

# AMR Seminar #65

## Case – 1

**Contributed by:** Abbas Agaimy, M.D.

**Clinical history:** 79-year-old man was diagnosed with a large ulcerated cecal tumor and underwent right-sided hemicolectomy. Six months later, he developed extensive intra-abdominal tumor recurrence and died of his disease.

**Macroscopic features:** The resection specimen contained a transmural extensively ulcerated tumor 9x5x2 cm. The cut-surface was grey-white to brown and friable with extensive areas of hemorrhage and necrosis.

**Histological, immunohistochemical and molecular findings:** Histologically, the tumor showed extensive infiltration of all gut wall layers and the adjacent peritoneal fat with diffuse sieve-like pattern. Extensive mucosal ulceration was seen but no residual adenomatous tissue or intraepithelial neoplasia was detected. Histological examination showed poorly cohesive cells lacking stromal component and forming trabeculae and nests separated by thin fibrovascular septa occasionally forming acantholytic pseudoalveolar spaces. Although mucoid areas were focally seen, a true mucinous component was not detected. The tumor cells were small to medium-sized to large sized with polygonal configuration and large vesicular eccentrically located nuclei that contained one or two prominent nucleoli. The cytoplasm of many cells contained large hyaline "rhabdoid" filamentous paranuclear inclusions that pushed the nucleus to the periphery of the cell. Binucleated and multinucleated tumor cells were a frequent finding but there were no osteoclast-like giant cells. Areas of coagulative necrosis were easily identified. One regional node metastasis was detected and showed similar features. Prominent lymphovascular invasion and diffuse sieve-like infiltration into adjacent fatty tissue were seen.

Immunohistochemistry showed strong cytoplasmic paranuclear expression of vimentin and pankeratin in almost all of tumor cells in all cases (Fig. A). EMA and p63 were also variably expressed in the tumor cells. The tumor cells showed complete loss of nuclear MLH1 (Fig. B) and PMS2. SMARCB1/INI1 was also lost in almost all of tumor cells. The proliferation index (Mib1) ranged > 50% as well as TP53 expression. All other markers (including CK7, CK20, CDX2, CD34, CA125, ERG, CD30, CD31, CD56, synaptophysin, LCA, ALK1, etc.) were negative.

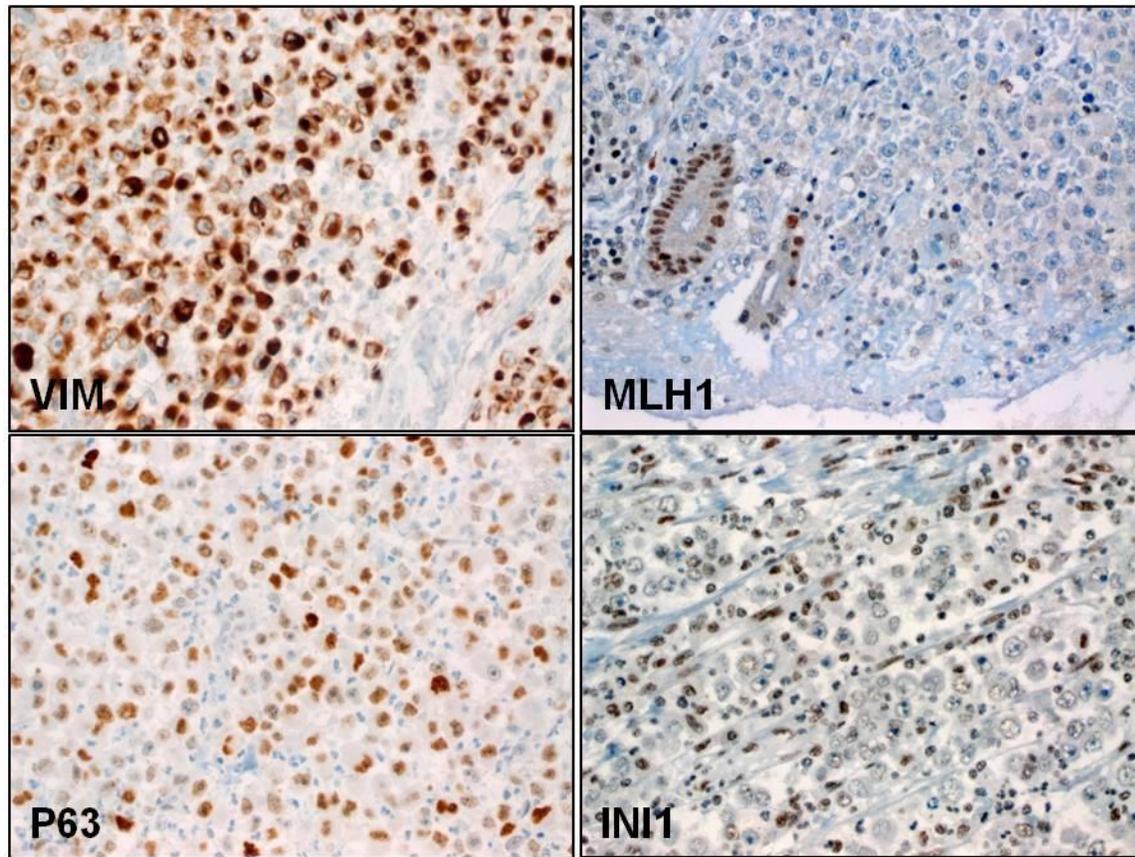
Molecular analysis revealed a BRAF mutation (V600E), high microsatellite instability (MSI-H), and CpG island methylator phenotype (CIMP).

**Diagnosis:** Sporadic microsatellite unstable colorectal carcinoma of the CIMP methylator phenotype (BRAF+) with extensive rhabdoid features and "probably secondary" SMARCB1 loss.

**Comment:** Carcinomas with rhabdoid features were first reported by Sommers and Meissner in 1954 as "pleomorphic giant cell carcinoma" of the pancreas followed by several reports from the lung, pancreas, gallbladder and other organs. Bak and Teglbjaerg were the first to report this variant in the tubular gastrointestinal tract in a series of four cases. We recently reported the current case and another one (from stomach) and reviewed 37 detailed previous cases (total: 39 cases). Review of these cases suggests a heterogeneous group of true epithelial neoplasms (carcinomas) that have undergone "dedifferentiation" probably through different secondary molecular mechanisms. Notably, 3 of 6 cases tested showed complete loss of SMARCB1/INI1. This variant is highly lethal with 83% of patients with follow-up > 12 months dying of disease at a mean period of 4 months (irrespective of INI1

status and presence or absence of glandular differentiation). Only 1/3 had a detectable glandular component. Interestingly, it is not uncommon for this variant to display pure rhabdoid morphology "dedifferentiation" in the primary tumor and to show higher glandular "redifferentiation" in the metastasis. This phenomenon was described in more than 5 cases (we observed such a case from the pancreas with pure adenocarcinomatous component limited to regional lymph nodes). The term rhabdoid carcinoma seems justified for these neoplasms to emphasize both their highly aggressive course and to stress their epithelial derivation. The CIMP phenotype represents another argument for the epithelial derivation of tumors without clear cut glandular epithelial differentiation. This phenotype has been reported in 3 of 4 cecal tumors analyzed; 2 of them also showed SMARCB1 loss.

This phenomenon of "rhabdoid dedifferentiation" nicely highlights the close association between genotype and phenotype in different neoplasms and also demonstrates that when genetic alterations known to be associated with a specific tumor morphology do arise in an otherwise distinctive entity it may cause a morphological shift towards a new looking lesion. A couple of composite neoplasms showing transition from a SMARCB1 positive ordinary adenocarcinoma (endometrium, pancreas, etc) to a SMARCB1 deficient rhabdoid neoplasm mimicking proximal type epithelioid sarcoma have been well documented. One case of INI1 positive ganglioglioma showed transition "dedifferentiation" to an INI1 deficient AT/RT. Thus the old saying "by one way or another, the daughter is a copy of her mother" is challenged by these uncommon "divergent daughter neoplasms". The nomenclature represents another unsettled issue. A question seems justified: should we classify by morphology (phenotype) or genetic (genotype) or both? Should we consider clinical parameters such as age, site etc. when classifying? Should we consider SMARCB1 deficient pure rhabdoid neoplasms at visceral location (esophagus, uterus) better as "rhabdoid" carcinoma variant than visceral epithelioid sarcoma? Looking for reading the comments of the club members, particularly regarding these controversial classification issues.



#### References:

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# AMR Seminar #65

## Case – 2

**Contributed by:** Phil Allen, M.D.

**Case Identification:** FMC 13/S09719,

**Contributors:** Drs. Nicole Sladden and Tony Thomas, SA Pathology at Flinders Medical Centre, Bedford Park, South Australia.

**History:** A female aged 50 had a hysterectomy and bilateral salpingo-oophorectomy performed in July 2012. The pathology revealed cervical endometriosis, an atrophic inactive endometrium with progestogen effect, adenomyosis, uterine leiomyomas, adenomyosis, bilateral ovarian endometriosis and bilateral ovarian adrenal rests. The patient made a good recovery but in April 2013 complained of pelvic pain. On examination, a large mass was palpable in the pouch of Douglas. MRI performed in June 2013 revealed a well-defined, heterogenous, necrotic, midline, extraperitoneal mass measuring 43x74x52 mm lying between and separate from the vagina and rectum. Close to the left pelvic side wall, there was an additional less well defined exophytic component measuring 16x13x16mm which demonstrated some peripheral spiculation/tethering. There was no increased T1 signal to suggest blood, nor any hypointensity on gradient echo to suggest blood products; no fat was present within the lesion and there were no enlarged regional nodes. The differential diagnosis suggested by the radiologist included a sarcoma and a gastrointestinal stromal tumor. No residual ovarian tissue was identified radiologically and the chest x-ray was normal. Most expected that the pelvic mass, which had appeared within 12 months of the hysterectomy, would be a sarcoma but a core biopsy was interpreted as endometriosis. This opinion provoked considerable scepticism amongst the gynecologists who proceeded to excise the mass, which they easily separated from the rectum and vaginal vault in July 2013. We received eight fragments of partly solid and partly cystic cream tissue, the largest measuring 30x11x8 mm. The patient had received some preoperative hormones including a progestogen but the dosage and duration of the therapy are still not clear.

**Diagnosis:** Polypoid endometriosis with necrosis clinically simulating a sarcoma in the pouch of Douglas 12 months after hysterectomy and bilateral salpingo-oophorectomy for conventional endometriosis.

**Comments:** Polypoid endometriosis was first described in 1980 by Mostoufizadeh and Scully<sup>(1)</sup> in a journal that had escaped my attention or memory, leaving me no option but to abide by one of pathology's most important rules, namely, when all else fails, consult the textbooks. Sure enough, the case comes close to the description on pages 723-725 of the second edition of Crum's excellent book,<sup>(2)</sup> where I also found a reference to Parker and associates key paper.<sup>(3)</sup>

The stroma in the circulated slides overshadows the rather atrophic endometrial glands and there is extensive pseudodecidual change with a pronounced chronic inflammatory cell infiltrate as well as numbers of small blood vessels reminiscent of those seen in the stroma of endometrial polyps. In some areas, the copious decidualized stroma forms polypoidal fronds that project into the histologically bland endometrial glands, reproducing the pattern seen in adenosarcoma. However, there is no stromal atypia or mitotic activity but there is extensive tumour necrosis, which Parker associates did not describe in any of their cases. I assume that these changes are the result of preoperative hormonal manipulation.

Have any club members seen necrosis and an adenosarcoma-like appearance in polypoid endometriosis and do you accept that these atypical features are due to hormonal therapy?

**References:**

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# AMR Seminar #65

## Case – 3

**Contributed by:** Michele Bisceglia, M.D.

**Clinical history** (slide labeled MB-856): An 11 year and eight month-old male was seen in the hospital because of a 3-day history of abdominal pain associated with nausea and vomiting. Laboratory and physical examination revealed profound microcytic hypochromic anemia, leukocytosis, mild left abdominal tenderness and a palpable abdominal mass. MR imaging of the abdomen disclosed a large, heterogeneous, multiloculated, partly contrast enhancing mass, which was centered in the left lobe of the liver causing marked displacement of the neighbouring viscera. There was also a modest accompanying ascites. Following transfusions and correction of his coagulation parameters, the patient underwent left hepatic lobectomy with attached adherent omentum.

**Gross features:** The left liver lobe weighed 2053 g, measured 22 x 19 x 9.5 cm and was extensively replaced by a well demarcated 22 x 17 x 9.5 cm variegated tan, pink to red tumor with a multiloculated gelatinous cut surface and areas of necrosis.

**Microscopic features:** A markedly pleomorphic tumor composed of undifferentiated stellate and spindle-shaped cells embedded in a loose to dense myxoid stroma with delicate vasculature is seen. Intracytoplasmic hyaline globules are visible in numerous tumor cells. Mitotic figures, including atypical mitoses, are also readily identified. Entrapped bile ducts can be noted in the tumor context, and a rim of normal liver parenchyma at the periphery of the tumor.

Immunohistochemically the tumor cells were diffusely positive for vimentin, and negative for Hep-par1, alpha-fetoprotein, cytokeratins, and skeletal muscle markers. CD34 was totally negative, highlighting a moderately developed vaguely hemangiopericytomatous-like vascularization. The intracytoplasmic hyaline globules were strongly PAS-diastase positive.

**Diagnosis:** Undifferentiated embryonal sarcoma of liver.

**Staging:** The tumor was adherent to the anterior wall of the stomach and to the transverse colon. The tumor invaded the omentum and was present at the surgical margin of resection. There was no evidence of regional lymph node metastases.

**Follow up:** Soon after the patient recovered from surgery, he was started on adjuvant chemotherapy, consisting of ifosfamide and doxorubicin, followed by radiotherapy. Subsequently the patient developed massive hemoptysis associated with ulcerative, radiation-induced gastropathy for which he underwent gastrectomy. He is now 14 year-old, with intermittent complains of epigastric abdominal pain, but with no evidence of residual disease by imaging.

**Discussion:** Undifferentiated embryonal sarcoma of liver (UES-L) is the 3rd most common hepatic malignant tumor in children, after hepatoblastoma and hepatocellular carcinoma (the latter developing on the background of cirrhosis due to metabolic causes (mostly) resulting from tyrosinemia type 1, bile salt export transporter deficiency, and long-standing total parenteral nutrition).

UES-L occurs predominantly under the age of 10 years, and over the age of 5 years. UES-L was first reported as an entity in 1978 by Stocker (the surgeon) and Ishak. A little more than 200 cases of UES-L have been reported so far. Around 60 cases of UES-L have been reported in patients over the age of 30 (age range 33-83years).

Janez Lamovec presented in Istanbul in 2011 at the 4<sup>th</sup> Int'l AMR symposium a case occurring in an adult female patient, which was incidentally discovered (patient asymptomatic!!). Please use Janez's handouts comment on UES-L both in adults and children as an integral complement to this comment of mine. Janez's case is posted on our AMR website at the below link/address (see references).

The possibility that UES arises from the malignant transformation of benign mesenchymal hamartoma (MH) has been raised, because of epidemiologic data (most of MH are diagnosed under the age of 5) and pathologic observations (pathologic evaluation of UES-L sometimes reveals the synchronous association of areas of MH as well as the pathologic evaluation of MH sometimes reveals the association of benign MH with malignant sarcomatous elements). However molecular evidence establishing this pathogenetic relationship has not been firmly assessed yet. Cytogenetic studies of MH have described aberrations in chromosome band 19q13.4, such as the translocation t(11;19)(q13;q13.4). Rearrangements of this region have also been found in UES-L harbouring areas of MH, but unfortunately it was unclear whether the cells with translocation were sampled from MH or UES. Other chromosomal aberrations involving chromosomes 6, 11, 12, 14, and Chr.X have been reported in UES-L.

Tumor size greatly varies, ranging from around 3 cm up to more than 30 cm.

Immunohistochemically, the tumor profile is the following: immunopositivity for vimentin in all cases and for Bcl2 in most of them. Focal expression of CD10, p53, calponin, smooth muscle actin, and desmin was reported in some of the cases. Also pancytokeratin (AE1/AE3), cytokeratins 18 and 19 has been reported as focally positive in some cases. The tumors are always negative for HepPar 1, myogenin, myoglobin, CD34, h-caldesmon, ALK-1, CD117 (c-kit), HMB45,  $\alpha$ -fetoprotein, and S100. The Ki-67 proliferation index ranged from 30% to 95% in tumor cells. Glypican-3 is positive in 50-60% of the cases which have been so investigate.

The differential diagnosis include poorly differentiated or sarcomatoid hepatocellular carcinoma, and hepatoblastoma with prominent mesenchymal or small cell component (these tumors are usually positive for Hep-Par1 and/or  $\alpha$ -fetoprotein, and for Glypican-3), and hepatic rhabdomyosarcomas (which can also be positive for glypican-3, but for diagnostic differential purposes is obviously positive for skeletal muscle markers).

UES-L is an aggressive tumor with poor prognosis in the great majority of cases, although modern multimodality therapeutic strategies have significantly improved the outcome and the expectancy of survival for these patients.

## References

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## AMR Seminar #65

### Case – 4

**Contributed by:** Ira Bleiweiss, M.D.

**Case History:** A 60-year old female presented with a 1.5cm well-circumscribed breast mass which was radiodense on mammogram. Ultrasound showed that the mass was solid and well circumscribed. Core biopsy was performed under sonography and was followed by excision.

**Pathology:** Histology reveals a spindle cell proliferation composed of plump occasionally epithelioid cells in clusters interspersed with dense keloid-like collagen bundles typical of myofibroblastoma. In some areas, the lesion appears to have the pattern of fibroadenoma/phyllodes with the spindle cell population investing itself into the epithelial-lined fronds. The spindle cell proliferation also involves surrounding fatty stroma. CD-34 was positive. Negative stains were desmin and beta-catenin.

**Diagnosis:** Myofibroblastoma (I think) possibly involving fibroadenoma (or is the whole thing a weird phyllodes?).

**Comment:** I thought this case was interesting in the sense that it is not the typical picture for myofibroblastoma. I had admittedly looked at this case over-and-over and I still can't quite decide what it is, except that it's benign and deserving of negative margins, which were achieved.

I have occasionally seen "rare" lesions of breast involving "common" lesions of breast either by arising within the latter or growing into the latter. I have always thought why not? Particularly if the common lesion is composed of normal breast elements, why couldn't any rare lesion arise within it? I wonder if the Club members have any similar experiences.

## AMR Seminar #65

### Case – 5

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

**Case History:** A 32 year old man underwent total colectomy for refractory ulcerative colitis. At three days of age, he was diagnosed with tricuspid atresia, hypoplastic right ventricle, and pulmonary atresia, and underwent immediate Blalock-Taussig shunt and at three months of age, underwent an atrial septectomy. He has known pulmonary hypertension and atrial fibrillation and has been on amiodarone. His diagnosis of ulcerative colitis was made at age 28, four years prior to colectomy. MR scan of the chest shows extensive systemic collateral supplying the lungs with enlargement of bronchial arteries, bilateral subclavian arteries, intercostal arteries, phrenic arteries, and subcostal arteries, including systemic vessels of the soft tissues in the upper abdomen.

Grossly, the intestine looked typical of ulcerative colitis. Many of the histologic sections of the colon showed a dramatic vascular proliferation similar to that in the slide cut for distribution. I thought that there was evidence of both ulcerative colitis as well as vascular proliferation. Typical cryptitis of ulcerative colitis was identified in the appendix, a site in which there was no vascular proliferation. An alternative conclusion had been that the ulcerative-like changes might be secondary.

I share this case for the interest of the group. I thought it was a dramatic example of secondary vascular proliferation. It was appealing to consider the possibility that this patient might have circulating angiogenic factors secondary to his underlying heart disease and associated collaterals (blood that bypasses the liver supposedly produces these factors), but I could not incite the interest of any of the clinicians to carry this any further. I welcome thoughts and comments.

**Possible Reference of Significance:** McMenamin ME and Fletcher CD. Reactive angioendotheliomatosis: A study of 15 cases demonstrating a wide clinicopathologic spectrum. *AJSP* 2002;26:685-697.

# AMR Seminar #65

## Case – 6

**Contributed by:** Kumarasen Cooper, M.D.

**Clinical History:** This two-year-old female child presented with hematuria and a left renal mass. She was born at 39 weeks with heterotaxy comprising situs inversus and polysplenia. Pediatric cardiology examination revealed no functional anomalies with her heart. Ultrasound revealed a left renal mass with cystic components.

**Radiology:** MRI demonstrated a mixed solid and cystic mass in the upper pole of the left kidney extending into the left renal sinus. Additionally the stomach was in the right upper quadrant with multiple spleens (polysplenia) present above the right kidney. The small bowel was predominantly in the right hemiabdomen whilst the large bowel was present in the left hemiabdomen. Vascular anomaly with an interrupted IVC with azygous continuation was noted.

CT scan revealed a complex partially enhancing mass epicentered in the central left kidney and extending to the surface of the renal cortex. The mass measured 2.9 cm in length x 1.5 cm transverse and 2.6 cm antero-posterior. The remaining parenchyma showed no abnormality. The right kidney was normal. Radiological differential diagnoses of the renal mass included Wilm's Tumor and mesoblastic nephroma.

**Gross Pathology:** Examination of the total nephrectomy specimen weighed 69 grams and the tumor measured 2.5 cm in diameter. The cut surface was firm, yellow-white and deeply lobulated filling the superior pelvo-calyceal system. A single cystic cavity measured 2.0 cm. Intra-operative consultation was relayed as: Stromal Tumor, negative for Wilms Tumor.

**Microscopic examination:** This unencapsulated tumor comprises entirely stromal cells imparting a lobular architecture and variable areas of alternating cellularity. The spindle cells entrap native renal tubules with an onion-skin cuffing and intracanalicular growth pattern. The spindle cell tumor extends to the pelvo-calyceal system. Focally, especially adjacent to the calyx, clusters of epithelioid cells are noted. However, there are no nodules of epithelial cells nor evidence of angiodysplasia and heterologous (cartilage and glial) elements in this tumor. Importantly there is no blastema, cytological atypia, nor mitotic activity. There is no morphological evidence of malignancy. Immunohistochemistry showed the spindle cells to be positive for CD 34, negative for pan-keratins (although entrapped tubules were positive) and positive for WT1 (both spindle and epithelioid stromal cells).

**Diagnosis:** Metanephric stromal tumor (MST)

**Discussion:** Stromal renal tumors of childhood comprise 15% of all primary pediatric renal neoplasms: congenital mesoblastic nephroma (CMN), rhabdoid tumor of the kidney (RTK) and clear cell sarcoma of the kidney (CCSK). Cellular variant of CMN bears the same t(12;15)(p13;q25) as congenital fibrosarcoma and is considered to represent the renal presentation of that entity. RTK carries the hSNF5/INI1 deletion on chromosome 22q (as with extra-renal rhabdoid tumors of children) and is considered to be part of the rhabdoid family of tumors. Hence true primary kidney-specific stromal tumors has diminished. The metanephric adenofibroma (previously nephrogenic adenofibroma) comprises bland embryonal epithelial cells (similar to metanephric adenoma) and bland spindle stromal cells (similar to MST).

In 2000 Argani and Beckwith described 31 cases of renal-specific MST with a mean age of 2 years presenting with an abdominal mass, treated with surgical excision without recurrence nor metastases. Most of these tumors were previously characterized as CMN. Distinction of MST from the latter can be difficult since both tumors are renal medulla centered and comprise bland spindle cells. The following features are helpful in this distinction:

- The subtle infiltrative border of MST is in contrast to the deeply invasive pattern of CMN.
- MST has a distinct nodular/lobular growth pattern, not seen in CMN.
- Prominent perivascular or peritubular collarettes are a feature of MST (and not CMN).
- Heterologous elements and angiodysplasia are unique to MST (although cartilage has been described in CMN).
- MST is CD 34 positive whilst CMN is desmin positive.
- CMN is now defined as presenting below 29 months. Any patient above this age is likely MST.

Even more important is the distinction from CCSK which requires chemotherapy and radiation treatment. CCSK comprising spindle cells is the crucial differential from MST. Both share bland spindle cells, a subtle infiltrative border, myxoid change and palisaded, storiform and hemangiopericytomatous patterns. However, the regular branching capillary vascular pattern is characteristic of CCSK but absent in MST. CCSK is also CD 34 negative.

The distinction from metanephric adenofibroma (MAF), a rare biphasic epithelial-stromal tumor, is much more complex. The question of whether the epithelial elements are entrapped (as in the present case) or whether they comprise part of the tumor remains the key deciding factor in deciding whether to diagnose MAF (discrete nodules of epithelial proliferations unassociated with native kidney) or MST (presumptive non-neoplastic epithelium entrapped at the periphery of the tumor). In reality metanephric neoplasms are probably a spectrum of differentiated tumors comprising a pure stromal tumor (MST), a pure epithelial tumor (metanephric adenoma) and mixed epithelial-stromal tumor (MAF). A single report of a complex 17q rearrangement in MST in a 3yr old boy has been described.

Finally whilst the origin of MST is not clear, Argani and Beckwith favor MST to be related to Wilms tumor (WT); postulating that MST may represent maturation of intralobar nephrogenic rests (with loss of the active blastemal components). The diffuse WT1 in the present case supports this theory. Interestingly, MST has a tendency to show cartilage and glial heterologous differentiation whilst WT tends to show rhabdomyoblastic and adipose differentiation. Accordingly MST should be treated with complete excision to avoid the potential risk for superimposed epithelial or stromal malignancy.

#### **Selected References:**

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## AMR Seminar #65

### Case – 7

**Contributed by:** Ivan Damjanov, M.D.

**Clinical History:** A 62-year-old, who was otherwise in almost perfect health, experienced some nasal congestions and rhinorrhea, which he thought was just a "common cold". After a few days he developed shortness of breath, accompanied by a dry cough, and was hospitalized. An x-ray disclosed bilateral interstitial infiltrates considered to be interstitial pneumonia. A work-up disclosed no obvious pathogens and he was discharged after 10 days. The discharge diagnosis was presumptive viral pneumonia and tachycardia thought to be a sign of viral myocarditis. At home his condition deteriorated and he was readmitted to the hospital one week later. His shortness of breath became more severe and the clinical work-up revealed persistent pulmonary infiltrates, pleural effusion, and a pericardial effusion. Ventricular fibrillation was noted and it led to cardiac arrest, which was, however, reversed. He nevertheless developed signs of multiple organ failure, which was thought to be due to sepsis, even though no bacterial infection could be identified. Pericardial fluid was aspirated and it contained atypical lymphocytes, which turned out to be positive for Epstein Barr virus and had a phenotype of NK/T cell lymphoma. His cardiac and pulmonary functions continued to deteriorate and he was placed on a respirator. His family decided to terminate all life sustaining measures and he died in cardio-respiratory failure, 2 months after the onset of first serious symptoms.

**Pathological Findings:** At autopsy we found cardiomegaly, with pericardial effusion. On gross examination of the heart we noticed some white and pale brown areas in the myocardium of both ventricles and thought that these were recent hypoperfusion type infarcts. The lungs were heavy and airless and we thought that he had diffuse alveolar damage (DAD) with hyaline membranes, corresponding to the clinical diagnosis of acute respiratory distress syndrome (ARDS). Upon histologic examination of the lungs we realized that the lungs also contained interstitial infiltrates of NK/T lymphocytes, often forming confluent nodules in the parenchyma. Similar lymphoma was found infiltrating the pancreas and focally the wall of the stomach. Lymphoma infiltrates were microscopically found in the myocardium and epicardium of all four chambers.

**Diagnosis:** Midline NK/T cell extranodal lymphoma, nasal type involving the lungs, heart, pancreas, stomach.

**Comment:** You have received a histologic section of the heart which contains infiltrates of neoplastic lymphocytes in the myocardium of the left ventricle. Adjacent cardiac myocytes show signs of injury and some myocytes have been replaced with fibrous tissue. Immunohistochemically, lymphoma cells reacted with antibodies to CD2, CD3 (cytoplasmic), CD56 and were negative for B cell markers. In situ hybridization confirmed that the lymphoma cells contained intranuclear virions of the Epstein-Barr virus. Identical lymphoma cells were found in the lungs, stomach and pancreas. Lymph nodes were sampled from several parts of the body but were not involved by lymphoma. We were not allowed to dissect the nasal area, but the x-ray images repeatedly taken over the last 2 months of his life showed no discrete lesions in the nasal-sinusoidal area.

Several autopsy studies show that lymphoma may involve the heart, usually in the terminal stages of the disease. After lung carcinoma, lymphomas are the second most common malignancy involving the heart in the US (1). Kanavar et al (2), who reported a nasal NK/T cell lymphoma

involving the heart and causing malignant arrhythmia, quote that 14-24% of terminal lymphoma cases showed cardiac involvement at autopsy. This paper is available on Internet and I recommend it to all those who want to learn more about cardiac lymphoma as well about NK/T cell lymphomas in general. The paper by Tiholoe et al (3) is yet another one that I found quite informative.

The case which I submitted is the first NK/T cell lymphoma involving the heart that I have seen in my practice. Arguably it might be also the first NK/T cell lymphoma first diagnosed in the US cytologically on a sample taken from the pericardial fluid. On the other hand NK/T cell lymphomas are much more common in the Far East, and thus I would not be surprised if some of our colleagues from the Far East have previously diagnosed NK/T cell lymphoma from pericardial fluid aspirates.

Lymphoma in the present case did not involve the nasal cavity or the sinuses. In the US, approximately 25% of "nasal type" NK/T-cell lymphomas do not involve the nose and appear first in other sites, such as nasopharynx or palate, or even outside the upper aerodigestive tract (4). These "extranasal forms of nasal" NK/T-cell lymphoma have a more aggressive clinical course (3).

### References

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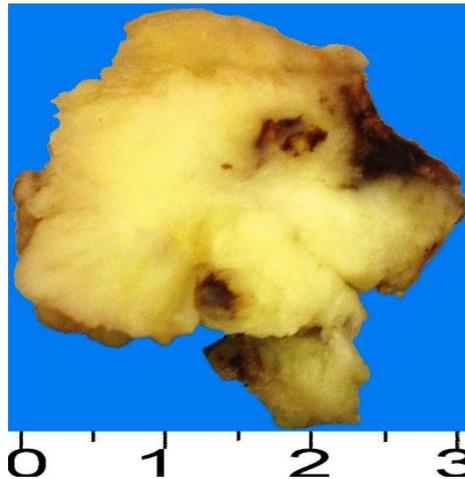
## AMR Seminar #65

### Case – 8

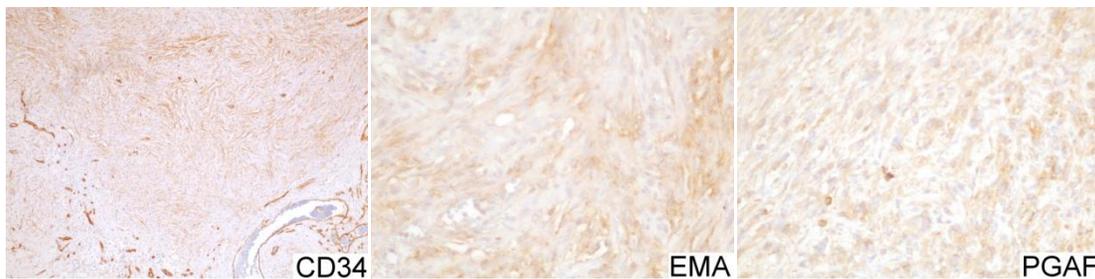
**Contributed by:** Hugo Dominguez Malagon, M.D.

**Case History:** A 47 year old male presented with a polypoid mass in the left maxillary sinus, he complained of obstructive symptom but was otherwise asymptomatic, the mass was removed by endoscopy.

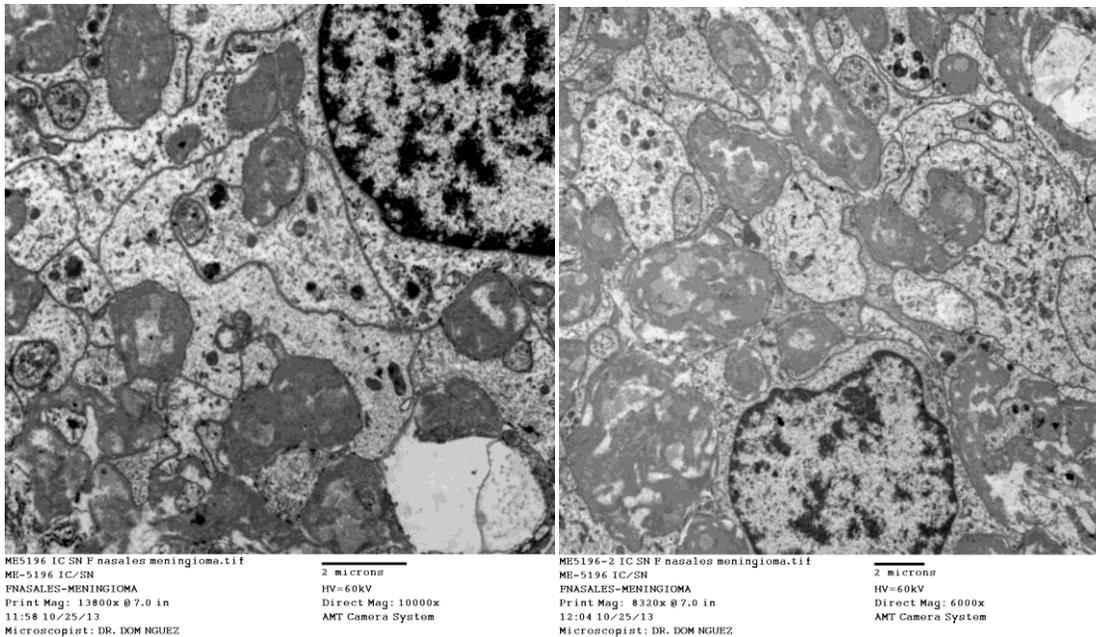
**Morphological Findings:** The tumor is composed of a rather uniform population of spindle-shaped cells arranged in fascicles and whorled pattern, occasionally there are plump cells; the cytoplasm is pale and fibrillary with undefined borders, the nuclei are slightly irregular, and occasionally have pseudoinclusions, chromatin is finely granular.



**Immunohistochemistry:** The neoplastic cells are positive for vimentin, EMA, and GFAP. Negative for S100 and keratin.



**Ultrastructure:** The cells are characterized by curved cytoplasmic processes and collagen deposits among them.



**Diagnosis: Extra Axial (Nasal meningioma)**

**Discussion:** Nasal meningioma is a rare entity with less than 40 cases published to date, the diagnosis could be straight forward when the typical meningiomatous histology is present, but it can be difficult in cases of desmoplastic and atypical ones. The immunohistochemical studies are usually confirmatory but like in this case the immunophenotype can be ambiguous. The ultrastructure is confirmatory as sometimes happens.

# AMR Seminar #65

## Case – 9

**Contributed by: Otto Dietze, M.D.**

**Case History:** 67-year old lady with a history of Coombs positive hemolysis which responded to steroids and moderate splenomegaly. Splenectomy was considered, but before it was carried out, bluish skin lesions developed on both breasts. In a small punch biopsy the diagnosis of Intravascular Lymphoma was made.

**Diagnosis:** Intravascular large B-cell lymphoma.

**Discussion:** Intravascular B-cell lymphoma is a type of large B-cell lymphoma and an aggressive disease. Our oncologists asked for a lot of stains and unstained sections for reference institutions, which we could not get from the small biopsy. A second biopsy was ordered by the clinicians and we could do all the staining they wanted and got even enough material for the AMR Seminar

**Reference:**

- Intravascular Large B-Cell Lymphoma. Arch Pathol Lab Med.2012;136;333-338.

# AMR Seminar #65

## Case – 10

**Contributed by:** Vincenzo Eusebi, M.D.

**Case History:** A nodule in the upper outer quadrant of the left breast was found in a 81 year old lady. No remarkable previous history of any kind. No diabetes present. A core biopsy was obtained for what has been diagnosed high grade invasive duct carcinoma (B5). Left mastectomy was performed together with sentine lymph nodes that proved negative. In spite of the negativity of the latter, axillary dissection (30 lymph nodes) was done. The removed breast measured 14x12x3cm. Nipple was normal. The nodule measured 2.4 cm across, was firm in consistency, whitish in color and showed fairly circumscribed margins.

**Histologic Features:** Histologically, the lesion shows, at the same time, features of low grade (syringoid) carcinoma, intermingled with areas with the features of adenoid cystic carcinoma. The stroma is partly fibrous, partly desmoplastic. Keratin 14 decorated most of the neoplastic cells, while keratin 7 was positive in glandular structures lined by luminal cells (true glands). Smooth muscle actin and calponin stained myoepithelial in 50% of the cord-like structures as well as myofibroblasts of the desmoplastic areas. Ki67 decorated 5% of neoplastic cells. ER, PR, HER-2 were consistently negative. All lymph nodes are reactive. A peritumoural and intratumoural lymphocytic lobulitis is well evident.

**Diagnosis and Discussion:** The lesion was regarded low grade (G1) invasive carcinoma. Nevertheless, we did not know how to precisely label the tumour. A compromise was reached as it was called syringoid (low grade adenosquamous) carcinoma merging with adenoid cystic carcinoma. Nothing is clear cut in pathology, and cases of adenoid cystic carcinoma have been seen in association with adenomyoepithelioma (1) and low grade adenosquamous (syringoig) carcinoma (2) which suggests the existence of a close relationship among these epimyoeplithelial tumours. The se tumours probably all represent part of the same spectrum.

The remarkable lymphocytic lobulitis seen in the present case is difficult to explain. The patient is not diabetecic. To the best of our knowledge, lymphocytic lobulitis is observed in cases of lymphoepithelial-like carcinomas (3) and rarely around medullary carcinomas. We have seen a case of intense lobulitis in a case of Hashimoto thyroiditis. The patient apparently does not suffer from the thyroid. Therefore, the nature of the present lobulitis is open to question and to your comments. The patient has no diabetes.

### References:

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## AMR Seminar #65

### Case – 11

**Contributed by:** Giovanni Falconieri, M.D.

**Clinical History:** The patient is a 20 year-old woman with an irregularly pigmented lesion of the back measuring 1 cm in largest dimension. Excision in carried out

**Gross and microscopic features:** A skin ellipse harboring a raised, tan nodule with irregular spotty brown areas is received. Histologic examination of H&E stained sections shows a compound, well circumscribed although slightly asymmetrical melanocytic proliferation. The junctional component is mostly unremarkable and made up of melanocytes either in small nests or in linear, lentiginous arrangement along the dermoepidermal junction, with rare upward migrating cells. The dermal component shows a distinct central area composed of epithelioid, larger cells with slightly eosinophilic and pale cytoplasm with distinct granular quality and small nuclei. No mitotic figures are recognized. These cells are immunopositive for Melan A and HMB45 (a picture is submitted). Aside from this area, a minor component featuring smaller melanocytes growing around adnexal units and splaying the deep collagen is recognized, positive for Melan A but not for HMB45.

**Diagnosis:** Compound melanocytic nevus with granular cell changes.

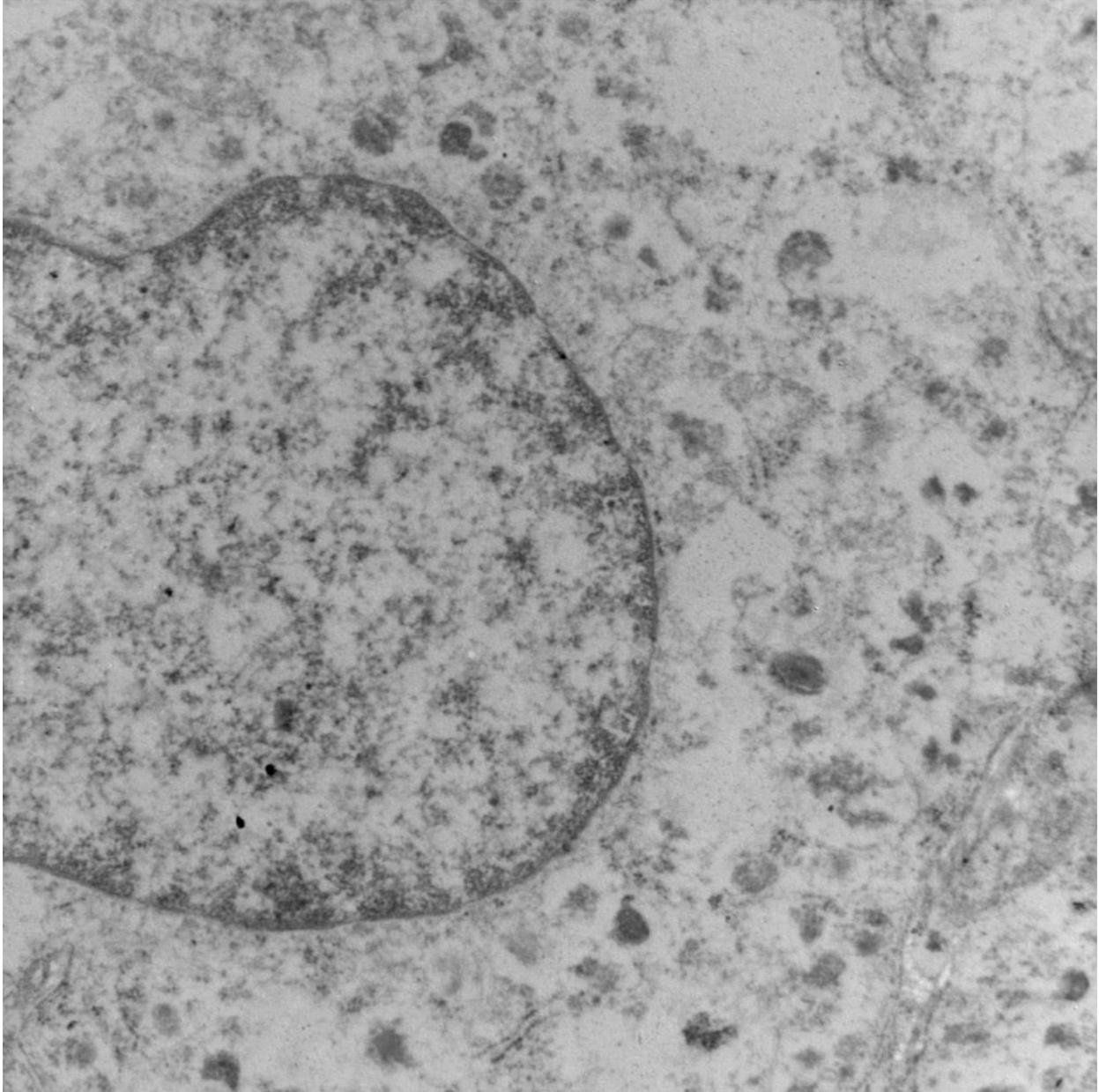
**Comment:** Although this case does not pose diagnostic challenges as long as the diagnosis of benignancy is concerned, I am circulating it since "granular cells" are apparently an underreported feature in melanocytic proliferation. Based on the immunophenotypic profile of the granular cells, which were strongly reactive for HMB45 in contrast to the adjacent "trivial" nevus, a possible explanation is a combined nevus made up of a dendritic, epithelioid-blue nevus-like cells, associated with a compound congenital nevus. Ultrastructural examination on deparaffinized tissue (performed by Dr Suster) indicates that the cell granularity might reflect lysosomal origin (EM picture enclosed).

I have already obtained some comments from accredited experts in the melanocytic/ dermatopathology area who have confirmed the interpretation above and who have indicated that "graunular" cells in nevi are quite unusual indeed. I have retrieved just one report addressing 2 similar cases (see below)

What do the club members believe? Any experience with similar lesions?

**Reference:**

- El-Gamal et al, JAAD 2004; 50: 765.



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EMR 2/13

#7

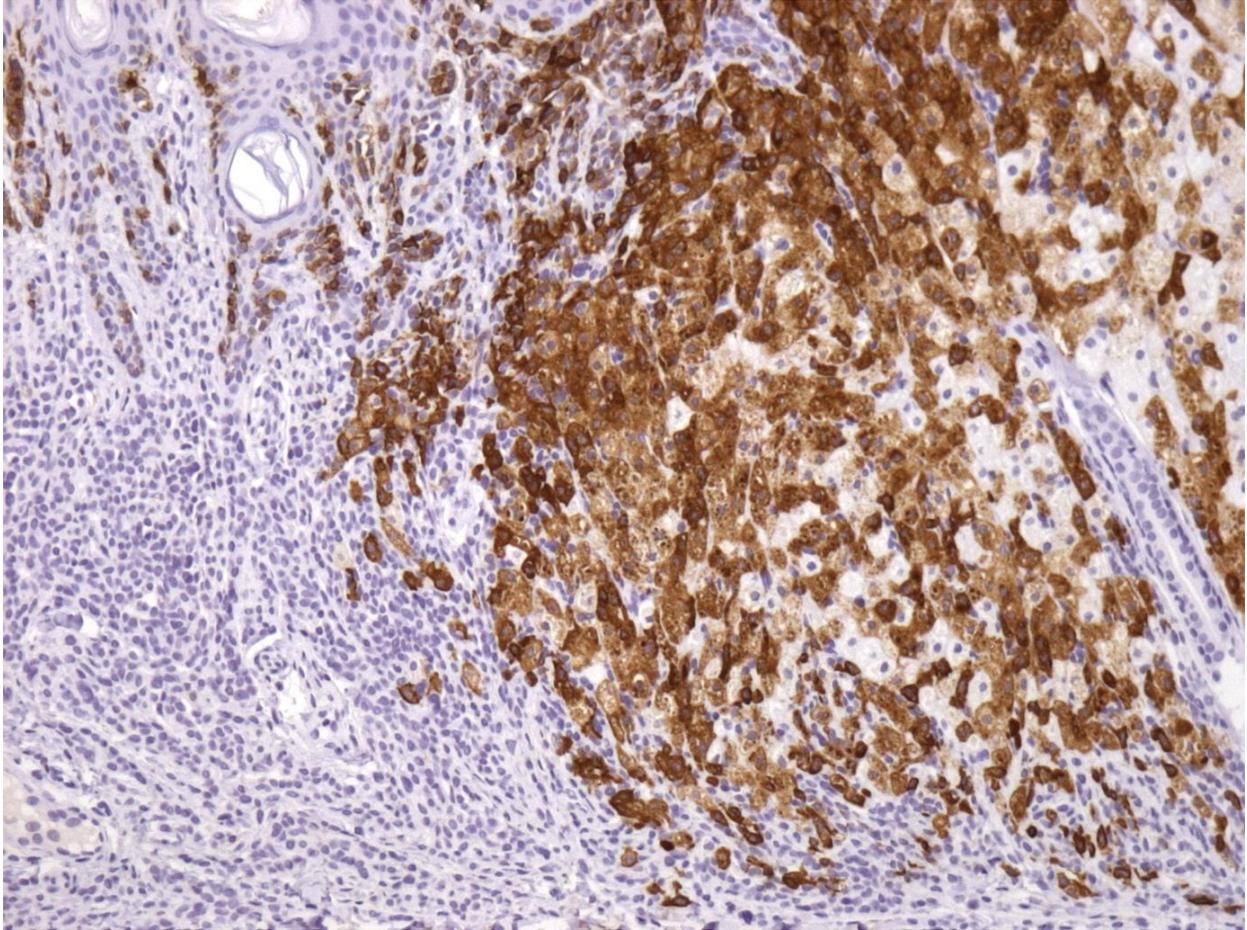
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# AMR Seminar #65

## Case – 12

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

**Case History:** A 25 year-old female had a hysterectomy for a clinically fibroid uterus following a biopsy diagnosis elsewhere of leiomyosarcoma. The hysterectomy specimen contained a fibroid-like mass, microscopy of which revealed nests of large rounded or polygonal cells with variable amounts of cytoplasm, and smaller adjacent or focally admixed, blander-looking spindle cell component. Mitotic index was 17/10HPF and there was focal necrosis. Immunostains were negative in polygonal cells for desmin, h-caldesmon, CD10, ER and PgR, and positive for cyclin D1. We demonstrated *YWHAE-FAM22* transcripts by RQ-PCR, with confirmation of the fusion by direct sequencing analysis.

**Diagnosis:** Endometrial stromal sarcoma with *YWHAE-FAM22A/B (NUTM2A/B)* rearrangement.

**Comment:** Up to half of typical low grade endometrial stromal sarcomas have a *JAZF1-SUZ12* fusion, with a smaller number harboring *JAZF1-PHF1* fusion.<sup>1,2</sup> Recently, a subgroup of higher grade and more aggressive ESS has been described with t(10;17)(q22;p13) rearrangement resulting in *YWHAE-FAM22A/B* gene fusion<sup>3,4</sup> (the *FAM22* partner gene, a *NUT* family member, has also been termed *NUTM2*). The findings in this case are similar to those reported.

This rearrangement appears to be specific (though similar changes have been found in pediatric clear cell sarcomas of the kidney) but breakages at the same loci *YWHAE* (17p13), *FAM22A* (10q23) and *FAM22B* (10q22) have been described in a uterine angiosarcoma.<sup>5</sup> The fusion results in activation of 14-3-3 oncogene, altered expression of which is associated with development and progression of cancer.<sup>6</sup> ESS with this translocation have cells in nests, often with large nuclei and irregular nuclear contours, and variable amounts of cytoplasm, as well as more than 10 mitoses per 10 hpf and focal necrosis. In 7 of 11 uterine tumors so rearranged, there was an additional cytologically bland and mitotically weakly active spindle cell component with a fibrous/fibromyxoid stroma (ESS, fibromyxoid variant<sup>3</sup>).

With immunohistochemistry, the bland spindle cells are diffusely positive for CD10 and estrogen and progesterone receptor, in contrast to the polygonal cells, which are negative for these markers but show nuclear positivity for cyclin D1,<sup>7</sup> and also membranous KIT (CD117)<sup>8</sup> (which can cause confusion, though DOG1, a.k.a. ANO1,<sup>8</sup> is negative).

These tumors arise in adults from 28-67 years (mean 50).<sup>3</sup> They usually present with higher stage disease and behave as high grade neoplasms. Metastases can comprise both components or the spindle cell component alone.

### References

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## AMR Seminar #65

### Case – 13

**Contributed by:** Christopher Fletcher, M.D.  
(Slides labelled – CFST 2382E)

**Clinical History:** A 71-year-old man was being worked up for abdominal pain of uncertain aetiology and, incidentally found on CT scan, there was a 4 cm mass in the region of the upper pole of the left kidney.

**Diagnosis:** Renal cell carcinoma, clear cell type, with very prominent smooth muscle proliferation

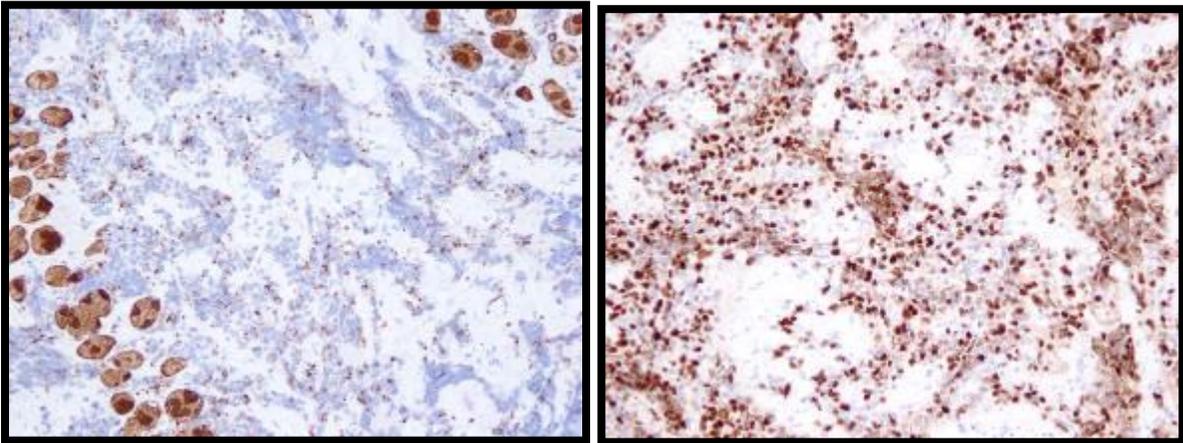
**Comments:** At least in my experience, this was a most unusual case. The bulk of the mass consisted of cytologically bland smooth muscle proliferation, within which there are just tiny microscopic foci of clear cell carcinoma (I hope that these are still visible on all of the sections which I have provided!). This lesion would seem to fall in the general category of tumors originally described by Kuhn et al in *Am J Surg Pathol* 2006; 30:1372-1381. The nature of the smooth muscle proliferation associated with a subset of renal cell carcinomas seems to have been disputed since that time – some authors believing that this represents a form of vascular proliferation induced by the carcinoma, other authors suggesting that this is a specific type of stroma intrinsic to the tumour and yet others suggesting that lesions of this type may in some (to me not very believable) way be related (at least mechanistically) to angiomyolipoma. Certainly this seems to be a rare occurrence, the biologic significance of which is poorly understood and I would be very interested to hear how our GU experts in the Club interpret this case.

## AMR Seminar #65

### Case – 14

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

**Case History :** A 93 year old woman presented to an outside hospital for evaluation of a rapidly growing mass of the left upper eyelid. Biopsy at the outside hospital showed a “small round blue cell tumor” which expressed

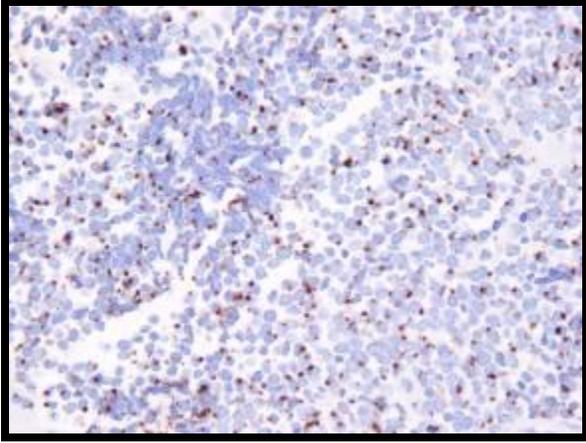


Desmin and Myogenin

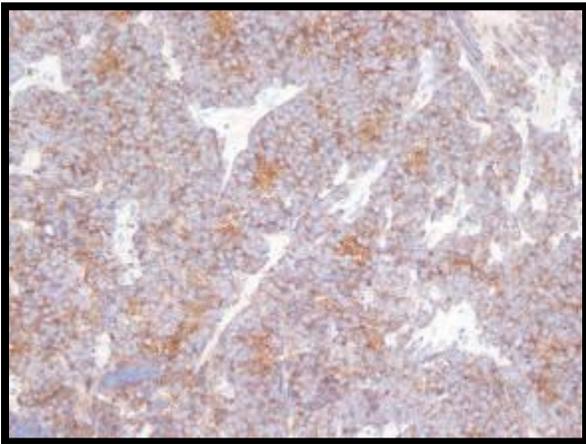
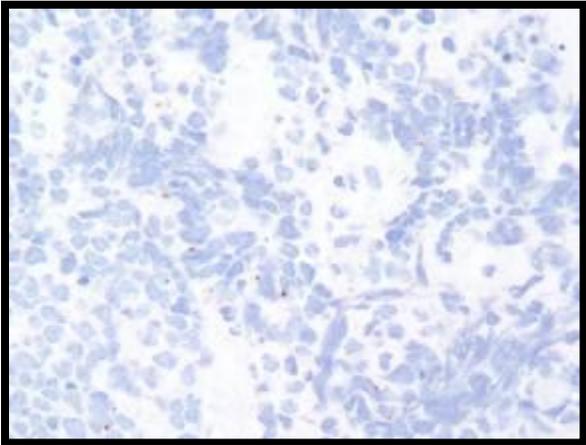
RT-PCR for alveolar rhabdomyosarcoma -associated fusion products was negative and the biopsy was signed out as a “fusion negative alveolar rhabdomyosarcoma”. The patient was then referred to our institution for definitive surgery.

#### **Re-excision**

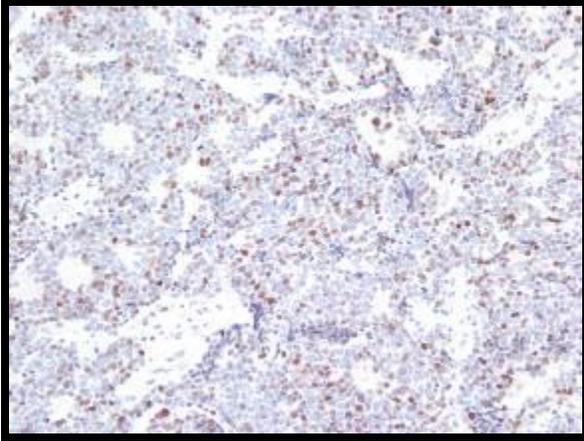
The slide you have for review is from the excision specimen, not the biopsy, but the morphological features of the tumor are identical. The subsequent excision of the eyelid mass showed a dermal and subcutaneous proliferation of primitive round blue cells with round, regular nuclei containing finely granular chromatin and inapparent nucleoli arrayed in a sheet-like, pseudoalveolar and vaguely organoid configuration. Cells in mitosis were frequent and necrosis was present. Rhabdomyoblasts were not identified. Metastatic tumor was also identified in one peri-parotid and one facial lymph node. By immunohistochemistry, the great majority of the tumor cells expressed keratins (OSCAR and Cam5.2 antibodies) in a paranuclear dot-like configuration



Rare cells showing dot-like CK20 expression were also present

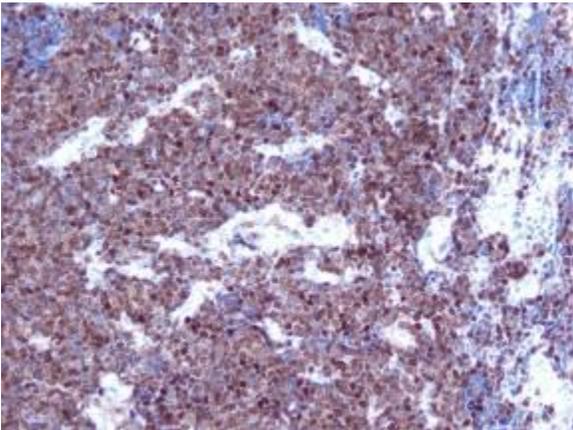


The tumor was diffusely positive for synaptophysin and contained scattered desmin and myogenin positive cells, as before.



Strong PAX5 and TDT expression (shown) was present.

Immunohistochemistry for Merkel cell polyomavirus large T-antigen was positive



**Diagnosis:** A final diagnosis of *Merkel cell carcinoma showing heterologous rhabdomyoblastic differentiation* was made.

**Discussion:** Heterologous rhabdomyoblastic differentiation in Merkel cell carcinoma (MCC) is extremely rare, and to my knowledge only 2 cases have been previously reported (before this one, which we reported in *J Cutan Pathol.* 2012 Jan;39:47-51). The first reported case presented on the buttock of a 70 year old male and was otherwise identical to the present case, as it showed typical features of MCC by conventional microscopy and also exhibited co-expression of CK20, synaptophysin, desmin and myogenin (1). The second reported case showed typical morphological and immunohistochemical features of MCC in the primary tumor, while light microscopical, ultrastructural, and immunohistochemical evidence of skeletal muscle differentiation was found in a lymph node metastasis (2). In neither of these cases was expression of MCPV demonstrated.

Alveolar rhabdomyosarcoma is the most important and challenging differential diagnosis for MCC with heterologous rhabdomyoblastic differentiation. Alveolar rhabdomyosarcoma most often presents in older children, adolescents and young adults, but occurrence in elderly adults has also been documented (3). Although rare, cutaneous alveolar rhabdomyosarcoma have been reported (4, 5). Further complicating matters, it is now well-recognized that alveolar rhabdomyosarcoma may show aberrant expression of epithelial and neuroendocrine markers, including keratins (but not CK20), synaptophysin, chromogranin A, and CD56 (6). Additionally, PAX5 expression may be seen in alveolar

rhabdomyosarcoma (7, 8). At the genetic level, alveolar rhabdomyosarcoma are characterized in approximately 75% of cases by t (2;13)(q35;q14) (*PAX3-FOX1A*) and in approximately 10% of cases by t (1;13) (p36;q14)(*PAX7-FOX1A*) (9). Although approximately 15% of alveolar rhabdomyosarcoma have traditionally been considered to be “fusion-negative”, the non-canonical translocations t(2;2)(p23;q35) (*PAX3-NCOA1*) or t(2;8)(q35;q13) (*PAX3-NCOA2*) have recently been identified in subsets of these cases (10). To date, all of these molecular genetic events are specific for alveolar rhabdomyosarcoma.

Demonstration of MCPV in tumor cells, considered to be specific for the diagnosis of Merkel cell carcinoma (11), may be very valuable in the distinction of Merkel cell carcinoma with heterologous rhabdomyoblastic differentiation from alveolar rhabdomyosarcoma. Although I am not aware of any studies that have specifically examined alveolar rhabdomyosarcoma for expression of MCPV, it would seem highly unlikely for it to be positive in such tumors. Immunohistochemistry for MCPV has been shown to be valuable in the distinction of Merkel cell carcinoma from other poorly differentiated neuroendocrine carcinomas that may involve the skin (11).

## References

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# AMR Seminar #65

## Case – 15

**Contributed by:** Ondra Hes, M.D.

**Case History:** Case sent to me by Ivan Damjanov in 2005. At that time I was not able to make diagnosis. After years we came to some conclusions regarding this tumor. A 54-year-old female underwent partial resection of the right kidney for an asymptomatic tumor, which was incidentally discovered on ultrasonography performed in conjunction with a traffic accident. The patient is alive and well 6 years after nephrectomy. Grossly, the well circumscribed tumor measured 3.0 cm in largest dimension. Tumor was located in the cortex with no connection to the pelvicalyceal system. Cut sections were solid with a gray to tan color. Necrosis was not seen.

**Histological findings:** The tumor was composed of two distinctive neoplastic cell populations which were arranged in various patterns, including a variety of complex lace-like patterns and solid aggregates composed of larger neoplastic cells. These alveolar nests were rimmed by distinctly smaller tumor cells. The large cell population was polygonal in shape and had abundant, dense eosinophilic cytoplasm which in many areas displayed a squamoid appearance. No definitive intercellular bridges or keratin pearls were identified. Mitotic activity was almost exclusively seen in the large cell component. An interesting phenomenon was the focal presence of emperipolesis.

The squamoid cells were immunoreactive for cytokeratins (AE1-AE3, Cam 5.2, CK 5/6, CK 7 and CK 20), EMA, racemase, and carboanhydrase IX (in 1 case focally). The small cell population was positive for CK7, EMA and racemase/AMACR. CK20, AE1-3 and carboanhydrase IX were negative. CD10 was focally positive in the large squamoid cells. Cathepsin K, E-cadherin and CD117 displayed focal positivity. Vimentin, RCC-marker, parvalbumin, c-kit, S100 protein, S100 A1, p63, p53, CDX2, uroplakin III, HMB45, TFE3, cathepsin K, WT1, synaptophysin, chromogranin A, thyroglobulin and TTF1 were negative. The proliferative activity (Ki-67) was low (1%) in the small cell component in both cases whereas the large neoplastic tumor cells displayed a significantly higher proliferation (20-35%).

**Ultrastructure:** Tonofilaments and well-developed desmosomes were revealed using electron microscopy.

**Diagnosis:** Biphasic alveolo-squamoid renal carcinoma.

**Comments:** The squamoid appearance of the large tumor cells were supported by the diffuse expression of cytokeratin 5/6 and the presence of desmosomes and tonofilaments in the ultrastructural study. Definitive morphological proof of full squamous differentiation was not confirmed by light microscopy (intercellular bridges and/or keratin pearl formation). The absence of nuclear expression of p63 is in line with the light microscopical impression, i.e. with „squamoid“ rather than complete squamous differentiation.

Squamous/squamoid differentiation is rarely seen in renal cell carcinomas (RCC). Only few such cases have been published [1, 2]. In all reported cases of RCCs with squamous differentiation this has consistently been found in the setting of sarcomatoid chromophobe RCCs.

Our case presented herein differs from chromophobe RCC not only by morphology, but also the immunohistochemical and molecular genetic profile is not compatible with chromophobe RCC.

The vast majority of kidney tumors with squamous differentiation are of urothelial origin [3, 4, 5]. Our tumor showed no evidence of urothelial differentiation; tumor was located in the cortex with no relation to pelvicalyceal system. Although coexpression of CK 7 and CK 20 is frequently encountered in urothelial neoplasms, uroplakin 3 and both p63 and p53 were completely negative. Tumor also differs from squamous cell carcinoma or adenosquamous carcinoma of the renal pelvis [5-9].

We encountered 2 cases of such tumor and the report has been published in *Annals Diagnostic Pathology* [10]. Actually we have 12-15 similar cases collected around the world and preparing a new paper. There is striking relation to papillary RCC, as it is possible to conclude from bigger series examined by IHC, arrayCGH and FISH.

**Conclusion:** 1) "biphasic alveolo-squamoid renal carcinoma" appears to be a unique and distinctive tumor; 2) emperipolesis present within large cell component is unusual phenomenon within RCCs; 3) the tumor showed no relations to urothelial carcinomas; and 4) it seems that such tumors have a close relation to papillary RCC.

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## AMR Seminar #65

### Case – 16

**Contributed by:** Janez Lamovec, M.D.  
(Courtesy of Dr. Olga Blatnik)

**History:** A 53-year-old man presented with a tumor on the dorsal surface of his right foot of 3 months duration.

**Gross pathology:** The excision specimen was represented by skin, subcutaneous tissue and a segment of the tendon of m. extensor hallucis longus. In the central part of the specimen, a partly delineated tumor was seen measuring approximately 3 cm in its largest dimension. Tumor was relatively soft, yellow-brown in color; it was grossly close to excision margins.

**Microscopic pathology:** The major part of the tumor is represented by solid nodules involving subcutaneous adipose tissue and focally extending into a deep dermis. Tumor cells are predominantly spindle shaped, focally more ovoid or epithelioid, with indistinct cell borders and pale eosinophilic cytoplasm. Nuclei are mostly spindle, partly ovoid or vesicular with indistinct or small nucleoli. Mitoses are very sparse. There are occasional large cells, with pleomorphic or lobulated nuclei and prominent nucleoli, somewhat resembling so-called virocytes, Reed-Sternberg-like cells or even ganglion-like cells. Tumor tissue is mostly dense, particularly at the periphery of the infiltrate myxoid areas are seen with paucicellular spindle cell population. Entrapped islands of adipose tissue are found in several foci; many deposits of hemosiderin highlighted by iron stain are scattered throughout the tumor, extracellularly or inside histiocytes. Small aggregates or individual lymphocytes are also seen in the central and peripheral parts of the tumor infiltrate which is richly vascularized.

**Immunohistochemical results:** Tumor cells were diffusely positive for vimentin, mostly for CD34 and negative for several other markers including S-100 protein, CD-68, SMA, cytokeratins and CEA. EMA showed focal weak membranous positivity in more pleomorphic foci. CD68 was strongly positive in histiocytic cells.

**Diagnosis:** Hybrid hemosiderotic fibrolipomatous tumor/myxoinflammatory fibroblastic sarcoma.

**Follow up:** Since there was a microscopic involvement of surgical margins the patient received postoperative irradiation; at this moment, 10 months following surgery there is no evidence of local recurrence.

**Comment:** We believe that this lesion exhibits histologic features both of HFLT and MIFS. Both lesions have been previously discussed in AMR seminars (29, 35, 49, 57). Recent cytogenetic studies demonstrated the high incidence of t(1;10)(p22;q24) in both MIFS and HFLT as well as common amplifications on 3p11-12. FISH analysis showed rearrangements in both TGFBR3 and MGEA5 genes in both lesions. VGLL3 gene on 3p12 showed frequent high level of amplification in both tumors as well. All these cytogenetic studies confirm the close relationship of these two lesions; hybrid tumors, as in our case, give further credence to such a proposition.

In our case, we were unable to test this tumor by FISH or other cytogenetic methods. The case was also examined by Dr. Folpe who concurred with our diagnosis.

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## AMR Seminar #65

### Case – 17

**Contributed by:** Michal Michal, M.D.

**Case History:** 64 year old woman presented with a subcutaneous tumor on the right neck 4.5 x 4 x 2 cm. The tumor was composed of mixture of tissues containing malignant glandular component, rather benign looking squamous component, undifferentiated neuroendocrine component, glial tissue (not present in the slides), and cartilaginous component (not present in the slides). FISH showed absence of p12 isochromosome. I inquired the submitting ENT specialist, whether the patient does not have a neoplasm in the nasal cavity-nasopharynx-paranasal sinuses and he confirmed with me that the patient has had a neoplasm removed from nasal cavity with subsequent irradiation several years ago.

**Diagnosis:** Metastasis of teratocarcinoma of the nasal cavity.

**Comment:** Teratocarcinoma is enigmatic neoplasm with dismal prognosis, that is different from any germ cell tumor and, to my knowledge, it has never been found in other regions than nasal cavity-nasopharynx-paranasal sinuses. Very typical, in my experience, is the (nearly) benign-looking squamous epithelium component abruptly changing into the glandular epithelium, nicely shown in the paper of Heffner and Hyams on their Figure 12 (1), which was well seen in other block from this case as well. In my experience, this benign-looking squamous epithelium component abruptly changing into the glandular epithelium is rarely seen in genuine germ cell tumors.

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## AMR Seminar #65

### Case – 18

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

**Clinical history:** 56 year-old man with a large retroperitoneal mass. Partial excision was accomplished with a difficulty for complete removal because of proximity to large retroperitoneal vessels.

**Diagnosis:** Rhabdomyosarcoma (pleomorphic), high-grade.

**Description and special studies:** The tumor is composed of epithelioid to spindled cells with pleomorphism, including multinucleated tumor giant cells. Mitotic rate is high >20/10 HPFs and tumor necrosis is present. Immunohistochemical studies were positive for desmin (extensive) and myogenin and MyoD1 (variable numbers of positive cells). Focal smooth muscle actin-positivity was also detected, whereas the tumor was negative for CD34, EMA, and keratin cocktails.

**Discussion:** This appears to be a monotypic rhabdomyosarcomatous tumor and therefore a rhabdomyosarcoma. It fits best under pleomorphic rhabdomyosarcoma, although also has similarities to tumors recently reported as epithelioid rhabdomyosarcoma. As no other components were detected in the sampling, the tumor was designated rhabdomyosarcoma. However, in the adults most tumors with rhabdomyosarcomatous elements are something else – other tumors with rhabdomyosarcomatous elements. In men the main choices are dedifferentiated liposarcoma and malignant Triton tumor (MPNST with rhabdomyosarcomatous differentiation). Additionally, germ cell tumors and certain carcinomas and even GIST may acquire a rhabdomyosarcomatous component. In women, uterine carcinosarcoma/MMMT is an additional choice for especially abdominal tumors. Quite possibly, some adult rhabdomyosarcomas could be just other tumors overgrown by a high-grade rhabdomyosarcomatous component.

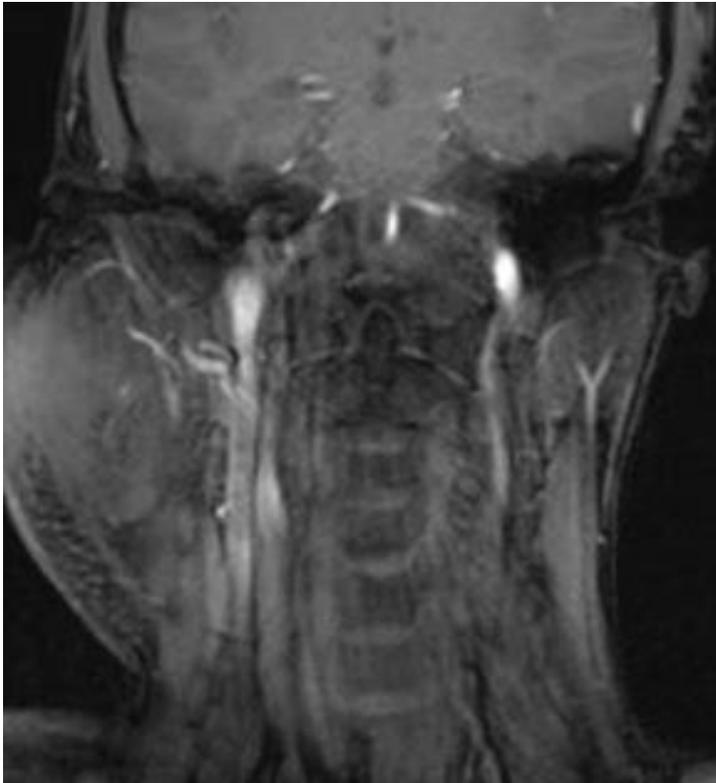
## AMR Seminar #65

### Case – 19

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

**Clinical history:** The patient is a 24-year-old Canadian First Nations man with a vascular mass on the right side of the neck with associated lymphadenopathy. Radiologically, the patient was thought to have a vascular lesion. Prior to the procedure, he was also found to have significantly increased eosinophils in the peripheral blood (6.62, Ref 0.0-0.4x10<sup>9</sup>/L; 49.5%, Ref 0.0-5.0%). The mass was embolized immediately prior to resection and one of the associated lymph nodes was biopsied out of concern for a hematolymphoid neoplasm. Following the surgical resection, the patient's eosinophils returned back to normal limits (0.33, Ref 0.0-0.4 10<sup>9</sup>/L, 3.7%, Ref 0.0-5.0%).

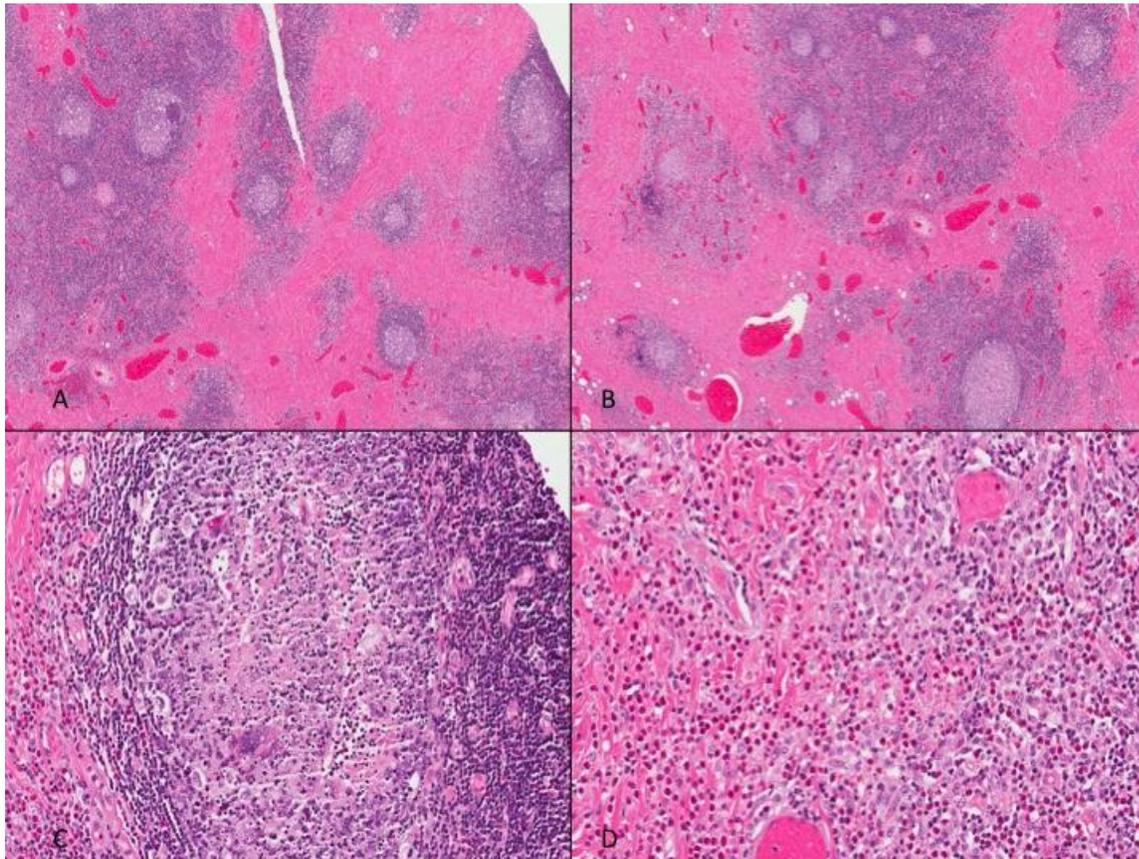
**Radiology (MRI):** Hypervascular mass lesion in the right posterior-lateral face and lateral neck with involvement of the parotid gland, sternocleidomastoid and trapezius muscles. Hemangioma was of diagnostic consideration.

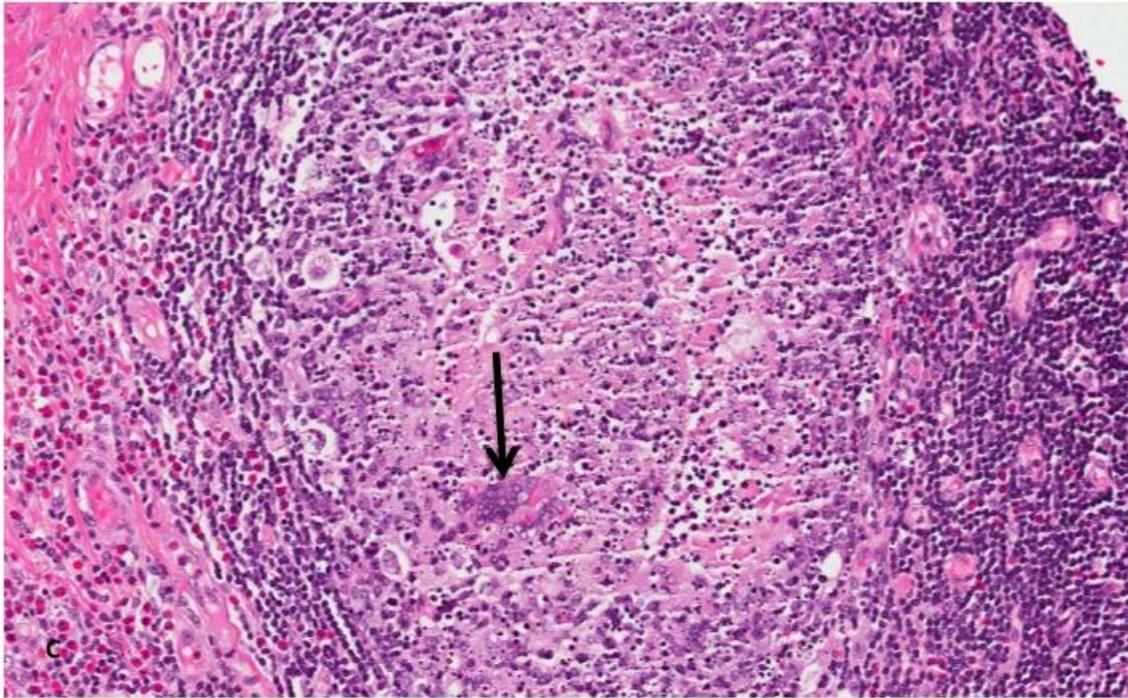


**Macroscopic features:** The resection specimen contains a vague fibrous density with ill-defined borders.



**Histological findings:** The sections of the mass (in submitted slide) demonstrate dense sclerotic areas (Figure A) of fibrosis with aggregates of lymphocytes with associated germinal centers and numerous vessels of varying size. (Figure B). These germinal centers show an extensive amount of central apoptosis with associated proteinaceous debris present (Figure C). In one of the germinal centers a polykarocyte was identified (Figure C expanded, see black arrow). Towards the periphery of these lymphoid aggregates there are varying amounts of significantly increased eosinophils. (Figure D).





The sections of the lymph node (section not submitted) showed similar findings in the germinal centers with scattered areas of eosinophilic microabscesses.

**Diagnosis:** Kimura disease (in both soft tissue and regional lymph nodes).

**Comment:** Kimura disease is an inflammatory process of unknown etiology that is understood to occur in Asian males and is commonly known for its associated lymph node involvement (otherwise known as Kimura lymphadenopathy). However, in a previous case series of Kimura disease in North America, only about a third of the cases were from patients of Asian descent. This case had many of the common histologic findings associated with Kimura disease, including follicular hyperplasia, germinal center proteinaceous deposits, germinal center necrosis, eosinophilic microabscesses, stromal sclerosis and occasional polykaryocytes.<sup>1</sup>

Because of overlapping histologic features and anatomic location, this entity has historically been lumped with angiolymphoid hyperplasia (which was discussed as he radiologically presented with a “vascular mass”), but Kimura disease is now regarded as a distinct diagnostic entity. In this case, the presence of associated lymphadenopathy, and peripheral eosinophilia (which resolved following resection) makes a much stronger case for Kimura disease. Morphologically, eosinophilic deposits in the germinal centers (likely IgE), polykaryocytes, and the lack of “epithelioid endothelial cells” would also be more consistent with Kimura disease.<sup>2</sup>

Special thanks to Dr. Ellen McPhail and Dr. Paul Kurtin for their assistance with this case.

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# AMR Seminar #65

## Case – 20

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

**Clinical History and Gross Features:** This male patient had a nephrectomy performed 2007 at the age of 44 years. The specimen contained an irregular 6 x 6.5 x 4 cm, solid, white-tan tumor which had invaded through the capsule and calyces and into the sinus fat. Tumor thrombi were present in the veins. Recently (2013) the patient suffered a local recurrence, confirmed on a core biopsy which contained malignant neoplastic tissue with the same histological features as the primary tumor.

**Histology** (section from the nephrectomy): The tumor displays the same morphological features throughout and is composed of sheets and nodules composed of small, rather monotonous neoplastic cells with limited cytoplasm and slightly irregular nuclei with fine to pale chromatin and absent to small – inconspicuous nucleoli. No formation of tubules or other organoid structures, including “real (pseudo- or non-pseudo) rosettes” are not present. Mitotic figures are easily seen, but the mitotic activity is not overwhelmingly brisk.

**Immunohistochemistry:** The limited immunohistochemical study that was initially performed showed that the tumor cells did not express cytokeratins (AE1-3) or desmin, but were positive for vimentin and NSE. The recurrence was moderately positive for CD56, negative for WT-1, cytokeratins (AE1-3) and LCA. Subsequently, after I was consulted on the case, additional IHC was performed on the primary tumor and this showed: diffuse nuclear expression of INI-1, no expression of CK7, EMA or CD56, but strong and diffuse membranous expression of CD99.

**Diagnostic considerations and Comments:** This is not an earth shattering case, but I still feel it has some points which makes it worth sharing with the members of the club. The initial diagnosis made on the tumor was “monophasic, blastematos, adult Wilms tumor”. I was given the opportunity to review the case and my opinion differed slightly.

Although Wilm’s tumor do occur in the adult population, this group has undoubtedly been “contaminated” by other unusual primary renal neoplasms [1]. Since ES/PNET was first described as a primary tumor of the kidney in 1975 [2], this is now a well established, albeit unusual primary renal neoplasm [3-8]. Many cases of adult “monophasic blastematos WT” in the non-pediatric population has turned out to be either Ewing sarcoma/PNET [7, 9, 10] or synovial sarcoma [11] and I think that most authorities would today be very hesitant to make a diagnosis of pure blastematos WT in an adult and require at least a biphasic, and ideally a triphasic line of differentiation. (In cases with a biphasic; blastematos and epithelial/tubular, appearance, one enters the somewhat murky waters of the area between WT and “atypical metanephric adenoma”).

**Diagnosis:** Based on the above and, given the histological features and the immunohistochemical findings, my preferred diagnosis was *primary renal Ewing sarcoma/PNET*.

A subsequent molecular genetic study (*EWS* rearrangement; FISH, break apart probe) was positive in almost all examined cell nuclei.

**Discussion:** This case highlights a few points and problems. Firstly, with application of new (molecular) techniques, "diagnostic habits" change over time as more refined (and true) classifications emerge, e.g. differences between tumors with overlapping microscopical features are carved out. Secondly, most of the literature on adult WT claims that the prognosis is significantly worse than in the pediatric population (with the same treatment protocols). Now, this may well be true, but given the high likelihood that the cohorts of adult WTs that have been studied with respect to treatment/prognosis, are mixed up with other tumors, this field has to be scientifically revisited. A third problematic area is the medico-legal aspect. Whenever, "new" information that may result in a reclassification of a tumor emerge (for example from scientific/academic endeavours), this information has to be conveyed to the treating team of physicians. This will generate problems that are not always easy to deal with.

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## AMR Seminar #65

### Case – 21

**Contributed by:** James Strauchen, M.D.

**Clinical History:** A 33 year old male with a right axillary mass. Excisional biopsy was performed. There was no significant past medical history.

**Pathologic Description:** The specimen consisted of an ellipse of skin over a well circumscribed, pink, fleshy, lobulated mass, consistent with an enlarged lymph node measuring 4.5 x 4.0 x 3.3 cm. Histology showed sheets of anaplastic cells with necrosis and scattered "hallmark" cells. Some sections showed sinusoidal involvement. Immunohistochemical stains were positive for CD4, CD5, CD30, CD43, CD68, CK8/18, EMA, and ALK-1 (cytoplasmic); negative for CD2, CD3, CD7, CD8, CD15, CD20, CD45, PAX-5, and PLAP.

**Diagnosis:** Anaplastic large cell lymphoma, ALK positive.

**Comment:** Although not particularly challenging diagnostically, this case did raise some interesting issues. There was positivity for cytokeratin with CAM5.2 (CK8/18), which is recognized to occur in some cases. The positive cytokeratin along with the positive EMA and the negative CD45 could cause confusion with metastatic carcinoma. CD68 positivity is also observed in some cases with KP-1 (but supposedly not with PG-M1), which could cause confusion with histiocytic sarcoma. In a young male with a CD30 positive malignant neoplasm, the differential diagnosis with embryonal carcinoma also arises. In this case placental alkaline phosphatase (PLAP) was negative and anaplastic lymphoma kinase (ALK-1) was positive. The cytoplasmic positivity for ALK suggests a t(2;5) variant translocation. ALK positive anaplastic large cell lymphoma occurs predominantly in children and young adults and has a favorable prognosis with conventional chemotherapy. Targeted therapy with the ALK inhibitor crizotinib will likely play an increasing role in the future. ALK negative anaplastic large cell lymphoma, in contrast, occurs in older individuals and has a less favorable prognosis.

## AMR Seminar #65

### Case – 22

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

**Case History:** This case is of a 64 y.o. lady that was diagnosed in her homeland with infiltrating ductal carcinoma of the breast. 5 paraffin blocks were submitted to our department via the medical tourism office of the hospital joined with a very short diagnosis of her medical condition. Except for her diagnosis, albeit great efforts, we could not get any medical history or imaging studies.

Because of the high expenses for their stay, medical tourists are advised to fly over only after completion of revision of their pathological material. We got 5 paraffin blocks of the tumor that were re-embedded into new paraffin blocks.

**Histologic Findings:** The first impression I got looking at the HE in low magnification was of an ill-defined lesion showing an infiltrating or a pseudo-infiltrating pattern. There are small tubular structures composed of bland appearing cells at areas with clear cytoplasm. The nuclei are small and regular without nucleoli. In high magnification myoepithelial cells are identified in those tubular structures. The stroma is fibrotic at areas replaced by fat tissue. Several attempts to perform immunostains failed, probably due to poor tissue quality or poor tissue processing. I did not have any radiology, immunos, and not even the original pathology report. I had to conclude a diagnosis based on the H&E alone.

**Diagnosis:** A benign breast lesion; the differential diagnosis includes adenomyoepithelioma, hamartoma, microglandular adenosis and adenosis tumor.

**Comment:** I emphasized in my report that due to the discrepancy of diagnosis, upon receiving this report the treating physician should obtain the original pathological report and confirm that those blocks actually belong to the patient. In addition, the pre-surgical imaging studies must be reviewed and reevaluated, in any case close patient follow up is recommended. The patient is lost for follow up.

This case highlights the great difficulty we have trying to do the best we can without clinical data, radiological data, provided with badly processed material and with no access to the patient or to the treating physician.

I would very much want to get comments about the diagnosis on this case, and about this troubling situation that I'm sure is shared by many of the club members.

## AMR Seminar #65

### Quiz Case – #1

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

**Case History:** A 60 year old woman underwent resection of a mass in the right buttock that had been present for over five years and slowly enlarging. The process shown in the slides presented are from the resection but similar features were noted in biopsies taken at the time of initial presentation five and a half years earlier.

### Quiz Case - #2

**Contributed by:** Saul Suster, M.D.  
(Courtesy of Dr. Guillermo Martinez-Torres, Columbian/St. Mary's Hospital, Milwaukee, WI).

**Case History:** A 70 year old woman with no significant past medical history was seen for multiple bilateral nodules on chest X-rays and CAT scans of the lung.