striking and distinctive and it looks like it ought to be "something", but I don't know what.

# AMR Seminar #71

## Case – 19

**Contributed by: Saul Suster, M.D.**

(Case contributed by Dr. Francisco Mucientes, University of Concepcion, Chile).

**Clinical History:** A 49 year old man without any significant past medical history was seen for lower GI bleeding. A colonoscopy showed an ulcerated tumor in the rectal mucosa. A biopsy showed a poorly-differentiated malignant neoplasm that was negative for melanoma, lymphoma, GIST, muscle and prostate markers. Wide spectrum keratin, NSE and CD56 were positive. At surgery, a solid mass was seen infiltrating the rectal wall as well as the prostate and seminal vesicles, and measured 12 cm. in greatest diameter. The main body of the tumor appeared to be located outside the rectum.

**Histology:** The tumor shows sheets of atypical cells with some clearing of the cytoplasm and a vague nested pattern of growth. There is marked cytologic atypia and numerous mitotic figures. I thought of the possibility of a malignant PECOMA, but HMB45 stains were negative and SMA showed only focal positivity in a few groups of cells. Stains for S100, DOG1, CD117, desmin, myogenin, chromogranin, synaptophysin and cytokeratin AE1/AE3 were negative.

**Diagnosis:** Undifferentiated malignant neoplasm, NOS (????).

**Discussion:** I got this case in consultation from Chile and was not able to offer anything other than UMN. The contributing pathologist was wondering about some type of undifferentiated sarcoma. Any help or suggestions for further work-up will be greatly appreciated.

# AMR Seminar #71

## Quiz Case – 1

**Contributed by: Saul Suster, M.D.**

**Clinical History:** A 47 year old man with no previous significant history was seen for the development of a slowly-growing soft tissue mass in his right flank. The mass was subcutaneous and attached to the fascia but did not involve skeletal muscle. The gross specimen showed a well-circumscribed, 6 x 4 x 3.5 cm nodule that shelled easily from the surrounding adipose tissue.