

AMR Seminar #72

Case – 1

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

History: A 59-year-old woman with a known diagnosis of Hashimoto thyroiditis complained of a right infra-auricular 4 cm. nodule for 2 years. FNA at an outside hospital diagnosed this nodule as mucoepidermoid CA. As a child (7 years of age), she was treated with radiation therapy (XRT) to shrink her tonsils because of repeated episodes of “tonsillitis”. Her sister had the same radiation therapy as a child, and she also developed a parotid tumor in 1991 which was reportedly benign.

Pathology: This slide is representative of the entire mass and shows a multilobulated infiltrative population of cells displaying a variety of patterns including solid, reticular, pseudopapillary, and tubular. As you will note, the inked margin is positive in some of the slides. Malignant cells are composed of monotonous large vesicular nuclei containing a single usually centrally placed and discrete macronucleolus. Cell cytoplasm is lightly eosinophilic to clear. A myxoid background is easily appreciated. Mitoses are infrequent, and necrosis is largely absent in this slide. Immunoprofile = diffuse positive staining with p63, calponin, AE1/AE3, S-100, CD117, and EMA confirming the myoepithelial differentiation of these cells. GFAP staining and *EWSR1* gene rearrangement testing were not performed. One of seven lymph nodes contained metastatic deposits (1/7).

Diagnosis: Myoepithelial carcinoma of parotid with lymph node metastasis.

Comment: Subsequent to superficial parotidectomy and radiation therapy, this patient has been disease free for 9 years. A couple of cases of myoepithelial carcinoma of the major salivary glands were shown at the AMR seminar in Bratislava 2015 by Drs. Alena Skalova and Goran Elmberger. However, since a significant number of club members were not at that meeting, I thought I would share this slide with the entire group. As highlighted by both Alena and Goran in the Bratislava conference, myoepithelial CA has a variable outcome ranging from widespread metastatic disease, to multiple local recurrences, to being disease free. This variation in biologic behavior cannot be predicted from analysis of the histopathology. As one would expect, the parotid is the most common site. Multilobulation and a myxoid or hyaline matrix are not uncommon. Because of the “plasticity” of these cells, a variety of histoarchitectural patterns is frequent in the same tumor as noted in this case. A definitive diagnosis requires IHC demonstration of myoepithelial differentiation. Alena and her colleagues described a clear variant harboring *EWSR1* rearrangement in a subset of cases.

The only slightly unusual aspect of this case is the history of radiation (dosage unknown) to her neck 52 years earlier to shrink her enlarged tonsils. Both she and her sister had this procedure performed on them as young girls and both subsequently developed parotid tumors, but no thyroid cancers. The increased risk of developing salivary gland cancer as a consequence of prior radiation exposure has been well documented.

Selected Reference:

1. Simpson RHW. Myoepithelial tumours of the salivary glands. *Current Diagn Pathol* 2002; 8:328.
2. Bell D, DiPalma S, et al. Myoepithelial carcinoma. In: *WHO Classification of Head and Neck Tumours*. El-Naggar A et al. (Eds.), 4th edition, Lyon, 2017, p. 174.
3. Skalova A, Weinreb I, et al. Clear cell myoepithelial carcinoma of salivary glands showing *EWSR1* rearrangement: molecular analysis of 93 cases. *Am J Surg Pathol* 2015;39:338.

AMR Seminar #72

Case – 2

Contributed by: Thomas Mentzel, M.D.

Clinical History: A 14-year-old male patient developed within one year a soft neoplasm on the left upper arm. The neoplasm was completely excised with tumor free margins.

Pathological Findings: Histologically, an ill-defined, infiltrative mesenchymal neoplasm is seen. The neoplasm is composed of spindled, stellated and multinucleated tumor giant cells that are set in a collagenous stroma with numerous vessels and dilated, pseudovascular spaces lined by neoplastic cells. In the periphery a diffuse infiltration of the subcutaneous fat by uniform spindled cells arranged in a storiform growth pattern is noted. Immunohistochemically, the neoplastic cells stained positively for CD34, the remaining antibodies (S-100 protein, desmin, CD99, EMA) were all negative.

Diagnosis: Giant cell fibroblastoma with areas of dermatofibrosarcoma protuberans.

Comments: Giant cell fibroblastoma represents a rare mesenchymal neoplasm arising predominantly in children and adolescents (M > F) as a slowly growing, painless mass at the trunk and the extremities. However, in general the anatomic distribution is wide and rarely elderly patients are affected as well. Clinically, giant cell fibroblastoma represents a locally aggressive neoplasm with an increased rate of local recurrences, whereas distant metastases do not occur. Although morphologically different, dermatofibrosarcoma protuberans and giant cell fibroblastoma are closely related, and shared cytogenetic changes as well as the presence of hybrid cases showing (as the presented case) features of both "entities" emphasize this classification. A problem in the differential diagnosis, especially if dealing with a small biopsy only, may represent fibrous hamartoma of infancy. Cases of fibrous hamartoma of infancy may lack the classical triphasic morphology and may show prominent hyalinized zones with cracking artefacts and an expression of CD34 by tumor cells mimicking morphological features of giant cells fibroblastoma. In these cases FISH-analysis for PDGFB rearrangement is very helpful for the diagnosis.

References:

Al-Ibraheemi A, Martinez A, Weiss SW et al. Fibrous hamartoma of infancy: a clinicopathologic study of 145 cases, including 2 with sarcomatous features. Mod Pathol 2017; 30: 474-485

Jha P, Moosavi C, Fanburg-Smith JC. Giant cell fibroblastoma: an update and addition of 86 new cases from the Armed Forces Institute of Pathology, in honor of Dr.Franz Enzinger. Ann Diagn Pathol 2007; 11: 81-88

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Case – 3

Contributed by: Masaharu Fukunaga, M.D.

Clinical history: A 76-year-old, gravida2, parity2, female was admitted because of abnormal uterine bleeding. She had no history of malignancy. Image analyses indicated an endometrial tumor with myometrial. Cervical and endometrial cytology and biopsies showed "adenocarcinoma". Simple abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph nodes dissection. The patient is alive with disease 3 months after surgery. Ascites cytology indicated adenocarcinoma.

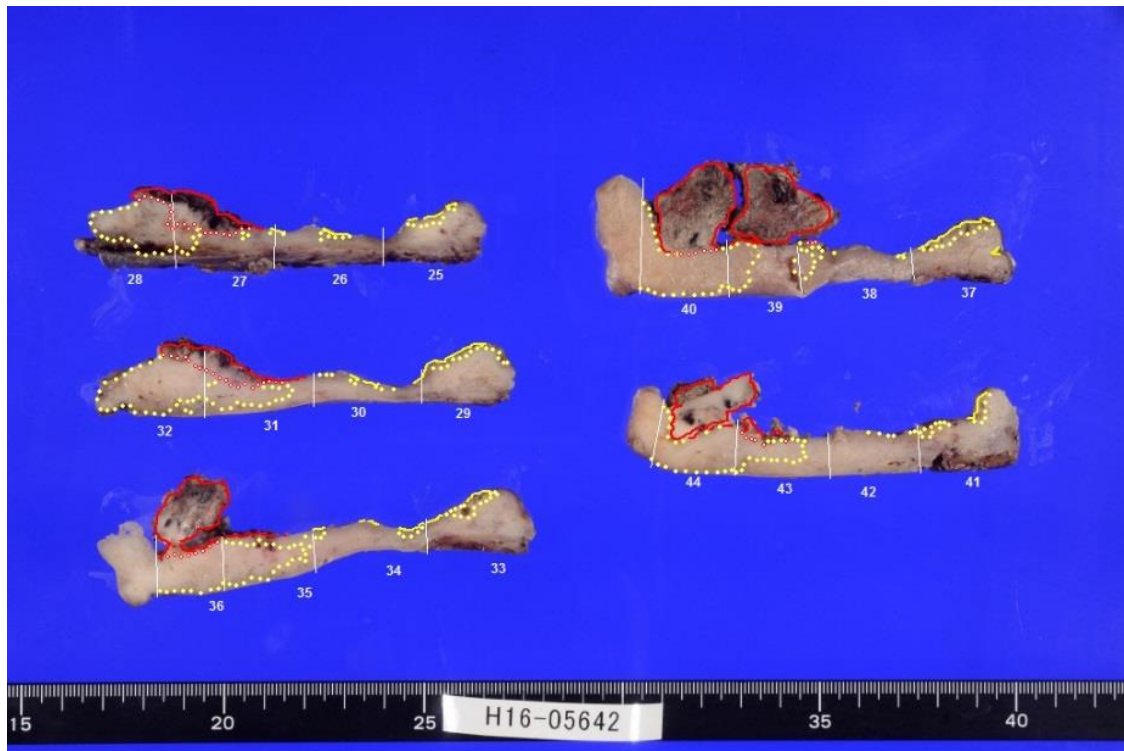
Pathologic findings: Macroscopically the uterus measured 8x12x5cm and the cavity was filled with 7cm polypoid soft tumor. The uterine was elastic hard without apparent nodules. The left ovary measuring 4cm was mature cystic teratoma. There was no abnormality in the right ovary and tubes. Distributed glass slides were from the uterine body. Microscopically, two types of carcinoma were identified. The first was mucinous carcinoma, gastric type, characterized by glandular proliferation of cuboidal cells with round nuclei, clear cytoplasm and distinguished cell borders. This tumor diffusely infiltrated into full thickness of the uterine body. The second tumor with polypoid growth in the endometrium was hepatoid carcinoma. It showed trabecular, sinusoidal, or alveolar arrangements of moderately atypical cells. The two types of carcinoma seemed to grow independently. No lymph node metastasis was found.

Immunohistochemically, the gastric type mucinous carcinoma was positive for HIK1083, MUC5AC, and MUC6 and negative for p16. The hepatoid carcinoma was positive for AFP, Glicopican3, Arginase1, p53 and negative for Hepatocyte, ER and PgR.

Diagnosis: Combined hepatoid carcinoma and gastric type mucinous carcinoma of endometrium.

Comment: Combined uterine case of hepatoid carcinoma and gastric type mucinous carcinoma (GMC) has not been reported to date. GMC is a new entity of cervical adenocarcinoma in WHO 2014(1). Minimal deviation adenocarcinoma (adenoma malignum) is now considered an extremely well differentiated type GMC. This type of tumor shares 25% of the cervical mucinous carcinoma in Japan. GMC is composed of cells with abundant clear or pale, eosinophilic cytoplasm and distinct cell borders. GMC is positive for HIK1083 and MUC6, MUC5AC and negative for HPV and p16 (2,3). GMC are thought to have a worse prognosis compared to the usual type (2).

Hepatoid carcinomas in the female genital track have reported and are often associated with Mullerian tumors, including serous, endometrioid, and mucinous carcinomas. The present case may represent gastric type mucinous adenocarcinoma with hepatoid differentiation.



A mapping of the uterine tumor: red indicates hepatoid carcinoma and yellow indicates gastric type carcinoma

References:

1. Wilbur et al. Glandular tumours and precursors. WHO Classification of Tumours of Female Reproductive Organs. WHO 2014.183-194
2. Kojima A et al. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of uterine cervix. Am J Surg Pathol 2007; 31:664-672.
3. Mikami Y et al Gastrointestinal immunophenotype endocervical adenocarcinoma of the uterine cervix and related glandular lesions: A possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and 'adenoma malignum'. Mod Pathol 2004;17:962-972.

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Case – 4

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

Clinical History: A 42-year-old female was seen for abnormal vaginal bleeding for 2 months. She had a history of left oophorectomy for a endometrioid adenofibroma. Two months prior, clinical evaluation and abdominal ultrasound showed a mass occupying the uterine cavity. A D&C was performed as a diagnostic approach with a diagnosis of endometrioid and clear cell carcinoma. During hysterectomy, the gynecologist reported multiple implants in the omentum. Serum alpha-fetoprotein post hysterectomy was 62,328 ng/ml.

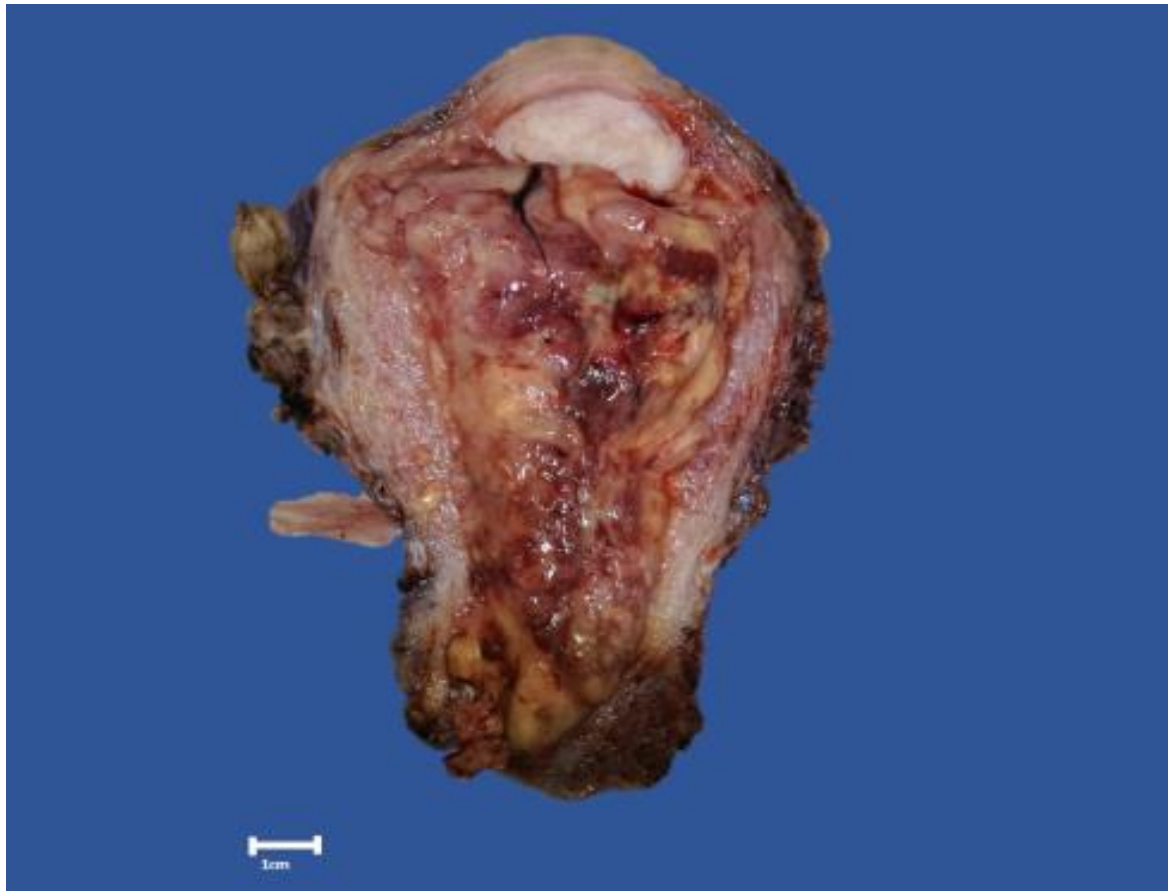
Pathologic findings: A large, friable mass occupied the whole uterine cavity with extension to the endocervical canal. Grossly the tumor invaded less than 50% of the myometrium. Microscopically the tumor shows extensive necrosis with areas of viable tumor composed of papillae, glandular and microcystic structures lined by cells with clear an amphophilic cytoplasm, and large nuclei with nucleoli. Schiller-Duval bodies were identified. Because of the previous diagnosis of endometrioid carcinoma, multiple cassettes were submitted and only scant and superficial areas of low grade endometrioid adenocarcinoma (FIGO1) were seen. The lesion in the omentum was consistent with YST.

Immunohistochemistry: The YST component was positive for SALL4, AFP, HepPar and EMA. PAX8, Napsin-A, CK7 and estrogen receptors were negative in the YST cells. Endometrioid adenocarcinoma was positive to PAX8, CK7 and estrogen receptor, and negative for SALL4, AFP, HepPar and Napsin-A.

Diagnosis: Endometrioid adenocarcinoma with extensive yolk sac tumor (YST) component.

Comment: Germ cell tumors rarely arise from somatic epithelial neoplasm. Germinal components include most frequently YSC and less frequently immature and mature teratoma, and choriocarcinoma. This “retrodifferentiation” has been reported in the sinonasal area, stomach, bladder, kidney, ovary, uterine corpus and endometriosis. In contrast to pure germ cell tumor, patients with this type of tumor tend to be older.

In the female genital tract, the epithelial neoplasm more frequent associated with germ cell tumors is endometrioid adenocarcinoma, however, carcinosarcomas, clear cell carcinomas, high grade serous and mucinous adenocarcinoma have also been described. A series by Retamero et al showed a mean age of 63 years with a range from 30 to 80 years and most premenopausal cases associated to endometriosis or cystoadenofibroma. They did not have evidence of a 12p gain. Germ cell tumor arising in Mullerian tumors probably originate from tumor stem cells behaving as induced pluripotent stem cells. (JW Oosterhuis and Looijenga L, personal communication). Endometrial stem cells have been demonstrated in endometrial adenocarcinoma and indeed, pluripotent stem cells with a phenotype analogous to germ cell have been obtained from surface ovarian epithelium. Formation of pluripotent stem cells probably is due to epigenetic factors.



Selected References:

Retamero JA, Nogales FF. Yolk sac tumors in postmenopausal patients arising in endometrioid adenocarcinoma. *Am J Surg Pathol: Reviews & Reports* 2016;21: 189–194

Nogales FF, Prat J, Schuldt M ET AL. Germ cell tumour growth patterns originating from clear cell carcinomas of the ovary and endometrium: a comparative immunohistochemical study favoring their origin from somatic stem cells. *Histopathology* 2017 <https://doi.org/10.1111/his.13426>

Clement PB, Young RH, Scully RE. Endometrioid-like variant of ovarian yolk sac tumour. A clinicopathological analysis of eight cases. *Am J Surg Pathol.* 1987;11:767-778.

AMR Seminar #72

Case – 5

Contributed by: Ira Bleiweiss, M.D.

Case History: A 40-year-old female with a history of CLL presented with PET scan enlarged axillary lymph nodes. The patient was referred to a breast surgeon by her primary care physician to whom she had complained of right axillary pain. She had radiographic evidence of abnormal right axillary lymph nodes. A PET scan a few weeks before was positive (SUV 7.5) in the enlarged right axillary lymph nodes. She was referred by her family MD (a Dr. Marilyn Rodriguez) for excision to rule out lymphoma.

Pathologic findings: Several large lymph nodes were removed and microscopically hyperplastic. Flow cytometry was performed with the following antibodies CD3,4,5,7,8,10,16/56,19,20,22,23,25,38,103,138,kappa,lambda and revealed no abnormal phenotype. Our hematopathologist's diagnosis: Nonspecific reactive lymphoid hyperplasia with pigment deposition.

A few days later the surgeon asked me to review the slides because she couldn't understand how the PET scan was positive. I did so and noticed the black pigment in the lymph node parenchyma, identical to what we all see (particularly in urban centers) in hilar lymph nodes as anthracotic pigment. So we both wondered 1)how did it get into axillary nodes and 2)why would the PET scan be positive.

We looked back at the patient's history provided by Dr. Rodriguez:

Family history: Mother-breast cancer @16 and 23, bilateral mastectomy

Maternal grandmother-breast cancer @ 28

Paternal grandmother-breast cancer @ 38

Sister-breast cancer @ 31

Maternal aunt-ovarian cancer @ 39

Father-colon cancer, dead of disease @ young age

As per patient: +BRCA1 mutation AND +Lynch syndrome mutation (HNPCC)

Past medical/surgical history:

1992- Left Breast Cancer-Lumpectomy/axillary dissection, Rx-CMF,RT,Tamoxifen

2002- fatigue, night sweats, wt loss, diagnosed with CLL - sacral soft tissue bx, bm bx (stage IV), CHOP in remission

2009- colectomy-premalig polyps

TAH- early stage endometrial carcinoma

Also- Crohn's Disease, Borderline Diabetes, inactive Multiple Sclerosis

Occupation: Police force, military, LPN (licensed practical nurse)

As per patient-CT and Ultrasound guided core bx of her axillary nodes both failed

Physical exam: Surgical scar Left breast,

Right axilla-no palp nodes, extreme pain, tender "out of proportion" to clinical findings

Verticle midline surgical scar abdomen

Hypertrophic surgical scar lower back

If this all sounds a bit unbelievable, it is because none of her diagnoses was real. As we discussed the case, the surgeon recalled a swelling on the patient's right arm, near a new tattoo which had been placed a few days before the PET scan. The surgeon also noted that while all the history had been related by Dr. Rodriguez when she originally called the surgeon, yet each time the surgeon tried to call Dr. Rodriguez, she always reached an answering machine, the last time realizing that the voice on the greeting sounded like the patient. The surgeon paid for a reverse phone number lookup and discovered that the address of the phone number was the same as the patient's home address. The patient was confronted and admitted in fact to pretending to be the non-existent Dr. Rodriguez. She had caused her positive PET scan by having a tattoo placed on her arm a few days before the scheduled PET scan (scheduled by her real MD). She had been convincing many doctors of her many different conditions for years, even having surgery, always in a different hospital with different doctors. Two years later a different breast surgeon became suspicious and called our surgeon when the patient came to see her wanting to have bilateral mastectomies.

Final diagnosis: Tattoo-induced lymphadenitis/adenopathy in a patient with Munchausen's Disease.

Comment: Since we as surgical pathologists rarely think about and never diagnose psychiatric disorders, for fun here is the Wikipedia definition: A factitious disorder imposed on self, wherein those affected feign disease, illness, or psychological trauma to draw attention, sympathy, or reassurance to themselves. History of recurrent hospitalization, travelling, and dramatic, extremely improbable tales of their past experiences. In some extreme cases, people suffering from Munchausen syndrome are highly knowledgeable about the practice of medicine and are able to produce symptoms that result in lengthy and costly medical analysis, prolonged hospital stays, and unnecessary operations. Munchausen's "By Proxy" is factitious disorders imposed on another person, usually a child.

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Case – 6

Contributed by: Justin Bishop, M.D.

Clinical History: A 45-year old woman presented with a thyroid nodule. A prior FNA diagnosis suggested the possibility of anaplastic thyroid carcinoma. She presented to our institution for total thyroidectomy and selective lymph node dissection.

Macroscopic features: The thyroid gland demonstrated an ill-defined red-brown 2.7 cm nodule in the left lobe. No other lesions were identified.

Histological and Immunohistochemical Findings: The tumor consisted of a poorly circumscribed collection of nests comprised of primitive small round cells. The mitotic rate was high, and foci of necrosis were present. Extensive vascular invasion was present, but the tumor did not extend beyond the thyroid gland. Despite its high-grade appearance, the tumor cells were very monotonous, with little pleomorphism. There were scattered foci of overt squamous differentiation in the form of keratin pearls, and in areas there were subtle structures resembling rosettes. Although entrapped thyroid follicles were seen within the tumor, there was no well-differentiated thyroid carcinoma component. All lymph nodes were negative for tumor.

Immunostains demonstrated that the neoplasm was diffusely positive for AE1/AE3, Cam5.2, p40, CD99, NKX2.2, and FLI-1. There was focal positivity for synaptophysin. It was negative for TTF-1, thyroglobulin, PAX8, calcitonin, CEA, chromogranin, CD5, c-kit, and NUT. Finally, FISH analysis was positive for an *EWSR1-FLI1* fusion.

Diagnosis: Adamantinoma-like Ewing sarcoma of the thyroid gland.

Discussion: Ewing sarcoma is a high-grade mesenchymal neoplasm of unclear histogenesis. It usually occurs in the bone or soft tissue of children or young adults, and its diagnosis is usually straightforward. It is consistently positive with the markers CD99, NKX2.2, and FLI-1, and often exhibits limited neuroendocrine differentiation. Ewing sarcoma is characterized by consistent gene fusions, most commonly *EWSR1-FLI1* (although alternate fusions are well documented).

Cytokeratin positivity is not uncommon in Ewing sarcoma (seen in about 1/3rd of cases) but it is usually focal, with low molecular weight cytokeratins only, and unlikely to cause diagnostic difficulty. The adamantinoma-like variant of Ewing sarcoma, on the other hand, is a rare form that demonstrates overt squamous epithelial differentiation at the histologic, immunophenotypic, and ultrastructural levels.

Until recently, adamantinoma-like Ewing sarcoma had only rarely been described in the bone or soft tissue near bone (hence the “adamantinoma-like” terminology) but two separate case reports of this tumor in the soft tissue of the neck alerted pathologists to its existence in other locations. Bishop, et al. described 7 cases of adamantinoma-like Ewing sarcoma in various locations in the head and neck (thyroid gland, sinonasal tract, salivary glands, and orbit). Interestingly, only one of these cases occurred in the pediatric age group; the mean age was 31 years. In my updated experience, I have seen a total of 16 cases with a mean age of 42 years.

Adamantinoma-like Ewing sarcoma resembles conventional Ewing sarcoma in some ways. It consists of nests of primitive cells with frequent fibrosis, and often exhibits rosettes. It is diffusely positive with the Ewing markers CD99, NKX2.2, and FLI-1, and often has focal positivity with synaptophysin. All cases have harbored the *EWSR1-FLI1* gene fusion. On the other hand, adamantinoma-like Ewing sarcoma also has findings that are unexpected: squamous pearls, basaloid morphology with peripheral palisading, and diffuse positivity for epithelial and squamous markers.

Because most pathologists are not aware of the existence of adamantinoma-like Ewing sarcoma, it is a very challenging diagnosis. This tumor challenges the conventional wisdom of sarcomas lacking this diffuse squamous epithelial differentiation. The differential diagnosis depends greatly on the location of the tumor. In the thyroid gland, the diagnostic considerations are poorly differentiated thyroid carcinoma, anaplastic thyroid carcinoma, medullary carcinoma, intrathyroid thymic carcinoma (CASTLE), and NUT carcinoma. Poorly differentiated carcinoma and medullary carcinoma are excluded by a lack of staining with TTF-1, thyroglobulin, PAX8, calcitonin, and CEA. Thymic carcinoma is excluded by a lack of staining with CD5 and c-kit, and positive reactions for CD99 and NKX2.2. Anaplastic thyroid carcinoma may exhibit squamous differentiation and characteristically loses expression of TTF-1 and thyroglobulin, but it also shows much more profound cellular atypia and pleomorphism than adamantinoma-like Ewing sarcoma. NUT carcinoma closely resembles adamantinoma-like Ewing sarcoma, but is consistently positive for NUT protein immunostain. Finally, the *EWSR1-FLI1* fusion that characterizes adamantinoma-like Ewing sarcoma is absent in the other diagnostic considerations.

Most patients with adamantinoma-like Ewing sarcoma have been treated with Ewing sarcoma chemotherapy protocols and, with limited follow up, most patients have survived without recurrences or metastases. The true behavior and optimal treatment of adamantinoma-like Ewing sarcoma, however, are not yet known. More cases with longer term follow up are needed.

There is some controversy surrounding the diagnosis of adamantinoma-like Ewing sarcoma. Some soft tissue pathologists believe that it represents a form of soft tissue myoepithelial carcinoma (personal communications). In addition, a group in Europe has described a few cases of an identical tumor as "carcinoma of the thyroid with Ewing family tumor elements." The same group has described *EWSR1* rearrangements in conventional papillary thyroid carcinomas as well, data that is difficult to reconcile with other studies like the Cancer Genome Atlas.

I would be interested to hear the members' opinions of the nature of this unusual neoplasm.

References:

Bishop JA, Alaggio R, Zhang L, Seethala RR, Antonescu CR. Adamantinoma-like Ewing family tumors of the head and neck: a pitfall in the differential diagnosis of basaloid and myoepithelial carcinomas. *Am J Surg Pathol*. 2015 Sep;39(9):1267-74.

Eloy C, Cameselle-Teijeiro J, Vieira J, Teixeira MR, Cruz J, Sobrinho-Simões M. Carcinoma of the thyroid with Ewing/PNET family tumor elements: a tumor of unknown histogenesis. *Int J Surg Pathol*. 2014 Sep;22(6):579-81.

AMR Seminar #72

Case – 7

Contributed by: Brian Rubin, M.D., Ph.D.

Brief Clinical History: 48-year-old man presented for laparoscopic cholecystectomy with suspected chronic cholecystitis with acute exacerbation.

Clinical History: The patient is a 48 year old man with history significant for obesity, smoking (1 pack per day for 20 years), and hyperlipidemia. His medications are 20mg/day lovastatin for hyperlipidemia. Of note, he does not have a history of neurofibromatosis or other tumor syndrome. The patient presented 1 day prior to surgery to the emergency room with acute right upper abdominal pain and was found to have a mildly elevated white blood cell count. Ultrasound revealed gallstones and hepatic steatosis but no signs of acute cholecystitis. His pain continued for 24 hours so he was taken to the operating room for a laparoscopic cholecystectomy, which was performed uneventfully.

Gross Pathology: The gallbladder was unremarkable grossly with the exception of a single yellow ovoid stone measuring 3.5 cm in greatest dimension that compacted the cystic duct. No suspicious masses were identified.

Histology: The serosal surface was congested and contained sparse chronic inflammation. There was chronic cholecystitis. In addition, the mucosal surface revealed many small mucosal polyps containing what appear to be sheets of Wagner-Meissner-like corpuscle-like structures covered by relatively normal appearing epithelium. There were also three 1-2 mm nodules adjacent to each other in the section of the cystic duct (see Figure below). The nodules were circumscribed and unencapsulated and contained benign appearing spindle cells arranged in short fascicles with a focally myxoid stroma. Immunohistochemistry for SOX10 was uniformly positive in a nuclear pattern in the Wagner-Meissner-like corpuscle and the spindle cells within the nodules adjacent to the cystic duct (see Figure below). I took ten extra sections of the gallbladder and every single section had the same pattern of diffuse tiny polyps with sheets of Wagner-Meissner-like corpuscles covered by relatively normal appearing epithelium. I used one of those sections to make the slides for the club.

Diagnosis: Diffuse mucosal Schwann cell proliferation with Wagner-Meissner-like corpuscle-like structures of the gallbladder in association with a small plexiform Schwannoma of the cystic duct region in the setting of chronic cholecystitis.

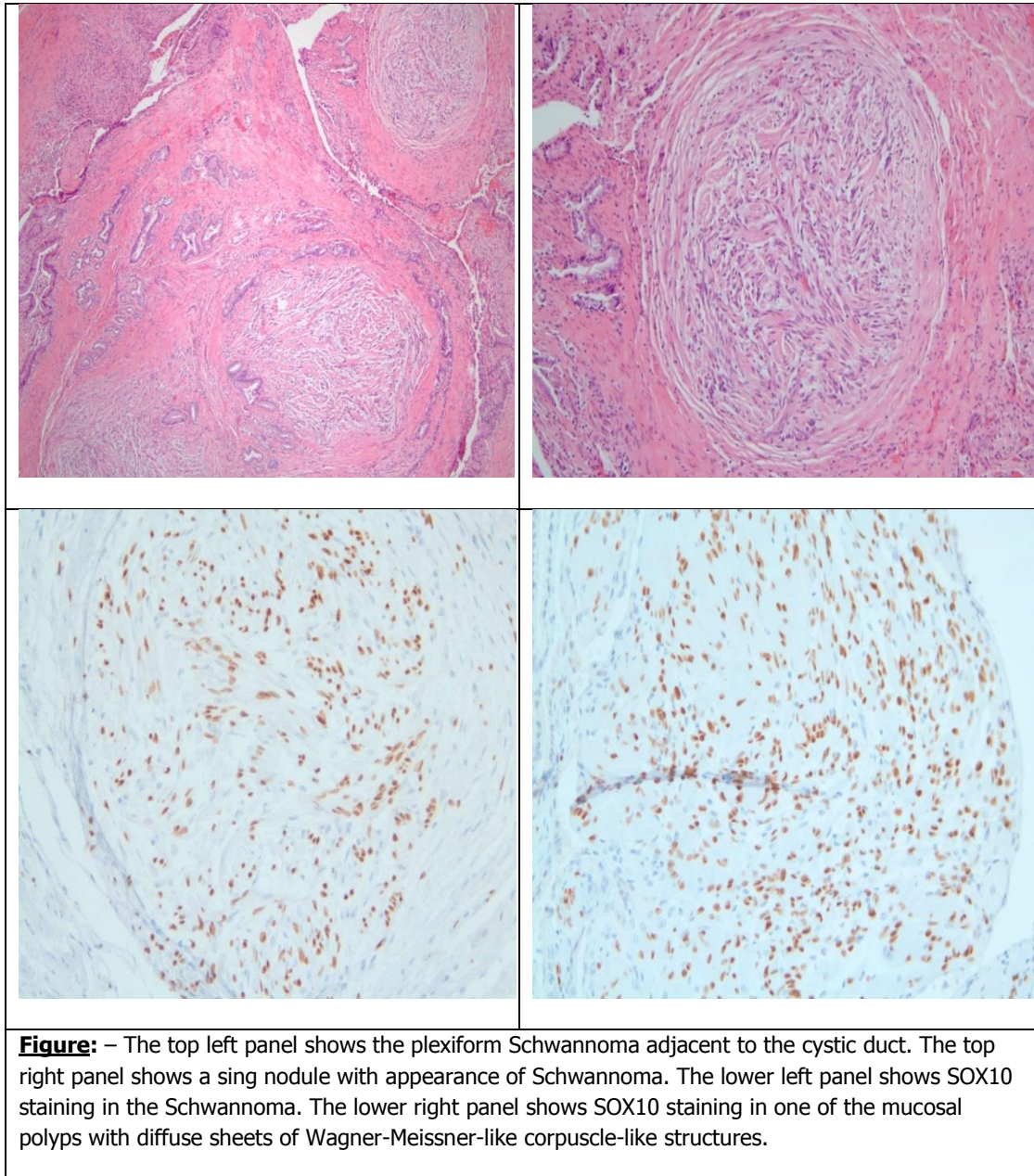
Discussion: Nerve sheath tumors of the gallbladder are exceptionally rare with less than 10 neurofibromas or Schwannomas reported in the literature. I couldn't find any mention of perineuriomas of the gallbladder. This particular case shows a diffuse proliferation of Schwann cells within the mucosa, each exhibiting Wagner-Meissner-like corpuscle differentiation associated with what appears to be a tiny plexiform Schwannoma adjacent to the cystic duct. The lesion in the mucosa is different than a diffuse neurofibroma because it seems to be missing the ordinary neurofibroma counterpart with the disorganized spindle cells, mast cells, etc. and the bit in the cystic duct is consistent with a tiny plexiform Schwannoma. The lesions must be related but I'm not sure of the relationship. I found one paper of interest that described a polypoid neurofibroma (7 x 5 x 5 mm) of the gallbladder that had areas of more typical neurofibroma as well as an area with Wagner-Meissner-like corpuscle differentiation (see reference). In contrast to the slide presented here, the lesion was localized and looks like a neurofibroma.

Follow-up: The patient has had no further sequelae approximately one month after surgery.

Summary: I present what I think is a unique case of a diffuse mucosal Schwann cell proliferation with Wagner-Meissner-like corpuscle-like structures of the gallbladder associated with a small plexiform Schwannoma in the setting of chronic cholecystitis. I wonder if anyone in the slide club has seen a similar case, has a better diagnosis, or any theory about the pathogenesis of this lesion. I look forward to your comments.

Acknowledgment: This case was shared with me by one of my colleagues at the Cleveland Clinic, Dr. Tommy Plesec.

Reference: Morizumi H, Sano T, Hirose T, Hizawa K. Neurofibroma of the gallbladder seen as a papillary polyp. *Acta Pathol. Jpn.* 1988;38:259-268.



AMR Seminar #72

Case – 8

Contributed by: Thomas Krausz, M.D.

Clinical History: This 49-year-old woman with a history of iron deficiency anemia presented with acute on chronic fatigue and recent episode of hematemesis. She was found to have a hemoglobin of 2.7 g/dL and was subsequently transfused six units of packed red blood cells. An upper gastrointestinal endoscopy was performed, which revealed a large, ulcerated mass in the gastric body and markedly thickened gastric folds extending from the gastroesophageal junction up to the antrum. Due to her ongoing bleeding, she underwent total gastrectomy.

Gross Findings: Multiple, thickened, cerebriform gastric folds were present along the greater curvature of the stomach while the antrum appeared normal.

Histopathologic Findings: Massive foveolar hyperplasia with elongated, tortuous foveolar glands and focal cystic dilatation were appreciated. Decreased parietal cell mass was seen with scattered foci of chronic inflammation and intervening strands of smooth muscle in the lamina propria.

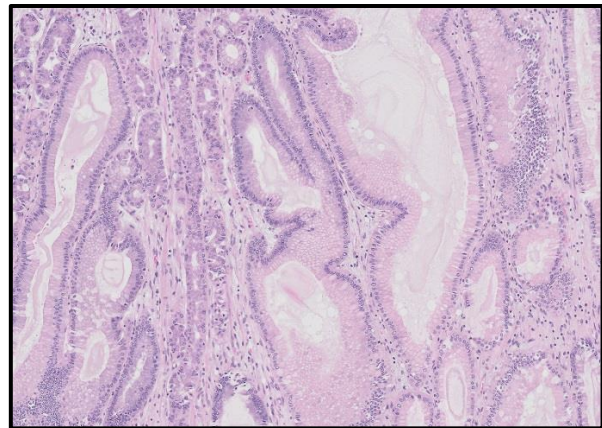
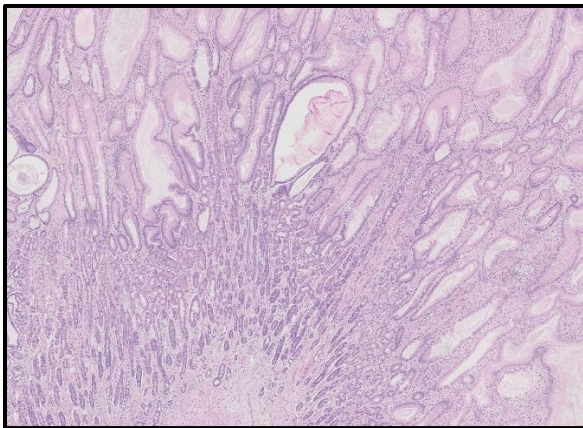
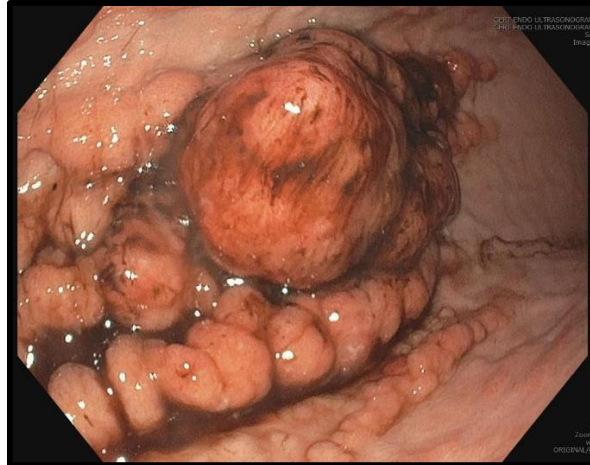
Diagnosis: Ménétrier disease.

Discussion: Ménétrier disease, also known as hypoproteinemic hypertrophic gastropathy, is a relatively rare, acquired, protein losing gastropathy localized to the gastric body that can present in a chronic, adult form or an acute, spontaneously resolving pediatric form that has been associated with cytomegalovirus infection.¹⁻³ The adult form presents at an average age of 55 years and is more common in men. It is characterized by an insidious onset with symptoms resulting from hypoproteinemia and hypochlorhydria, including peripheral edema, abdominal pain, anemia, and weight loss. Adult patients have an estimated 2-15% lifetime risk of gastric cancer.²

The differential diagnosis for thickened gastric folds is quite broad, and in this case included Ménétrier disease as well as polyposis syndromes, such as Juvenile Polyposis and Cronkhite-Canada. Gastritis cystica profunda/polyposa and Zollinger-Ellison Syndrome warranted consideration as well. Possible neoplastic etiologies included carcinoma and lymphoma. There was no evident lymphoproliferative process or any infiltrative cells in multiple representative sections, and thus suspicion for malignancy was low. The distinct and impressive foveolar hyperplasia made Zollinger-Ellison Syndrome, which shows parietal cell hyperplasia and hypertrophy in response to substantially elevated gastrin levels, and gastritis cystica profunda/polyposa, an entity with displacement of mucosal glandular elements into the gastric submucosa, much less likely. Involvement confined to the upper gastrointestinal tract, namely the gastric body, in the context of these histologic findings strongly favored a diagnosis of Ménétrier Disease.

Transforming growth factor- α (TGF- α) is a ligand that binds the epidermal growth factor receptor (EGFR), which is present in a range of different epithelia, including stomach, breast, pancreas, and intestines.⁴ EGFR stimulation activates downstream signaling pathways in the stomach that lead to gastric epithelial repair and inhibition of gastric acid secretion in response to gastric injury. Transgenic mouse models with gastric overexpression of TGF- α demonstrated a gastric phenotype of foveolar hyperplasia and decreased parietal cell mass analogous to Ménétrier Disease.^{5,6,7} While the mechanism is not completely understood, it is hypothesized that impaired negative feedback inhibition of TGF- α release may result in exaggerated or sustained downstream effects that account for the Ménétrier Disease phenotype.^{8,9}

Gastrectomy remains the cornerstone of treatment of the adult form of Ménétrier Disease due to the increased lifetime risk of gastric cancer. Octreotide and steroids have shown inconsistent results. However, the monoclonal antibody, cetuximab, which binds EGFR, has demonstrated rapid improvement in clinical symptoms and histologic remission in several cases.^{8,9}



References:

1. Ménétrier P. Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac. *Arch Physiol Norm Pathol* 1888;1:32-55, 236-62.
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AMR Seminar #72

Case – 9

Contributed by: Maria Pia Foschini, MD.

Clinical History: a 50-year-old woman, with a history of upper arms paresthesia, developed in October 2016.

At presentation electron-encephalography (EEG) was within normal limits. Magnetic Resonance Imaging (MRI) showed rare diffuse punctual areas consistent with suffering gliotic tissue. In March 2017, acute motor aphasia, ideomotor apraxia and memory troubles appeared. She was admitted to a hospital in her hometown, but, in spite of all the clinical efforts, her clinical condition deteriorated (fever, nuchal rigidity) and the woman was transferred to our hospital.

Computer Tomography (CT), MRI and brain angiography showed white matter alterations, referred to vasculitic disease. Therefore, immunosuppressive therapy was started. Clinical conditions slowly improved and the patient was also admitted to Intensive Rehabilitation after a few weeks. In August 2017 brain MRI revealed additional parenchymal lesions, consistent with multiple brain infarcts; laboratory tests showed progressive anemia and thrombocytopenia. The patient was admitted again to our hospital because of seizures, psychomotor agitation, hypothermia and then fever, hypotension and tachycardia. Chest X-ray revealed features of pneumonia; blood culture was positive for Klebsiella pneumonia; ventilation and intubation have been practiced but the patient finally died.

Gross features: Brain: showed multiple and bilateral parietal and frontal colliquative areas, macroscopically consistent with multiple infarcts; Lungs: basal cut-surface was solid and gray-red in color. No specific alterations were observed in other organs.

Microscopic: The present section was taken in one of the ischemic brain areas. It shows features consistent with brain infarct. In addition, cerebral parenchymal and leptomeningeal blood vessels are filled with atypical cells, with large, round nuclei with prominent nucleoli and atypical mitoses. Same intravascular neoplastic cells were present in lung capillary, spleen and adrenal glands vessels. No lymph nodes involvement was detected.

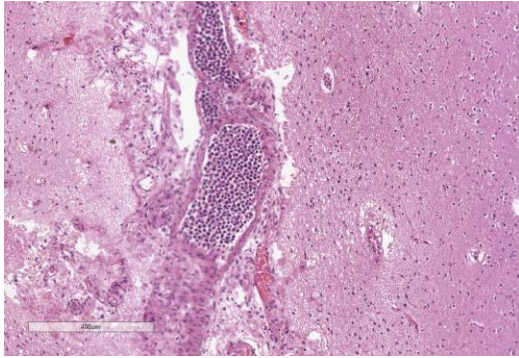
Diagnosis: Intravascular B-cell lymphoma, with massive brain and lung involvement.

Comment: Intravascular B cell lymphoma (IVL) is a rare distinctive entity characterized by exclusively intravascular growth. CNS involvement occurs in 75-85% of cases. Intravascular growth leads to clinical symptoms, mimicking those of brain infarction or progressive encephalopathy. Two different clinical variants are known: Western (symptoms related to single organ involved) and Asian (multiorgan failure). Radiologic findings are nonspecific.

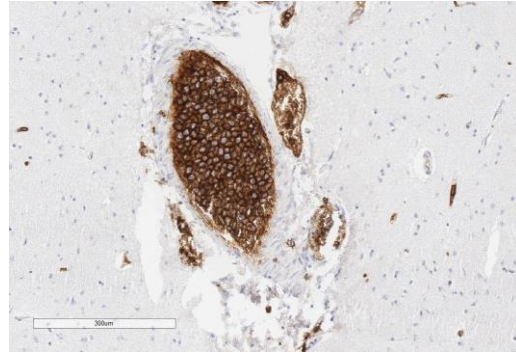
Pre-mortem diagnosis of IVL is difficult, as biopsy can fail to reveal intravascular neoplastic cells. Serum markers of IVL have been searched for, but no specific results were obtained. The treatment for CNS IVL has not been established yet. IVL is characterized by poor prognosis in most of the cases, with death due to the diseases occurring 5-7 months after presentation.

Clinical and pathological differential diagnoses comprise: diffuse large B-cell lymphoma of the CNS, Lymphomatosis cerebri, Diffuse subacute Encephalomyelitis and Nonspecific Chronic Inflammation, Progressive Multifocal Leukoencephalopathy. Diagnosis is based on the presence of intravascular neoplastic lymphocytes, in absence of lymph-nodal involvement.

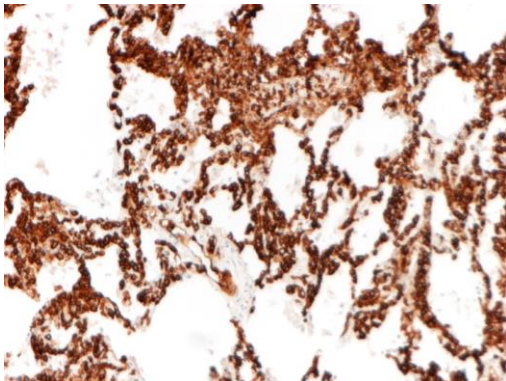
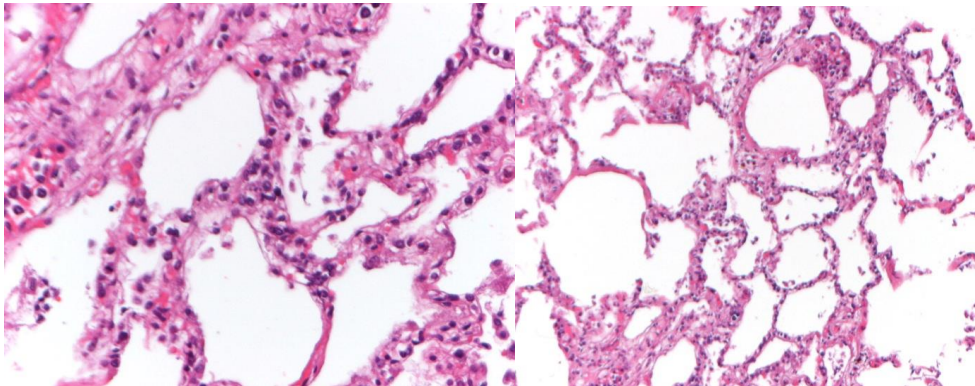
The neoplastic cells were strongly CD20 positive.



Most of the vessels are filled with neoplastic cells



The neoplastic cells are strongly positive for DC20.



Capillary vessels of the alveolar septa were filled with neoplastic cells, CD20 positive.

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AMR Seminar #72

Case – 10

Contributed by : Alberto Cavazza, M.D.

Clinical history : A 27-year-old woman presented with abdominal pain and a 5 cm partially cystic mass of the liver. During surgery, a stenosis of the hepatic flexure of the colon was also found. Both the hepatic lesion and the intestinal stenotic tract were excised.

Pathologic features and further clinical informations : The hepatic mass consisted in an abscess in which ghosts of placental tissue and keratin squames were found. The colonic resection (histology not shown) disclosed more subtle findings, consisting in a peri-intestinal inflammatory process engulfing scattered squames, with no placental villi. After we saw the histology, we contacted the clinician and we obtained more detailed informations. A couple of weeks before surgery, the patient had been admitted to hospital for cesarian delivery prescribed for umbilical cord prolapse and membrane rupture at 40th weeks, and she gave birth to a healthy male baby. A subsequent thoracic CT scan was negative and betaHCG levels were within normal limits. Three months after surgery, the patient is alive and well without any further complications.

Diagnosis : Amniotic fluid and placental tissue embolism.

Comments : This case and the following comments are due to my brilliant colleague Maria Cecilia Mengoli. Amniotic fluid embolism (AFE) is a well-known and feared complication of pregnancy, with a mortality rate ranging from 13% to 50% depending on the series. Death may be due to a massive pulmonary embolism or to an immune-mediated reaction to fetal antigens leading to disseminated intravascular coagulation. AFE occurs during labour in 70% of the cases, after vaginal delivery in 11% and after cesarean delivery in 19%. The presence of fetal material in the maternal circulation occurs in 20-33% of normal pregnancies and does not establish *per se* the diagnosis of AFE. Actually there are no routine diagnostic tests to confirm the diagnosis, and the histological detection of amniotic fluid elements (epithelial squames, hairs, fatty material, mucin, bile pigment) or placental villi in the maternal tissues is essential for a definite diagnosis, which is most of the time performed at autopsy but occasionally during live, like in our patient. In subtle cases immunohistochemistry with cytokeratins, betaHCG, PLAP and also PD-L1 may be helpful in highlighting the villotrophoblastic tissue (MC Mengoli, personal observation).

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AMR Seminar #72

Case – 11

Contributed by: Franco Fedeli, M.D.

Clinical History: A 53-year old man pleural biopsy was referred to my attention as a consult case from another institution. The patient had a recent history of lung carcinoma and during regular follow-up by contrast-enhanced CT scanning of the chest he was found to have several left pleural and pulmonary nodules. Some of them were removed by thoracoscopic wedge resection.

Microscopic Findings: Microscopically, pleural biopsy showed a vaguely nodular cellular proliferation, sometimes with evidence of focal whorled appearance areas. Tumor cells presented ovoid to spindle shape, weakly eosinophilic cytoplasm and round to oval nuclei, with a delicate chromatin pattern and some intranuclear inclusions. No atypia neither pleomorphism were evident. Mitotic figures were very rare.

Immunohistochemical findings: Immunohistochemical staining demonstrated focal expression of epithelial membrane antigen (EMA), and CD56 in tumor cells. On the other hand, S-100 protein, HMB45, synaptophysin, chromogranin, p63, p40, CK7, TTF-1, progesterone receptors (PR) were negative. Proliferation index MIB-1 was evaluated around 10%.

Diagnosis: A diagnosis of metastatic meningioma was made. Afterwards, central nervous system surveys revealed negative findings and a revision of the previous lung cancer was performed with a final diagnosis of primary pulmonary meningioma.

Comments: Pulmonary meningioma may represent a primary or a secondary lesion because primary pulmonary meningioma and metastatic meningioma share similar histological appearance. That is the reason why it is not possible to distinguish between primary and metastatic meningioma only by histological study, but radiological ones of the central nervous system are required to exclude an intracranial or spinal meningioma. In this regard the incidence of extracranial meningioma metastasis is about 0.1%. Lungs are the most commonly involved locations (60%), followed by abdomen (34%), cervical lymph nodes (18%), skeletal system (11%), pleura (9%), brain and spine (7%), and mediastinum (5%) (1) Metastatic pulmonary meningioma is usually detected after a diagnosis of central nervous system meningioma and may arise many years after the excision of the primary meningioma. The interval between diagnosis of central nervous system meningioma and diagnosis of pulmonary metastases ranges between 2 months and 26 years. On the other hand, Primary pulmonary meningiomas are rare and since the first description in 1982 by Kemnitz et al.(2) only a few cases have been reported in the medical literature. More commonly primary extracranial and extraspinal meningiomas occur in the head and neck region or less frequently in the skin and peripheral nerves. Two main hypotheses concerning the pathogenesis of PPMs have been put forward:

1. Origin from pluripotential subpleural mesenchyma.
2. Derivation from heterotopic embryonic rests of arachnoid cells, namely minute pulmonary meningotheelial nodules.

In this regard, a study performed by Suster, Moran and colleagues has indicated that pleuropulmonary meningotheelial lesions, including minute pulmonary meningotheelial nodules and pleural or pulmonary meningiomas, share common genetic pathways with CNS meningiomas, particularly the loss of the neurofibromatosis (NF) 2 gene on chromosome 22. In addition, this study provides support to the hypothesis that pulmonary meningotheelial nodules and pleural or pulmonary meningiomas are related lesions arising from the same precursor cell (3). Finally, histologic differential diagnosis of PPM includes all primary and metastatic spindle and clear cell tumors of the lung, but morphological and immunohistochemical features make pathologists able to correctly interpret the process.

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AMR Seminar #72

Case – 12

Contributed by: Göran Elmberger, M.D., Ph.D., Sweden

Case history: Our patient is a 57-year old Caucasian man, who has lived all his life in a small community in Sweden. He has never smoked. He has been exposed to chemicals in early professional life as a vehicle mechanic.

In his late twenties he was diagnosed with asthma that within a couple of years required full medication, including daily oral cortisone. His asthma was possibly triggered by chemical exposure. During the years from the asthma diagnosis until now he has been treated in periods with high doses of cortisone and different immunomodulating medication. During the summer of 2016 his asthma deteriorated, he had difficulties swallowing and reported weight loss.

When asked about his travel history, our patient reported several charter trips to the Mediterranean area but no longer stay abroad. At the end of August 2016, he travelled to Greece on a charter trip. On his way home, he had a high fever, chills and dyspnea.

He sought medical care and was referred to the Department of Pulmonary Medicine at Gavle hospital where he underwent bronchoscopy on the 19th of September. The patient had a very hoarse voice. On initial examination there was a pedunculated papillomatous tumor from the left side of hypopharynx. Also, from the posterior/right side of the wall of pharynx there was an elongated similar tumor which largely obstructed the larynx, only the most anterior part of the vocal cords could be visualized. The larynx was full of yellow stained secretions. The neck was examined without palpable pathological lymph nodes. Three days later a hypopharyngo- and laryngoscopy in general anesthesia W8;S performed. Biopsies were taken and sent to the Department of pathology at Gavle hospital. A CT-scan showed bilaterally in the lungs small scattered findings with inflammatory appearance but no lymphadenopathy.

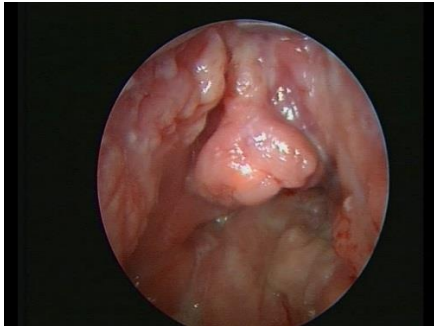


Fig. 1 Hypopharyngeal tumor.

Because of the initial pathological findings interpreted in Gavle as sarcomatoid carcinoma and after negative IHC as lymphoma. The case was sent to University Hospital Uppsala where a diagnosis of sarcoma was made. For this reason, the patient was referred to the Department of Otolaryngology, Head-neck surgery at the University Hospital of Orebro. I got my hands on the case just 15 minutes before MDT conference and noted some unexpected findings raising a quite different differential diagnosis.

Pathological Findings: A spindle cell pseudotumor with intracellular Leshmania-like Donovan bodies (amastigotes) were seen.

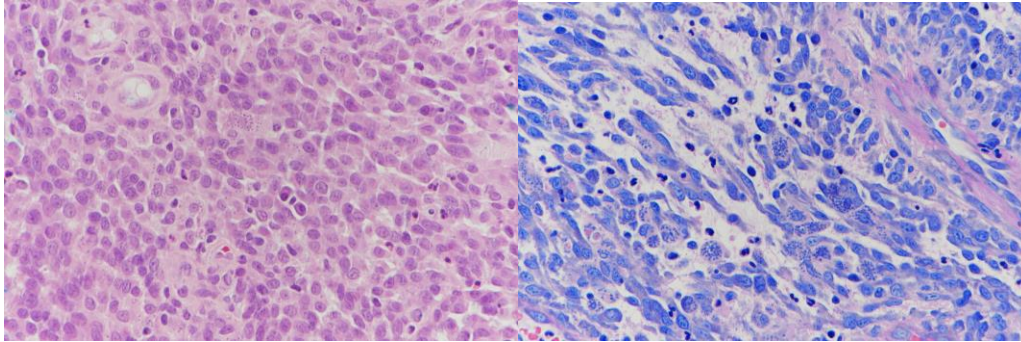


Fig.2 HTX

Fig.3. Giemsa. Amastigotes in histiocytes.

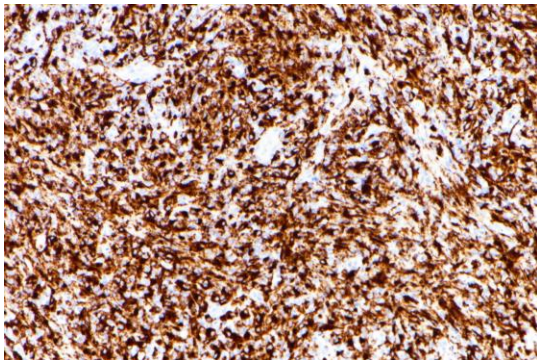


Fig.4. IHC CD68

Diagnosis: Hypopharyngeal mucosal Leishmaniasis-an unusual pseudotumor, at least in Sweden!

Follow-up: Additional biopsies were taken and to send them to the European Public Health Agency located in Stockholm for confirmation. The diagnosis was confirmed two days later from direct microscopy. Later on DNA for Leishmaniasis donovani complex, probably *L. infantum* is demonstrated. Treatment was started with intravenous amphotericin-B, an antibiotic against visceral Leishmaniasis although our patient had mucocutaneous Leishmaniasis. A bone marrow test was taken that tested negative for Leishmaniasis. Follow up examinations at our department during November showed that the status in the pharynx and larynx improved but the patient still reported severe pain. The pseudotumours progressed and the patient underwent surgery. Intraoperative findings revealed a pseudotumour measuring 4x2x2 cm, coming from the posterior wall of hypopharynx that was excised and also a pseudotumour coming from in between the arytenoid cartilage that was excised. A few weeks later the status of the pharynx/larynx was almost normal, and the patient was decannulated.

Discussion: Leishmania can involve almost any organ. It can present as cutaneous leishmaniasis (CL), localized leishmania lymphadenitis, mucosal leishmaniasis (ML), or diffuse multiorgan involvement (kala azar).

Demonstration of the parasite is necessary for the diagnosis of leishmaniasis. Cytologically, the cytoplasm of a typical Leishman- Donovan body contains a nucleus and a kinetoplast. The complete form of a Leishman- Donovan body can be seen in aspiration of bone marrow, lymph nodes, and skin smears. However, in histology sections the kinetoplasts are not visible, and the organisms can be easily mistaken for tingible bodies, fungal elements, toxoplasmosis.

Leishmaniasis is a protozoan parasite infection usually transmitted by the Sand fly. Most cases appear in endemic areas (Central and South America, parts of Asia and countries around the Mediterranean Sea). The mucocutaneous form is unusual but known to be misdiagnosed as other infections, autoimmune disorders or malignancy of the aerodigestive tract.

Leishmaniasis should be considered in patients with chronic mucosal lesions and exposure to transmission, especially if they are immunocompromised.

A case of hypopharyngeal Leishmaniasis without cutaneous involvement is described in a 57- year-old Swedish immunocompromised man travelling to an endemic Greek vacation island.

Microscopic examination of a pseudotumoral presentation disclosed scarce amastigotes and the definitive diagnosis was facilitated by direct microscopy and molecular diagnosis.

The clinical presentation of this lesion is unusual and underlies the importance of considering leishmaniasis in the differential diagnosis of mucosal lesions.

Interestingly a literature review revealed a published case from Australia with a patient acquiring Leishmaniasis after visiting the same Greek island as our case- a very popular Swedish tourist target!

Conclusions: Confirmatory histology before surgery still important! The clinical appearance of mucocutaneous Leishmaniasis can be similar to aerodigestive cancers and warrants awareness of its existence. With increased travelling, this is true not only in endemic areas.

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AMR Seminar #72

Case – 13

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

Clinical History: A 44-year-old woman with a 28 mm lesion with bilateral scattered calcifications on mammography. Ultrasound showed a hypoechoic lesion with poorly defined edges and a solid appearance. A BAG biopsy was performed with the diagnosis of well-differentiated adenocarcinoma, grade I, positive for estrogen and progesterone receptors, negative HER2 and a heterogeneous Ki-67, with up to 20% of positive tumor cells. It is diagnosed as luminal B HER2 negative.

She is treated with chemotherapy (protocol of Adriamycin, Cyclophosphamide and Taxol), and then the mastectomy. Radiological studies point out a partial response. The cut referred corresponds to the mastectomy piece.

Pathologic findings: In the specimen, an epithelial proliferation was observed, with elongated ducts, focal apocrine features, moderate cytological atypia and a Ki-67 of <5%. In the immunohistochemical study, no positivity was observed for hormone receptors or HER2. Positivity for androgen receptors was observed in the apocrine areas. Strikingly, a double layer was evident, with myoepithelial cells, positive for p63, in a large part of the ductal structures present in the biopsy.

Diagnosis: Breast ductal carcinoma with apocrine features – and with senescent cell component?

Comments: With the current data, we diagnosed this at the beginning as a persisting ductal carcinoma with apocrine features, but the case raises two important diagnostic problems or doubts that we want to share with you:

- The first is the meaning of the myoepithelial cells in the epithelial component that is interpreted as an infiltrating tumor and that we have just not understood. There have been cases of metaplastic adenosquamous carcinoma of low grade with persistence of myoepithelial cells, but this is not the case in this patient. In fact, the presence of an integral layer of myoepithelial cells rules out stromal invasion. It should be noted that the patient showed 3 positive lymph nodes in the axillary surgery (sentinel and lymphadenectomy), with a similar morphological pattern (very elongated glands with a single epithelial layer but without the presence of myoepithelial cells in this case).

Revising the case again, we realized that there was a tubular adenosis plus adencocarcinoma in the primary tumor and that most areas after treatment in the specimen were also tubular adenosis with some tumor glands.

- The second problem is the behavior of the residual neoplasm after neoadjuvant treatment that presents a very low Ki67 (<5% in this case). Very presumably, a large part of the cellular component could have features of cellular senescence and therefore not be viable, from the oncological point of view. In fact, we have stained it with p16 that was positive in practically all the glands (in the primary bed and in the lymph nodes) which, together with the low Ki67, would support that those glands can be senescent. This is a point of great interest since the biology of the residual disease after previous treatment has not been studied in great detail.

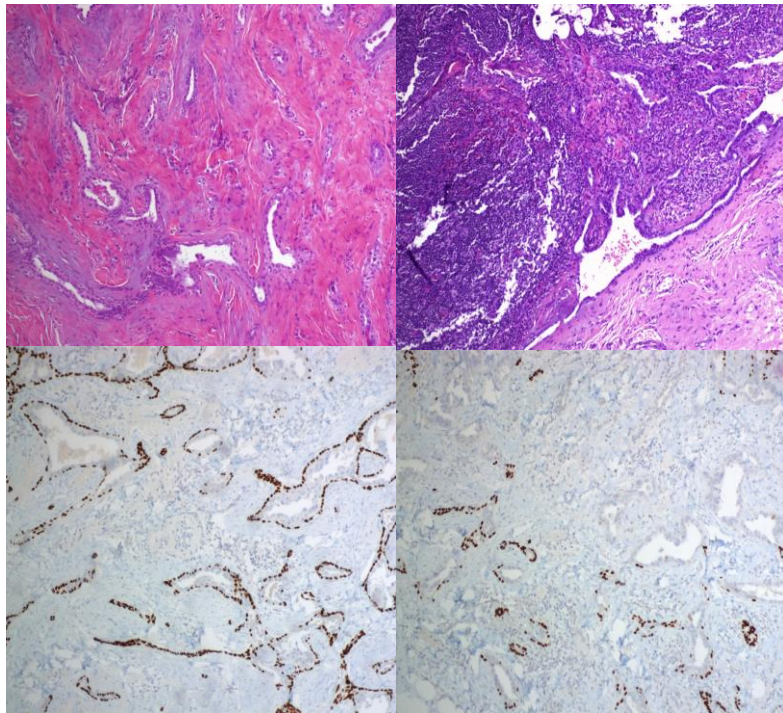
We interpret this lesion, by protocol, as a persistence of breast adenocarcinoma, but we want to know your opinion on how to interpret the presumed component of senescent cells, and how to transmit this message to clinicians for later treatment.

At present, the recommendations for the study of surgical pieces after neoadjuvant surgery include an extensive description of how to evaluate residual disease, from a point of view of the location of the tumor bed and its assessment (1-3). In fact, one of the most used and recommended methods at present is the Residual Cancer Burden, which is based on the residual cellularity load in the surgical piece (4). However, the diagnosis focus only on the histological

grade and the remaining disease, do not take into consideration the biological characteristics of the lesion. On the other hand, clinical studies have demonstrated the utility of expanding or complementing neoadjuvant treatment with adjuvant chemotherapy in patients with residual disease after the first treatment, and without having clearly outlined the characteristics of this disease beyond the tumor burden (5).

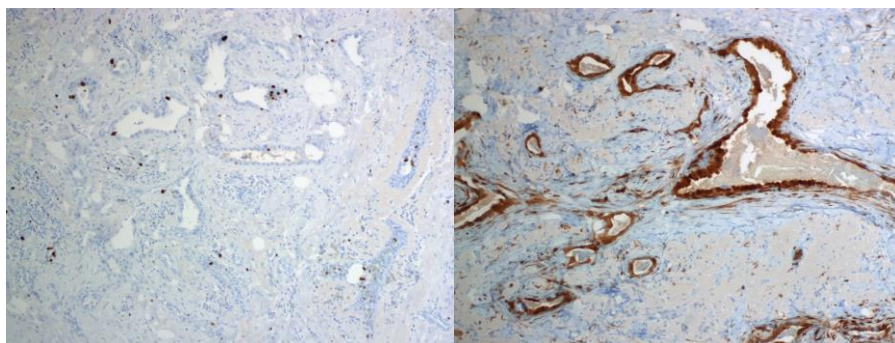
We believe that not all the residual disease means the same, so we should not only assess the tumor burden that remains after the neoadjuvant but also characterize the biological viability. So, we will be able to recognize those of high biological risk that, probably, need a complementary treatment.

AA



P63

P63



Ki67

P16

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AMR Seminar #72

Case – 14a & 14b

Contributed by: Phil Allen, M.D.
(15/9317453 1F & 1T)

History: A man aged 68 in 2015 had an invasive atypical pituitary adenoma excised in 2001. A recurrent pituitary tumor with apoplexy and visual loss was excised in 2014. The pituitary tumor was apparently not related to his subsequent bone tumors in the right leg.

In 2008, the patient had bilateral popliteal artery aneurysms treated by femoro-popliteal bypasses. In 2014, plain radiographic studies revealed multiple lytic lesions in the right metatarsals and tarsals, the right talus, right tibia, right patella and the lateral condyle of the right femur. The lesions increased in size over the next 12 months and were associated with worsening ankle pain. In November 2015, organ imaging showed no spread to the viscera. A core biopsy from the right distal tibia in November 2015 eventually established a diagnosis of epithelioid hemangioendothelioma. A right above knee amputation was performed in December 2015.

Follow-up: The patient developed bloody pleural effusions in January 2017. A pleural biopsy showed metastatic epithelioid hemangioendothelioma and the patient died of tumor later that year.

Pathology: Examination of the amputation specimen revealed an unsuspected primary epithelioid hemangioendothelioma in the previously bypassed popliteal artery aneurysm, with intraluminal spread along the distal arterial branches and multiple metastases in bones distal to the aneurysm. The macroscopic appearances of some of the bone lesions are illustrated below.

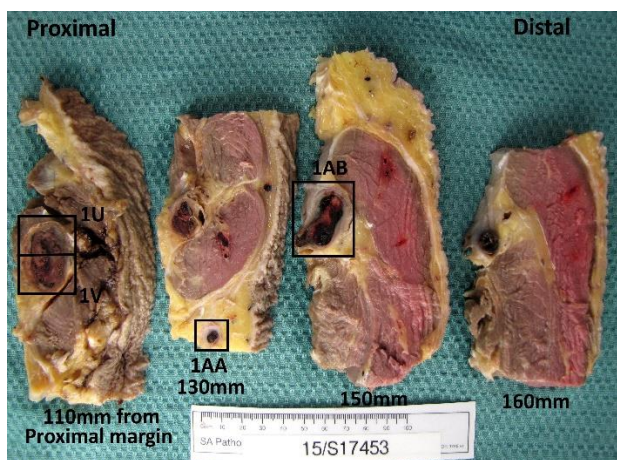


Coronal slice of the bisected lower end of the right tibia and fibula through the ankle joint. Two black tumor deposits are seen in the lower end of the fibula, one involving the syndesmosis (circulated slide FMC 15/9327453, 1F, to be labelled AMR slide A). An additional small black tumor nodule is apparent in the cancellous bone of the lower end of the tibia, approximately 10 mm proximal to the articular surface.



Slices of the talus showing black tumor deposits beneath one of the articular surfaces and in the cancellous bone.

Sections were also taken from the bypassed popliteal artery aneurysm seen in the gross photograph below (slide FMC number 15/9317453, 1T; to be labelled AMR Slide B).



Photograph of one of the transverse slices of the specimen from the right popliteal region, starting on the left at 110 mm from the proximal surgical margin. The popliteal artery is aneurysmal and filled with thrombus and tumor. The small subcutaneous artery in block 1AA is filled with thrombus, which on section is also mixed with tumor (slide not circulated).

The circulated slide A shows sarcoma infiltrating bone and adjacent soft tissues from the region of the tibiofibular syndesmosis. The tumor cells are keratin and CD31 positive and look like an epithelioid hemangioendothelioma to me.

The circulated slide B shows similar tumor in the wall of the thrombosed and fibrosed popliteal artery.

Diagnosis: Occult and ultimately fatal primary epithelioid hemangioendothelioma arising in a right femoro-popliteal bypass with multiple metastases to the distal bones simulating a primary multifocal epithelioid hemangioendothelioma of bone.

Comments: The tumor cells in the initial core biopsy of one of the bone lesions stained for epithelial markers, which was initially thought to indicate metastatic carcinoma. No tumor was clinically apparent outside the right lower leg and the subsequently performed CD31 indicated endothelial differentiation and established a diagnosis of epithelioid hemangioendothelioma. It was thought to be primary in the bone and “multifocal.” No visceral metastases were apparent and as the bone lesions were very painful, the amputation was performed.

I thought that the diagnosis of a primary but multifocal bone tumor was well established and only took sections of the old bypassed popliteal artery aneurysm to avoid criticism by the trainees. To my surprise, I found what I think is the source of the “multifocal” bone tumors in this case.

I have also seen one case of an epithelioid **hemangioma** (not hemangioendothelioma) of the radial artery. Some months after excision of the involved arterial segment, the patient developed histologically identical small metastases in the subcutis near the ends of two ipsilateral fingers distal to the arterial tumor.

I suspect that all “multifocal” epithelioid hemangioendotheliomas, and probably multifocal epithelioid hemangiomas as well, come from a primary tumor in a more proximal feeding artery. This supposition may be wrong but this case suggests that the proximal arteries feeding “multifocal” deposits of epithelioid hemangioendotheliomas should be investigated by high resolution organ imaging.

AMR Seminar #71

Case – 15

Contributed by: Saul Suster, M.D.

Clinical history: A 26 year old woman with a history of familial adenomatous polyposis (FAP) and chronic hepatitis C was found to have a 3.2 cm. left adrenal gland mass on CT scan during a preoperative evaluation prior to total colectomy. Her biochemical evaluation and hormonal workup was within normal limits. There was no family history of FAP or adrenal tumors. A left laparoscopic adrenalectomy was performed.

Pathologic findings: The resected left adrenal gland showed a well-circumscribed, thinly encapsulated yellow-brown nodule in the cortex that measured 3.2 x 2.5 x 2.5 cm. On cut section, the tumor showed homogeneous, rubbery tissue devoid of necrosis or haemorrhage. On histology, the tumor was characterized by cords of uniform tumor cells displaying a focal tubular and papillary architecture. There were ribbons of cells displaying stromal hyalinization. The tumor cells were uniform, large and polygonal with a speckled chromatin pattern, absence of nucleoli, and an abundant rim of plasmacytoid granular eosinophilic cytoplasm. There was no nuclear pleomorphism or mitotic activity, and no evidence of vascular or capsular invasion. Based on the modified Weiss criteria, the lack of necrosis, atypia, mitotic activity or invasion, the lesion was interpreted as a benign adrenal cortical neoplasm.

Immunohistochemical studies showed positivity of the tumor cells for inhibin, Melan-A, vimentin and CD99. Stains for cytokeratin AE1/AE3, chromogranin, WT1 and FOXL2 were negative. MIB-1 staining showed a low proliferative rate (~3% nuclear staining). B-catenin showed strong nuclear positivity in the tumor cells but only weak cytoplasmic and membrane staining. Electron microscopic examination showed discohesive sheets of large round to polygonal cells with abundant cytoplasm and centrally placed round nuclei. The nuclei showed margination of chromatin along the nuclear envelope with dispersed heterochromatin and small chromocenters. The cytoplasm contained abundant mitochondria admixed with rough endoplasmic reticulum. Occasional lipid droplets could be identified in most of the cells. There were no specialized cell junctions, microvilli or other organelles. The features were consistent with adrenal cortical cells.

Genetic findings: In light of the patient's clinical presentation of FAP, the patient was referred for genetic counseling and germline gene testing. Genetic testing using next generation sequencing (NGS) was done for the following genes: APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11 and TP53. Analysis of the NGS data revealed a low-level deletion signal at position c.3927 in the APC gene. Follow-up Sanger confirmation of the deletion also revealed a heterozygous deletion signal.

Diagnosis: Tubulopapillary adrenocortical adenoma in a patient with familial adenomatous polyposis.

Discussion: The present case is an apparent de novo Familial Adenomatous Polyposis (FAP) patient who was found to have a growing left adrenal mass during a preoperative evaluation. Adrenal neoplasms are a frequently occurring extra-intestinal manifestation of patients with FAP, partly because these patients often undergo abdominal imaging and have a raised incidence of adrenal masses being identified. A study by Smith et al on 107 FAP patients reported the prevalence of adrenal masses to be 13%.¹ So far over 50 cases have been reported in the literature, many of which were asymptomatic.²

Although adrenal cortical tumors have been reported frequently in FAP patients, the morphology of most tumors is that of a classic adrenocortical adenoma.³ The present case has unique features compared to the previous reports. The histologic appearance of this tumor is unlike that of conventional adrenal cortical neoplasms because of the unusual ribbon-like, tubulopapillary architecture and plasmacytoid features. The case reported by Wakatsuki et al³ documented an adrenocortical tumor with a similar histologic appearance in the setting of FAP, in which they described that the tumor was composed of polygonal cells that formed trabeculae and/or islands. In a study of an

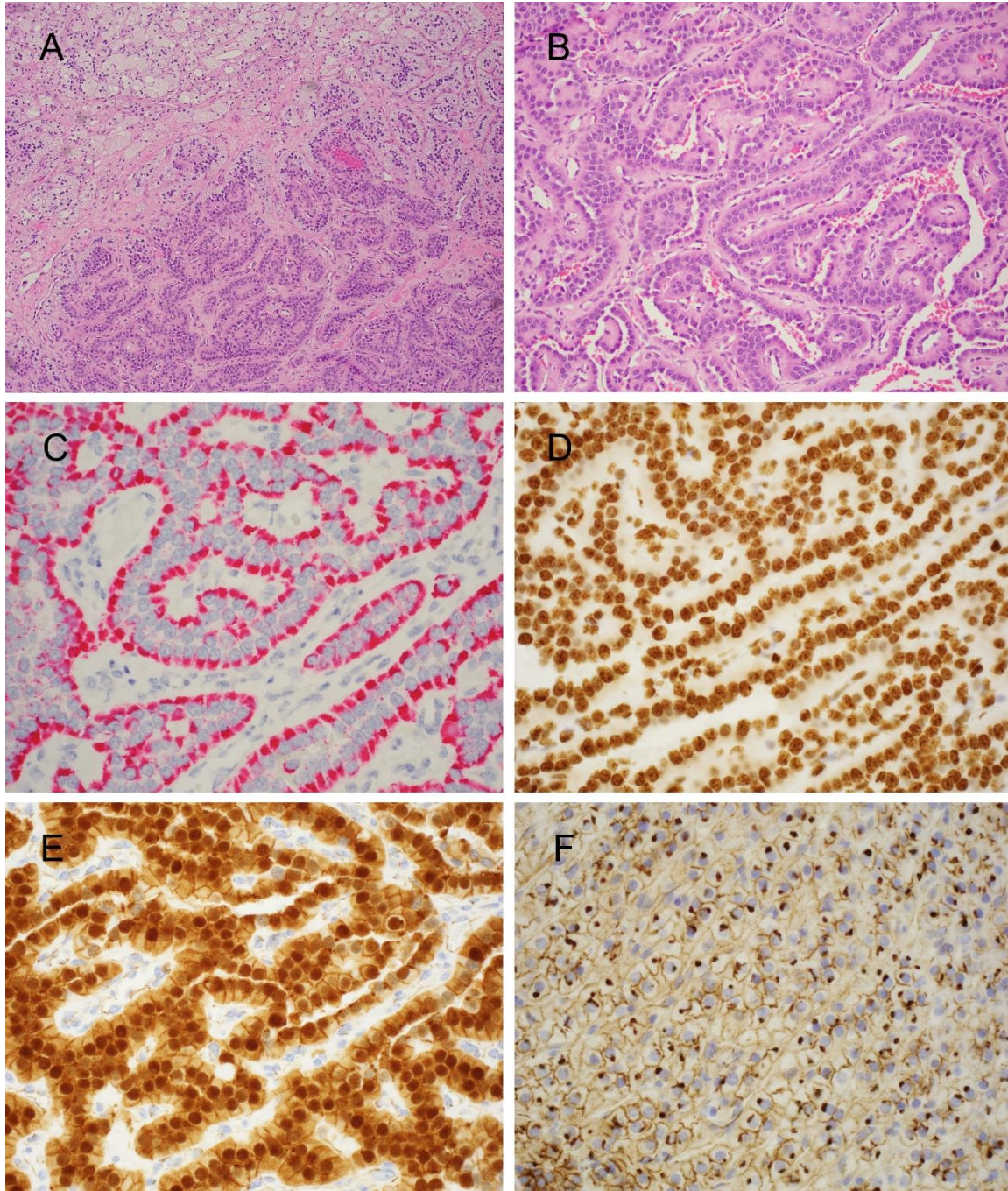
FAP patient with ovarian steroid cell tumor, Hu et al⁴ also reported an adrenal nodule containing cells with eosinophilic cytoplasm arranged in a corded, trabecular pattern. However, those cases showed a characteristic heterogeneity to the tumor nuclei. Our present case is unique in that the tumor cells are monomorphic with uniform plasmacytoid nuclei, which has not been demonstrated before. In addition, the prominent nuclear localization of β -catenin was not seen in the case reported by Hu et al. Wakatsuki et al³ mentioned the similarity of the morphology to gonadal sex-cord stromal tumor. For comparison, we performed FOXL2 IHC stain in our case. FOXL2 immunoexpression has recently been demonstrated as a sensitive and specific marker for sex cord-stromal tumors of the ovary. The negative IHC staining for FOXL2 in our case argues against its similarity to a sex-cord neoplasm.

The IHC findings of our case supports the origin of adrenal gland, and electron microscopic examination demonstrated features of a non-secreting tumor. IHC stain for β -catenin was performed to investigate the effect of APC gene mutation on the tumor, in which nuclear localization of β -catenin was observed in the tumor cells but not in the normal adrenal gland. It has been demonstrated that APC regulates the subcellular localization and turnover of β -catenin.^{5,6} Germline loss-of-function mutations of the APC gene results in accumulation and altered localization of β -catenin, and constitutive activation of the Wnt/ β -catenin signaling pathway and the β -catenin/T-cell factor (TCF) signaling pathway,⁶ leading to carcinogenesis. Therefore, the altered β -catenin-SF-1 pathway in FAP patients resulted from APC mutations may suggest a mechanism for the genetic predisposition to ACAs in this population.

The unusual and distinctive morphology displayed by this tumor is unique for adrenal cortical neoplasms, in my experience. I have seen a few adrenal cortical carcinomas that showed a similar growth pattern, but the cytology was obviously malignant in such cases. I shared this case with Dr. Jonathan Epstein to see whether he had encountered similar cases before, but he indicated he had never seen a tumor with these features. I'm circulating this case in the group to see whether any of you have encountered something similar before. I gave the case to one of my attendings and a resident to work up for publication. If anyone has seen similar cases, we could pool them for a joint publication.

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Figures: (A) Areas showing conventional adrenal cortical elements (upper left) and tubular and ribbon-like architecture (lower right). (B) A higher power view demonstrates uniform, large and polygonal tumor cells with abundant plasmacytoid eosinophilic cytoplasm. (C-E) Immunohistochemical stains of the tumor cells. (C) Melan-A, (D) Inhibin and (E) β -catenin. (F) β -catenin stain of the adjacent normal adrenal gland.