AMR Seminar #56 – Short Summary of Cases:

Case 1: F.23 with a mass in the ampulla.

Case 2: Mass of the parotid region in a 60-year-old woman.

Case 3: A 14 year old boy was seen for an 8cm. mass of the left lower lobe of lung.

Case 4: F.51 with solid mass in right breast adjacent to breast implant.

Case 5: F.33 with mural mass in abdominal wall.

Case 6: M.29 with long history of bilateral cervical lymphadenopathy.

Case 7: M.68 with "polyp" in nasopharynx.

Case 8: M.50 with polypoid mass in nasal cavity extending to maxillary sinus.

Case 9: M.61 with 8 cm. mass in left kidney.

Case 10: F.18 with slow growing mass in left leg.

Case 11: F.36 with soft tissue nodule on right thigh.

Case 12: Gastric body polyp in a 59-year-old woman.

Case 13: 3-month old baby with lesion of the rib protruding into the thoracic cavity.

Case 14: M.18 with large mediastinal mass.

Case 15: F.79 with a 25 mm mass in right breast.

Case 16: M.74 with a 12 cm renal mass.

Case 17: F.31 with massive splenomegaly following a viral illness.

AMR SEMINAR #56
CASE 1

Contributed by: Volkan Adsay, M.D.

History: 23-year-old African-American female who has a history of ascending cholangitis and obstructive jaundice. The workup performed revealed a pancreatic head mass and a pancreatoduodenectomy was performed.

Macroscopic Findings: The duodenal lumen showed a fungating centrally depressed mass measuring 6.0x 4.0 cm. The mass was located circumferentially around the ampulla of Vater. On cut sections a fleshy white lesion, protruding into the lumen of the distal common bile duct with no necrosis or ulceration was observed.

Microscopic Findings: The tumor showed a nodular growth pattern with pushing border type infiltration. A syncytial growth pattern of cells and prominent inflammatory infiltrate composed of lymphoplasmacytic cells and eosinophils distributed both within and around the tumor nodules were seen. No pre-invasive lesion was identified.

Immunohistochemical Findings: The neoplastic cells were positive for AE1:AE3 and negative for chromogranin, synaptophysin, CD56 and trypsin. Among microsatellite markers, MLH1 was retained but there was loss of MSH2.

Electron Microscopy: There were clear-cut evidence of epithelial differentiation including well-formed cell junctions. There were also subtle features of glandular differentiation including lumen formation. No evidence of any zymogen granules were identified. Occasional cells showed rare dense core granules reminiscent of neurosecretory granules, but there was no convincing evidence of neuroendocrine differentiation otherwise.

Diagnosis: Invasive poorly differentiated *medullary-type* carcinoma, arising in the ampulla.

Comment: With the overall morphology, the cytologic features, combined with the immunoprofile and the electron microscopic findings we concluded that this is an invasive poorly differentiated *medullary-type* carcinoma. The tumor shows all the hallmarks of medullary carcinoma as described in the breast or lower GI tract: Nodular growth pattern, pushing border type infiltration, syncytial growth pattern of cells, and prominent inflammatory infiltrates composed of lymphoplasmacytic cells and eosinophils, distributed both within and around the tumor nodules. Medullary carcinoma has been reported in the pancreas but it has not been well documented in the ampulla. Medullary carcinoma in the GI tract and pancreas has now been well established to have a genetic profile different from that of conventional adenocarcinomas. In the colon, they lack the association with "APC pathway" and instead represent the "MSI pathway". Immunohistochemistry for DNA repair markers like MLH1 and MSH2 can be useful in screening the cases for microsatellite instability. As in our case, the ones that express MSH2 but do not express MLH1 are more prone to have microsatellite instability and accordingly may be related to an inherited susceptibility to cancer. The young age of the patient here is in accordance with this possibility. The lack of a preinvasive lesion in this case is also typical for medullary carcinomas.

Regarding the prognosis, the experience with medullary carcinoma in this region is of course very limited. There are some hints that they may be more indolent than conventional pancreatobiliary type adenocarcinomas of this region.

References:

1. Wilentz, R. E., M. Goggins, et al. (2000). "Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: A newly described and characterized entity." Am J Pathol 156(5): 1641-51.
2. Sessa, F., D. Furlan, et al. (2007). "Prognostic factors for ampullary adenocarcinomas: tumor stage, tumor histology, tumor location, immunohistochemistry and microsatellite instability." Virchows Arch 451(3): 649-57.

AMR SEMINAR #56
CASE 2

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

Clinical Summary: A 60-year-old woman of Middle Eastern/North African origin (by name) was hospitalized for an orthopedic procedure following trauma to the shoulder when a mass was noted in the right parotid region. An FNA procedure performed then yielded only some lymphoid cells. The patient related that the mass was present for a number of years and seemed not to bother her. She was discharged following the orthopedic procedure and returned a few months later for removal of the facial mass.

Gross Pathologic Description: The specimen was sent with the clinical diagnosis of pleomorphic adenoma/Warthin tumor and was said to be located in the "right submandibular region close to or abutting on the parotid" (the surgeon later confirmed that the lesion was not inside the parotid). It measured 4.5x2.5 cm. and contained a well defined brown nodule measuring 3x2x1 cm surrounded by greyish soft tissue.

Microscopic Description: On low power the appearance is that of a lymph node complete with a capsule and subcapsular sinus (not well preserved everywhere) and containing many pink islands which could give the initial impression of sinus histiocytosis. However more careful examination reveals these to be solid epithelial aggregates composed mostly of plump to polygonal cells with some foci showing spindling and syncytial changes. If searched for carefully there is a small amount of hyaline material deposits focally between them. The cells stained positively and diffusely with MNF pankeratin and HMWK; p63 stained most but not all of the cells. Actin was negative and S100 stained single cells inside the epithelial aggregates and also in the lymphoid parenchyma while the epithelial cells themselves did not stain. The intraepithelial lymphocytes stained positive for CD20. There was no ductal differentiation histologically (though this wasn't tested immunohistochemically). To me they resembled squamous cells with "immature metaplastic" features, showing relatively large nuclei with some degree of polymorphism which I personally didn't consider to be malignant. Some of the islands are melding with their neighbors. There is one small focus (not present in the slides I am sending) which shows a few ductal cross sections with basaloid features. The lymphoid tissue shows reactive follicles (though some look like they're undergoing Castleman like involution) and there are small CD20 positive lymphocytes percolating into the epithelial islands, which here and there look like they're being lysed. In some blocks (not well demonstrated in the material I'm sending) there is non-lesional non-neoplastic salivary gland parenchyma surrounding the nodule which still remains well demarcated by its capsule. There is a focus in which the lesion is budding off into the surrounding parenchyma but still remaining separate from it. Alongside it the adjacent non-lesional salivary parenchyma is focally infiltrated by lymphoid tissue without undergoing encapsulation and in which the salivary epithelium has not undergone transformation.

Diagnostic Considerations:

1. benign/malignant (metastasis from occult nasopharyngeal tumor?)
2. tumor of parotid vs. intraparotid/periparotid lymph node
3. lymphoepithelial lesion (presenting as a nodular mass?) vs. lymphadenoma (non sebaceous type)

Discussion: First, I would like to point out that there were apparently fixation issues concerning the blocks so despite the valiant efforts of our lab technician the histology of the inner portions in some slides may be a bit choppy (though the cytological features are well preserved even in these areas). I apologize for any difficulties.
I originally considered the epithelial component to be consistent with benign lymphoepithelial lesions. As is well known, these non-neoplastic proliferations were originally considered to be composed of myoepithelial cells and arise from metaplastic changes in salivary ducts; but with the advent of immunohistochemistry, it was discovered that while some of the constituent cells may have myoepithelial features they are otherwise epithelial.

As is illustrated in the monograph "Surgical Pathology of the Salivary Glands" (ed. Ellis, Auclair, and Gnepp, W.B.Saunders 1991 p. 85-6), these islands are heavily infiltrated by lymphocytes. These structures also contain deposits of hyaline material consistent with basement membrane. Also as is well known these lesions are associated with autoimmune diseases and arise in the substance of the salivary gland without forming discrete nodular lesions. There was no clinical evidence of the former and as I pointed out my understanding was that the lesion was *not* from inside the parotid. However I speculated about the potential of benign salivary inclusions in lymph nodes to undergo the same pathological changes normally seen in intraglandular parenchyma.

I sent the case to a consultant who objected to my interpretation on anatomic grounds, noting the location inside a lymph node and the lack of residual ductal structures from which these lesions could arise (as I mentioned above I found a handful of small ducts in slides from one block which I didn't send to the consultant). This consultant considered a non-sebaceous lymphadenoma but disturbed by the atypia said that he couldn't rule out lymphoepithelial carcinoma and suggested investigation for nasopharyngeal tumor.

Sebaceous lymphadenoma of the parotid has been recognized for many years. This entity is consists of lymphoid tissue with islands and small cysts composed of or lined by squamous and ductal cells mixed with sebaceous cells. In more recent years lesions have been recognized that are similar to these for all intents and purposes but without sebaceous cells. The solid features seen in the epithelial component of this case would be at variance with the mixed ductal/squamous composition classically noted. However, the description given of this lesion in the recent WHO fascicle on head and neck tumors (p. 269) also points out that the epithelial islands can be infiltrated by lymphocytes (this is not depicted in the description given in the third series AFIP fascicle on salivary gland tumors) and in fact states that the differential diagnosis with lymphoepithelial lesions is based on the circumscription of the tumors. The gross descriptions given both in the WHO fascicle and the third series AFIP fascicle (p. 133) state that these lesions are encapsulated and if not then are well circumscribed and can arise either inside or "around" or in "the area of" the parotid so the origin in a periparotid lymph node is not ruled out.

In 2002 our friend Michele Bisceglia presented to the club a nodular lesion from the right parotid "mimicking a lymph node" from the region consisting of a proliferation of basaloid epithelial structures with squamous metaplasia on a reactive lymphoid background. He intuitively considered it to be a parotid lymphadenoma without sebaceous metaplasia; however at the time this case turned up (1998), there was no literature on it except for a brief mention of it in the AFIP fascicle under the rubric of sebaceous lymphadenoma. It was not given a separate passage and though there are photos of it these are tersely captioned "lymphadenoma". In looking at this case in comparison with the one I'm presenting, Michele's case does show a prominent component of small ducts with basaloid changes, and there is widespread mature squamous metaplasia with prominent keratin pearls (not seen in mine). The nuclei are small and round and without any atypia. I think that my case shows a more active lymphoid component and the abundant intra-epithelial lymphocytes are not seen in the one submitted by Michele.

It was interesting to re-read the comments of the other members to Michele's case in light of the points discussed above. Some would consider it to be sebaceous lymphadenoma with extensive squamous metaplasia (which is the other side of the coin of calling it lymphadenoma without sebaceous metaplasia), obviating the need of creating a new entity. John Chan looked at it as a basal cell adenoma with dual cell differentiation. Some used the term lymphoepithelial in describing the epithelium. I was surprised in reading my own comment that I was more concerned at the time with the atypia in the previous case than I am now with regard my own case.
Since Michele's submission to the club, several articles have appeared formally describing this lesion. In fact at that time an article co-authored by John Chan on this topic was in press (Ma et al, Histopathology **41**, 342-350, 2002). This article describes three lesions, one of which was clinically thought to be a lymph node and which was not attached to the parotid (the other two were in the parotid). The authors considered these lesions to be essentially proliferations of basaloid cells with a tumor associated lymphoid response. Their case no. 1 as photographed showed the epithelial cells to be "mildly atypical" without mitotic figures, and overrun with small lymphocytes to the point of being obscured by them. One of their cases was cystic. These lesions were well circumscribed but without sinusoids and thus considered not to be lymph nodes. They believed that the basaloid rather than squamous nature of the epithelial proliferation in these tumors and the lack of sebaceous cells differentiate them from sebaceous lymphadenoma.

In more recent years several other articles appeared on this entity. A brief report was submitted to the Journal of Clinical Pathology in **2004** (57(9): 1007.) by Musthyala et al. without discussion. Following that Dardick and Thomas (Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 105: 491-4, **2008**) reported on two cases, both of them intraparotid encapsulated nodules without sinusoids (the latter point ruling out the possibility of these lesions arising in lymph nodes). In one case, the epithelial component shows ductal differentiation while in the other the tumor cells are described as being "polygonal to irregular in shape with round to oval shaped nuclei" seemingly similar to what is seen in this case. In both cases, the epithelial islands are infiltrated by lymphocytes to the point of being obscured by them. The case reported by Yang et al (Virchows Arch. 450: 595-599, **2007**) was described as a well-circumscribed parotid mass without mention of the presence or absence of a capsule and the epithelial component showed ductal differentiation histologically. One additional case was just published (Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 107(4):555-8, **2009**) by Gallego et al. This tumor was found in the parotid and was well

circumscribed without sinusoids; there is no mention of a capsule. They described basaloid, tubular, or ductlike glandular differentiation with papillae and cysts.

In all the above articles, immunohistochemical stains reported by the authors show a mixture of cells with luminal or abluminal (i. e. basal cell for the most part) differentiation based on staining with low molecular weight keratins for the former and p63 for the latter. The immunohistochemistry I did in this case as described above would seem to go along with this, though I didn't perform stains more specific for luminal cells. There doesn't seem to be much myoepithelial differentiation as defined with actin and vimentin stains in these cases.

After reading his article, I sent the case to Dr Irving Dardick who also expressed concern about a metastasis from an occult nasopharyngeal carcinoma (though the lesion was present for a number of years, a fact which I may not have made clear to the consultants).

I am looking forward to the comments of other members of the group, including those with specific experience in head and neck pathology.

AMR SEMINAR #56
CASE 3

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

Case History: A 14-year-old boy, who was otherwise healthy, presented with left chest pain and dyspnea. Chest X ray and CT scan showed a large mass in the left lung. Wedge resection of an 8 cm. left lower lobe mass was performed.

Pathology: The mass was well demarcated, gray, soft, with focal hemorrhages.
Histology shows that the major cells of the mass are large xanthoma-like cells with foamy and vacuolated cytoplasm, vesicular nuclei with small nucleoli and occasional intranuclear cytoplasmic inclusions. Scattered mononuclear cells are present between these large cells.
Few, small foci of tumor cell necrosis were seen (including in the submitted slide, although most of the tumor blocks did not contain necrotic foci). The second, minor type of cells, which was limited to the periphery, subcapsular areas showed spindle cells with eosinophilic cytoplasm and vesicular, round to spindly nuclei with small nucleoli (somewhat similar to the nuclei of the larger cells). Mononuclear cells also infiltrated the spindle cell component, and the two cell populations merged with each other (no distinct border between them). Foci of hemorrhages and hemosiderin deposits were also seen. Few mitoses were seen in the spindle cell component, and the Ki67 index was less that 5%. In our hands some of the spindle cells were positive for CD68 (in the background of many histiocytes, while CD163 was negative in the tumor cells). All cells (both spindle and large) were negative for cytokeratin, EMA, ALK1, SMA, CD21, LCA, HMB45. PAS and ZN/AFB stains were negative. Stains for herpes virus, adenovirus and HHV8 (performed as desperate measures) were negative.

Discussion: We could not render a definite diagnosis. The closest diagnosis we could reach was a xanthomatous variant of "inflammatory pseudotumor"' considering the patient's age and the histologic features (combination of spindle cells, some with myofibroblast-like features, inflammatory cells and xanthomatous cells). However, stains for SMA were negative and the xanthomatous cells were not typical macrophages with small, bland nuclei. We were also concerned due to the focal nuclear pleomorphism, focal mitoses and focal necrotic foci. Thus, we asked for the opinion of Dr. Fletcher. Dr Fletcher admitted that he has not seen such a tumor in the past and is not aware of a similar entity in the literature. In his lab. the large polygonal cells showed some focal positivity for both EMA and inhibin, of uncertain significance, while both components (the very large cells with foamy/vacuolated cytoplasm and the spindle-shaped cells) were negative for SMA, desmin, ALK1, pan-keratin and CD68. He labeled the tumor as an "unclassified epithelioid and spindle cell neoplasm with pseudoxanthomatous features", and although he did not see overt features of malignancy, he would indicate that the biologic potential is uncertain due to the mild focal nuclear atypia and small foci of necrosis. Following Dr. Fletcher's response, the surgeon was not satisfied, and since he was educated in Mayo clinic he asked us to send the case to Dr. Colby. Dr. Colby, who also shared the case with Dr. Tazelaar, admitted that he did not know the nature of the lesion, which is probably neoplastic. He added that he did not know if the lesion is benign or malignant and that follow-up following the complete resection would be appropriate. In his lab. there was mild EMA positivity in the spindle cells, while HMB45, melan A, synaptophysin, TTF, AE1/AE3 and CD68: were al negative. He concluded that he remained perplexed by this lesion.

Thus, I would be grateful to hear your opinions concerning this lesion:
Do you think it is neoplastic? Dr. Colby raised this question: "We are not even sure it is neoplastic, although we suspect it is".

Did you see a similar lesion/tumor in your experience (in the lung or in other organs)?

Can you comment about the expected behavior of this tumor (I admit this may be impossible if we cannot classify this lesion/tumor)?

AMR SEMINAR #56
CASE 4

Contributed by: Gerald Berry, MD

History: This 51-year-old woman presented with a solid mass in the right breast adjacent to a breast implant. The mammogram was suspicious for a neoplastic process. An excisional biopsy of the mass and removal of the implant were performed.

Histopathologic Findings: I saw this case in consultation in April and do not have any follow-up yet. The lesion consists of an atypical lymphoid infiltrate arranged in sheets and clusters. There is infiltration of the fibroadipose tissue. The atypical lymphoid cells display round, vesicular nuclei with clear to amphophilic cytoplasm. The immunostaining profile showed: AE1/AE3, S100p, CK5/6, CD31, CD20, CD79a, ALK-1 and CD3 negative. Focal weak CD45 staining was observed. There was strong staining for CD30 and CD43. (see accompanying image)

Diagnosis: Anaplastic large cell lymphoma.

Discussion: There were 2 papers published last year (see references below) reporting the development of anaplastic large cell lymphoma in the proximity of breast implants in 5 cases. In the literature review in one of the papers a total of 8 published cases were accumulated from the published literature (beginning in 2006). Interestingly these are generally indolent tumors although the follow-up period is relatively short in the Mayo Clinic series. Treatment ranged from surgical excision to surgery +/- XRT +/- chemotherapy.

Comment: I thought the group would enjoy this case of anaplastic large cell lymphoma arising in an unusual setting.

References:

1. Roden AC, Macon WR, Keeney GL et al. Modern Pathol 2008; 21: 455-463.
2. Wong AK, Lopategui J, Clancy S, et al. Am J Surg Pathol 2008; 32: 1265-1268.

AMR SEMINAR #56
CASE 5

Contributed by: Michele Bisceglia, M.D.

Case Description: A 33-year-old female patient, with 2 children, born 9 and 3 years before, respectively. This patient was under oral hormone (estroprogestinic) treatment for 2 years due to polycystic ovaries. She had been previously operated 3 times in other institutions for multiple uterine leiomyomas (1, 3, and 6 years before, respectively). She was now referred to our hospital because of a mural mass of the abdominal wall she felt by autopalpation while taking shower. Ultrasonography and CT scan with and without contrast demonstrated 4 nodular intraabdominal lesions of various size ranging from 1 to 7. Laparoscopic approach was planned and 7 nodules (size range 1 cm to 10 cm) were excised and sent to our Anatomic Pathology division for histological examination, with the suspected diagnosis of extra-gastrointestinal GIST. The tumor nodules were circumscribed, firm, solid, and fibromyomatous in appearances. No necrosis, no myxoid or microcystic changes, no haemorrhage were seen on cut surface. Histologically, these tumor nodules and masses were comprised of spindle cells arranged in a fascicular pattern, with no cytological atypia, no necrosis, no atypical mitoses (MI extremely low). Smooth muscle differentiation was immunohistochemically proved (positivity for muscle specific actin and alpha-SMA as well as for calponin and H-caldesmon). CD34, CD117, EMA, and S-100 protein all were negative. Strong immunopositivity for estrogen and progesterone receptors was documented.

Attached are 2 slides labelled **5-138888-7/A** and **6-138888-7/B**, relevant to 2 of the intraabdominal peritoneal nodules removed laparoscopically in our institution.

In the meantime, a hectic search for the previous pathological specimens from "uterine leiomyomas" (surgical interventions performed in 2 other different hospitals) started and (with several personal phone calls directly to the patient's home) ended successfully.

On revision of the glass slides, relevant to all previously removed uterine tumors), we could confirm the diagnoses of conventional uterine leiomyomas made by the original anatomic pathology centers.

Diagnosis: Leiomyomatosis peritonealis disseminata.

Follow-up: The postoperative course was uneventful, and the patient was discharged with the therapeutic suggestion to interrupt hormone treatment. More than 2 years after the diagnosis of LPD the patient is well and free of disease.

Discussion: Leiomyomatosis peritonealis disseminata (LPD) is a rare condition of the females, which is hormone dependent. It presents with widespread numerous peritoneal nodules in the lower abdomen and pelvis (1-3) which are usually of small size (tumorlets). It mostly affects women either in their reproductive age (pregnancy) or in their perimenopausal age under hormonal treatment. After delivery or after discontinuation of the hormonal treatment, the tumoral nodules often regress. LPD is considered a proliferative or metaplastic process deviating from subcelomatic mesenchyme in the area of the hormone-sensitive secondary müllerian system. (4) It is practically always associated with leiomyomas of the uterus, but is usually per se asymptomatic, being occasionally discovered if a lady undergo a cesarian partum or undergo abdominal surgical interventions for other reasons. Molecular studies and cytogenetics have documented that LPD exhibits a clonal pattern (multicentric clonal proliferation), with associated chromosomal aberrations, similarly to what was also demonstrated in leiomyomas. (5) Both the preoperative and histological differential diagnosis include other diverse leiomyomatous conditions (i.e., intravenous leiomyomatosis, parasitic leiomyomas, pelvic leiomyomas from the same secondary müllerian system, metastasizing benign leiomyoma), extra-gastrointestinal GIST, and conventional leiomyosarcoma of intra-abdominal soft tissue. (6) LPD is practically always benign, even though exceptional cases of sarcomatous transformation are on record. The standard treatment is not surgery. Surgical exploration is indicated only for diagnostic purposes and for taking out voluminous masses, as in the case presented herein. Surgical intervention directed to extirpation of all nodules is not warranted. The interruption of the hormonal pathogenetic cause is necessary, and antagonist of GnRH drug administration is indicated.

Comments:

1. From the clinical point of view, this case seems to me a paradigmatic case, with a typical history, although a fragmented history we could collate in any parts.
2. The metachronous presentation of LPD in respect to the presentation of uterine leiomyomas is unusual.
3. In slide 6-138888-7/B one can see how the LPD arise. Even the muscle wall of small blood vessels show leiomyomatous changes (a finding which was noted initially, which attests for the autochthonous origin of all the nodules from the subcelomatic pelvic mesenchyme and militates against other histogenetic or pathogenetic possibilities).
4. Hope the Club members will enjoy looking at this case.

Query and courtesy: Few days before this writing, I was contacted personally by another LPD patient, 38-year-old female from Italy, with the following clinicopathologic history.

First intervention in March 2004 (in a certain hospital) due to 2 uterine leiomyomas (1 cellular leiomyoma, 1 conventional – sizes – fragmented materials of around 10 cm in aggregate).

Second intervention in February 2005 (in a different hospital) for the removal of 2 tumors (4 cm in size, each) arising from the peritoneal surface of the sigmoid: both were diagnosed as leiomyomas.

Third intervention (in a hospital other than the first two) in October 2005: 2 new nodules were removed - one (5 cm in size) from the uterine corpus, the other one (4 cm in size) from the mesentery. Both of these latter tumors of October 2005 were considered benign (slides also seen in a referral center from Gyne): in this specialized center, where slides from the previous interventions were also reviewed the following opinion/comment was made → *The (October 2005) mesenteric nodule could be either a metastasis from one of the previous leiomyomas (likely the first 2004 uterine tumor, which was reviewed in the referral Center and considered as mitotically active leiomyoma with 6M:10HPF, but with no atypia and no necrosis) or a product of multicentric (peritoneal) leiomyomatosis.* All the peritoneal lesions were immunohistochemically studied and proved to be of smooth muscle derivation and were also tested for ER and PGR and all were found to be strongly positive.

Subsequently other nodules (up to 20 in April 2006) were seen in the abdomen: the patient was given Megace (megestrol acetate / medrossi-progesteron) with no benefit, and then she was given Leuprozelin acetate (antagonist of GnRH) plus Letrozole (inhibitor of aromatises) with good response. In fact, after almost 1 and a half years of therapy, the detectable nodules were reduced in number to 3-4 only. Aiming to become pregnant, she interrupted the therapy. After that, the nodules increased again, both in size and numbers, she started again with the therapy but with **no** effect. Currently, she has around fifteen of them with two dominant masses of 7 and 11 cm, each, in size.

Her question to me, which I transmit as it was raised "*anything new about the therapy*" (in case that the one based on antagonist of GnRH is ineffective).

After saying that the history is typical for LPD and that I cannot believe that the 2006 nodule from mesentery is anything else than one of the nodule of LPD, and based on my knowledge as a pathologist, I would suggest that she get the main masses removed and then to try another commercial drug still based on GnRh antagonists . Also, if she hopefully gets a new good response, that she **not** interrupt it, aiming to become pregnant as pregnancy would worsen her clinical situation. If she eventually finds a new effective therapy in the future, she has to reduce it but not interrupt it.

Thank you for your opinions in regard to this new patient.

References :

1) Zotalis G, Nayar R, Hicks DG.Leiomyomatosis peritonealis disseminata, endometriosis, and multicystic mesothelioma: an unusual association. Int J Gynecol Pathol. 1998 Apr;17(2):178-82.
2) Butnor KJ, Burchette JL, Robboy SJ.Progesterone receptor activity in leiomyomatosis peritonealis disseminata. Int J Gynecol Pathol. 1999 Jul;18(3):259-64.
3) Thor AD, Young RH, Clement PB. Pathology of the fallopian tube, broad ligament, peritoneum, and pelvic soft tissues.Hum Pathol. 1991 Sep;22(9):856-67.
4) Lauchlan SC. The secondary müllerian system revisited.Int J Gynecol Pathol. 1994 Jan;13(1):73-9.

5) Quade BJ, McLachlin CM, Soto-Wright V, Zuckerman J, Mutter GL, Morton CC.Disseminated peritoneal leiomyomatosis. Clonality analysis by X chromosome inactivation and cytogenetics of a clinically benign smooth muscle proliferation. Am J Pathol. 1997 Jun;150(6):2153-66.
6) Cohen DT, Oliva E, Hahn PF, Fuller AF Jr, Lee SI. Uterine smooth-muscle tumors with unusual growth patterns: imaging with pathologic correlation. AJR Am J Roentgenol. 2007 Jan;188(1):246-55.

AMR SEMINAR #56
CASE 6

Case contributed by: Thomas V. Colby, M.D.

Clinical History: A 29-year-old black male had a long history of bilateral cervical adenopathy dating to age 14 when a diagnosis of Kimura's disease was made. Four years after presentation this region was debulked and over the next 11 years he has had progressive cervical adenopathy and at the time this specimen was taken (for debulking) there were bilateral masses (see gross below). The patient also has a diffuse truncal rash with hyperpigmented maculopapular lesions that were intensely pruritic. He had systemic eosinophilia, and elevated IgG and IgE. His serum tryptase was elevated. His skin rash was presumed to be related to his systemic eosinophilia. He had a polyclonal increase in gamma globulins with IgG at 2460 (normal 6-1500) and his IgE was 15,830 (normal of 0-127). IgA and IgM were normal. He had an absolute eosinophilia of 4.83 (normal 0-0.4). Platelets and hemoglobin were normal. There was no evidence of mastocytosis.

He underwent debulking of the right and left neck. The right neck issue measured 11 x 8 x 6 cm with an ellipse of skin measuring 10 x 5 cm. On cut section there was fibrous tissue with multiple tan nodules within it. The left neck specimen measured 11 x 7 x 4 cm and including an ellipse of skin 9 x 4 cm. The mass showed multiple pink-tan nodules grossly thought to be lymph nodes.

Flow Cytometry: No evidence of monoclonal B cell or aberrant T-cell population using the following markers: CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD14, CD19, CD20, CD22, CD23, CD38, CD45, CD16/56, FMC-7, and kappa and lambda immunoglobulin light chains.

Diagnosis: Kimura's disease with chronic clinical manifestations including bulky cervical adenopathy and associated soft tissue edema and fibrosis, cutaneous lesions.

Comment: I present this case for the interest of the group. The chronicity of this disorder is well illustrated with the clinical history above. Most affected patients are males of Asian heritage. The peripheral eosinophilia and elevated IgE are characteristic. The lymph nodes show typical reactive changes with prominent eosinophils. This case illustrates a dramatic surrounding edema and fibrosis. Perhaps the hematopathologists in the group have seen this sort of change but the dramatic findings in this patient were new to me.

AMR SEMINAR #56
CASE 7

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

Clinical History: A 68-year old man presents with a pharyngeal "globus" and previous history of nasal stuffiness. Inspection and CT reveal a 55 mm sized polyp in nasopharynx. Polyp originating from right upper posterior nasal septum. Previous work as carpenter with exposition for wood dust. On biopsy "reactive" findings. Excision in local anaesthesia. Postoperative follow-up after 6 months unremarkable.

Pathological Findings: In low-power a polypoid proliferation of small seromucinous glands covered by ciliated respiratory epithelium was seen. Invaginated respiratory epithelium also formed mucoid cysts linen by low cuboidal to flat epithelium. Focally the inverted ciliated epithelium was surrounded by a prominent hyalinized basement membrane reminiscent of what is seen in respiratory epithelial adenomatoid hamartoma (REAH). In high-power the proliferation of the seromucinous component was more obvious. Small glands, ducts and tubules with lobular and irregular haphazard distribution was noted. The haphazard component architecturally showed complex patterns such as suggested small cribriform areas, focal clustering to the extent of back-to-back pattern, insinuating infiltration-like growth and absence of a visible dual cell composition, i.e.: lack of basal-myoepithelial cells. On the other hand deep infiltration of polyp stalk was completely absent – on can almost draw a deep line respected by the seromucinous glands even if nasal mucosa don't have any recognizable anatomical deep definition such as lamina muscularis mucosae. No obvious destructive infiltration of normal structures were seen. No perineural or LVI growth documented. Cytologically very bland without atypia, apoptosis, necrosis or significant number of mitoses. Focally, densely eosinophilic cytoplasmic granules of zymogen-like type were noted. The stroma revealed slight fibrosis, focal edema, chronic inflammation but no desmoplastic response.

Special studies: Extensive IHC studies revealed complete absence of ME/basal cells around haphazard seromucinous proliferation: SMMS-1-, p63-, Actin HHF35-, SMA-, 34βE12-, Calponin-, CK5-, CK14-, S100-, WT1-. CT4 however delineated glands well. Laminin5 -. The lesional glandular cells were characterized by: S100+/-, MNF116+, CK5-, CK7+, CK14-, CK18+, CK19+, CK20-, Mucin1+/-, Mucin2-, Mucin5ac-, Calponin-, WT-1-Proliferation rate < 1 % (MIB-1).

Diagnosis: Nasal seromucinous hamartoma with focal REAH-like features.

Discussion: Since the original description by Baille and Batsakis circa 17 cases seem to have been reported. Some of these have been reported under other names such as microglandular adenosis. The lesions seem to occur on an inflammatory background, de-novo in adult individuals and with a peculiar predilection location unilaterally to posterior nasal septum. Recurrence rates are low and progression to unequivocal adenocarcinomas with potential for aggressive destructive growth and metastasis have to my knowledge not been reported. In a recent and, to date, the largest report of seromucinous hamartomas by Weinreb et al, the presence of occasional REAH-like features and common location in the posterior nasal septum was noted and a spectrum from pure seromucinous hamartoma to REAH was suggested.

In writing and reading up this case, I could not help thinking about the nomenclature and the possible tumor biology of these group of lesions. To me, hamartoma is a old term better reserved for congenital malformative tumefactive lesions as originally defined. An epithelial lesion presenting as a localized new growth ("neoplasia") in an adult patient population should probably better be named along the spectrum of metaplasia - hyperplasia – intraepithelial neoplasia – adenoma – dysplasia – intra epithelial carcinoma - low-grade carcinoma – high-grade carcinoma from a conceptual point of view. The recent publication by Ozolek and Hunt demonstrating a high incidence of LOH and FAL in REAH clearly challenges the hamartoma concept in favor of neoplasia – respiratory epithelial adenoma (REA)? Given the spectrum of seromucinous hamartoma – REAH, these types of studies would be very interesting in the seromucinous hamartoma group. Listening to Dr. Robboy lecturing about EIN recently at the Nebraska Pathology meeting, I could not help playing with the EIN concept on Bruce's original paper on REAH: < 50 % stroma; > 1 mm; focal lesion with different cytology! Do we have a lesion fulfilling those criteria of an intraepithelial neoplasia? Respiratory intraepithelial neoplasia (RIN) or nasal intraepithelial neoplasia (NIN)? Guess the tricky part could be the

omitting of mimickers... Furthermore, observations by Jo et al reports an association rate between REAH and low-grade tubular SNAC of more than 20 % (6/29) again suggesting a REAH – carcinoma sequence.

Not surprisingly, the most difficult differential diagnosis to seromucinous hamartoma is non-intestinal type low-grade sinonasal adenocarcinoma (LGSNAC). Given the low numbers of reported seromucinous hamartomas, not much experience and no well-founded guidelines on this differential has been published. On the other hand ,there are two recent papers dealing with the differential diagnosis between REAH and low-grade sinonasal adenocarcinomas by Jo et al and Sangoi et al.

Extrapolating from those papers and adding suggestions from the publications on seromucinous hamartomas and my own ideas findings:

In favor of carcinoma (LGSNAC):

- Complex architecture of some significant extent (Not defined)
    - Back-to-back
    - Papillary infoldings
    - Cribriform
- Trabecular – lobular – indian file like infiltration
- Destructive infiltration visavi normal structures
- Invasive growth beyond mucosal plane
    - Not respecting imaginary deep line
    - Growth in polyp stalk
- High-grade foci
- Perineural or LVI growth

In favor of hamartoma/REAH/adenoma are:

- Posterior septal location
- More intervening stroma
- Stromal chronic inflammatory background
- Residual lobular architecture – non-haphazard distribution of some seromucinous glands
- Ciliated epithelium expand with formation of mucin filled cysts
- REAH like proliferations intimately associated with seromucinous gland proliferation
- Serous glands budding from respiratory epithelial invaginated glands
- Occasional lymphangiomatous, osseous or chondroid mesenchymal proliferations
- MIB1 < 1 %
- CT4 + investigation of glands
- Laminin5 -

Questions to AMR group:

1. I realize the difficulty in classifying an individual case such as this without proper follow-up and without molecular profiling. Personally, I would weigh the evidence in this case as in favor of hamartoma or adenoma but it is really hard to definitively rule out a low-grade carcinoma with respect to the haphazard proliferation pattern without myoepithelial – basal cells. What is your opinion?
2. Nomenclature. Time to change hamartoma? But what should we call them? Seromucinous gland proliferation with low-malignant potential? Uncertain malignant potential? Microglandular adenosis? Adenomas? Intraepithelial neoplasias? Low-grade adenocarcinomas?
3. Should this lesion be considered under salivary gland pathology i.e.: salivary gland hyperplasia – adenoma – low-grade carcinoma? S100+. Derived from seromucinous glands which essentially are accessory salivary glands.

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AMR SEMINAR #56
CASE 8

Contributed by: Giovanni Falconieri, M.D., Udine, Italy

Clinical History: A 50-year-old man is evaluated at the ENT clinic because of nasal discharge. Nasal cavity inspection shows a polypoid mass. A subsequent CT scan also reveals a complex lesion involving the maxillary sinus as well, although with no evidence of facial bone involvement. Several grey-lucent fragments are received.

Microscopical Findings: Sections feature epithelial islands bordered by "palisading" columnar cells associated with a loose, reticulum-like, component with spindle/stellate nuclear appearance. There is also a variably collagenized stroma. Regressive changes may be noticed as well.

My first thought is sinonasal ameloblastoma, yet I would like to hear the accountable opinions of the club members.

Reference:

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AMR SEMINAR #56
CASE 9

Contributed by: Masaharu Fukunaga, M.D. (S06-2403, #13)

Clinical History: A 61-year-old Japanese male presented with hypertension. In systemic examinations, CT revealed a mass measuring 8cm in the left kidney. A radical nephrectomy was performed under the clinical diagnosis of renal cell carcinoma. The patient had no history of radiation therapy. He was free of von Hipple-Lindau or any other familial genetic syndrome. The patient died of multiple liver, bone and retroperitoneal metastases 13 months after surgery.

Macroscopic Features: The tumor was well circumscribed and measured 8.0 X 7.0 x 8.0 cm. It was located in the middle of the kidney and was brown in color with marked hemorrhage and necrosis. The tumor involved the renal cortex, medulla and perinephric fatty tissue.

Immunohistochemical Studies: The tumor was positive for vimentin, CD31, Factor-VIII, CD117 and CD34. It was negative for D2-40, CAM5.2, EMA, S-100, CD10, HMB45, alpha-smooth muscle actin and desmin.

Diagnosis: Angiosarcoma of the kidney

Comments: The lesion was initially considered a renal cell carcinoma clinically and angiomyolipoma histologically. The tumor cells were arranged in various vascular forming patterns; mainly anastomosing, sinusoidal, cavernous hemangioma-like, papillary and spindle cell patterns. The adipose tissue involvement by the tumor in a dissecting pattern was prominent; resembling "angiomyolipoma" However, the pathologic diagnosis of angiosarcoma was relatively straightforward in this case. The possibility that the tumor involving the kidney was actually retroperitoneal rather than renal in origin was considered. However, the main bulk of the gross tumor was centered in the kidney and the kidney therefore remains the most logical organ of origin. There have been 24 reported cases of primary angiosarcoma of the kidney in the English literature (1-5). The prognosis of renal angiosarcoma is uniformly fatal with widespread metastases and World Heath Organization reported mean survival of 7.7 months (4).

There are two questions among our colleagues. First, the possibility of angiosarcoma arising from benign hemangioma. The second, the parts of the adipose elements in the distributed slide is the adipose capsule and some of the adipose elements may represent adipocytic hyperplasia associated with the angiosarcoma. The adipose tissue is often observed around conventional hemangiomas, radiologically and histologically. I would appreciate very much if I could hear from your comments.

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AMR SEMINAR #56
CASE 10

Contributed by: Thomas Krausz, M.D.

Clinical History: An 18-year-old female presented with a slowly growing mass in the left leg. The excised tumor (8.5 x 3.8 x 2.8 cm) was well circumscribed and located in the anterior tibialis muscle.

Diagnosis: Reticular perineurioma.

Comment: The histologic features of reticular perineurioma are well described, but the diagnosis of this benign tumor can be problematic. Although a case of reticular perineurioma was submitted to AMR seminar in 2003 by Thomas Mentzel and an intestinal perineurioma with infiltrative features in 2006 by Carlos Bacchi, I thought members may benefit seeing another case as the morphologic spectrum of perineurioma is expanding (intraneural perineurioma, soft tissue perineurioma: conventional, sclerosing, reticular and plexiform). The current case shows the typical reticulated growth pattern with vacuolation between and in the cells. It exhibits more prominent sclerosis and more cytologic atypia than the reticulated perineurioma submitted by Thomas Mentzel previously. No mitotic activity is seen.

Immunohistochemical study was also typical (EMA, Glut-1, Claudin-1, collagen IV positive and S-100, keratins, SMA, MSA, CD34 negative). The S-100 negativity rules out microcystic/reticular schwannoma.

Ultrastructural features confirmed perineurial differentiation: spindle shaped cells with thin, long cytoplasmic processes with numerous pinocytotic vesicles and prominent basal lamina.

Molecular cytogenetic studies detected loss of 22q11.2/22q13 in 33% and loss of EWSR1 region at 22q12 in 37% of the interface cells from the paraffin sections. These findings likely represent loss of this region or monosomy 22 which is consistent with the diagnosis.

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AMR SEMINAR #56
CASE 11

Contributed by: Thomas Mentzel, M.D., Germany

Clinical Findings: A 36-year-old female patient developed an indurated nodule on her right thigh, that was completely excised. The encapsulated neoplasm measured 5.6 cm in largest diameter.

Pathological Findings: The well-circumscribed, nodular neoplasm is composed of two cell types. In addition to slender, spindle-shaped tumour cells containing elongated nuclei, plumper tumour cells with enlarged nuclei are seen, and both cellular components are irregularly admixed. Numerous nuclear pseudoinclusions are noted in the plump spindled tumour cells. The collagenous stroma contains numerous blood vessels with slightly fibrosed vessel walls. Immunohistochemical stainings confirm the presence of two cellular components. Elongated tumour cells stain positively for EMA and CD34 but are negative for S-100 protein, the plump spindled neoplastic cells express S-100 protein but are negative for EMA and CD34. No increased proliferative activity is noted.

Diagnosis: Hybrid perineurioma and (ancient) schwannoma.

Discussion: In addition to classical benign peripheral nerve sheath tumours comprising schwannoma, neurofibroma, perineurioma and variants of neuroma a number of hybrid peripheral nerve sheath tumours has been described in the last years. Despite well-defined clinicopathological entities in the spectrum of benign peripheral nerve sheath tumours, that are characterized by distinct genetic changes as well, the presence of schwannoma/perineurioma, schwannoma/neurofibroma, and neurofibroma/perineurioma hybrids emphasizes that these neoplasms are more closely related than previously believed.

Literature:

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AMR SEMINAR #56
CASE 12

Contributed by: Elizabeth Montgomery, M.D.

(Case 1 - S07-56904)

History: Gastric body polyp in a 59-year-old woman.

Diagnosis: Pyloric gland adenoma with high-grade dysplasia in a background of autoimmune metaplastic atrophic gastritis.

Comment: Since last time, when I sent a case I was not sure of, the group (correctly) cast doubt on my impression so I am sticking to cases I know without hesitation this time to spare my oversized but still delicate ego!

Unfortunately, much of the lesion is exhausted on the slide but there is enough to get the idea. The background gastric body mucosa should have lots of parietal cells (oxyntic mucosa) but they are all gone, presumably from autoantibodies. The history of a woman of a certain age is classic for autoimmune gastritis. Her oxyntic mucosa has been replaced by metaplastic mucosa both pyloric gland metaplasia and intestinal metaplasia. There is also endocrine cell hyperplasia but it is a bit tough to pick out on H&E. The adenoma part is seen in the smaller detached portion as well as in the larger portions, where is has expanded on top of the metaplastic mucosa. Normal surface foveolar epithelium can be seen away from the protuberant part and shows an apical cap of neutral mucin. The cells in the neoplasm, in contrast, have no apical mucin cap but, rather, have a ground glass cytoplasm and rounded monolayered nuclei. Most gastric adenomas show intestinal differentiation and presumably arise in association with intestinal metaplasia but patients with autoimmune gastritis also get pyloric metaplasia, which seems to have a neoplastic counterpart. Most observers have used a low threshold to regard the dysplasia in these lesions as high-grade, and certainly invasive carcinomas can be associated with lesions like this one. If one performs immunohistochemistry, these label nicely with MUC6 as do pyloric/antral and gastric cardiac glands. Such adenomas, of course, are known in various parts of the GI tract. The ones in the gallbladder are very bland-appearing. Colleagues in Europe [including Michal] and Japan have been good at recognizing these for some time but we have finally begun to catch on here in the US as well.

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AMR SEMINAR #56
CASE 13

Contributed by: Elizabeth Montgomery, M.D.

(Case 2 – S08-76039)

History: Three-month-old baby girl. The patient had been diagnosed with an "adrenal mass" by ultrasound in utero, an impression confirmed by a follow-up ultrasound after birth. The surgeon performed an operation to remove the "neuroblastoma" but at operation, realized that the lesion was not in the abdomen but instead inside the thorax, involving a thoracic rib and protruding into the thorax. Strong work, imaging team!

Diagnosis: Chest wall hamartoma.

Comment: These are rare but distinctive and arise in association with ribs. Like this example, many are congenital. They are also called "vascular hamartoma of infancy", "mesenchymal hamartoma of the chest wall" and "mesenchymoma". They are benign. They consist of cartilage, ossification, and areas of blood lakes as well as pockets resembling chondroblastoma.

References:

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AMR SEMINAR #56
CASE 14

Contributed by: Giuseppe Pelosi, M.D., Milan, Italy

Clinical History and Gross Pathology: A 18-year-old Caucasian man, nonsmoker, bricklayer, began to complain of cough and asthenia in December 2006, but only in March 2007 the patient decided to undergo chest X-ray examination, which showed a tumor mass occupying the medium and lower thirds of the left hemithorax (Figure 1A,B). This finding was further confirmed by CT scan examination performed immediately after that exhibited a 17x16x12 cm mass strictly adherent to the main vascular channels of the mediastinum and the left main bronchus with extent to the parietal pleura, lung parenchyma compression and right dislocation of the mediastinum (Figure 2A,B). Some mediastinal lymph nodes appeared to be enlarged (the largest one being 2 cm in diameter) in the right lung hilum, in subcarinal position and along the left mammary vessels, but no distant metastases or pleural effusion was documented. A core biopsy performed during admission at another hospital in March 2007 was diagnosed as being a myofibroblastic tumor of low malignant potential. The medical and family past history were unremarkable. The patient underwent in our Institution a left Hemi clamshell surgery with excision of the mediastinal mass, left pneumonectomy and pericardium resection and reconstruction. Grossly, tumor mass measured 21 cm in its greatest dimension, was solid and strictly adherent to the left lung and pericardium, which did not show tumor involvement. The cut surface was glistening, whitish to pink, and fibrous and fascicled in appearance, but exhibited some myxoid areas of gelatinous texture. Four hilar nodes, six peribronchial nodes of the upper lobe and five peribronchial nodes of the lower lobe were identified and processed for definitive histological examination. At two year follow-up, the patient is alive and well with no signs of local or systemic disease; in particular no other similar lesions were seen elsewhere in the body.

Microscopic Pathology: The tumor was moderately cellular and composed of a uniform and bland population of elongated cells resembling fibroblasts/myofibroblasts that were loosely arranged in sweeping fascicles and set up against a collagenous to myxoid background with scar tissue appearance. Mitotic figures were practically absent, and nuclear pleomorphism was not a feature. Tumor cells were seen to involve the parietal pleura and the fat tissue of the mediastinum, closely extending to visceral pleura and pericardium. Some mediastinal lymph nodes exhibited perinodal involvement vaguely resembling direct infiltration (see one of the two provided slides, labeled A and E). Immunohistochemical study showed labeling for smooth muscle actin in a certain number of tumor cells along with nuclear staining for beta-catenin, whereas desmin, S-100 protein, EMA, cytokeratin pool AE1-AE3, CD117, CD34 and CD99 immunoreactivity was completely lacking.

Diagnosis: Deep extra-abdominal fibromatosis (desmoid tumor) of the chest with involvement of the parietal pleura and fat tissue of the mediastinum. Lung parenchyma, pericardium and all examined nodes were free from disease, albeit some mediastinal nodes presented with a deceptive perinodal infiltration by tumor cells.

Comment: Although I am sure that all AMR members have been often faced with and are absolutely familiar to fibromatosis arising in different anatomical sites, I feel this case may be interesting, because of the unusual location in the chest and the huge dimension attained by the lesion, under the assumption that it has been present for a certain time. No history of antecedent chest trauma was recognizable, as well as no knowledge of similar lesions to arise elsewhere in the patient's body. The pathologists should be aware of this entity to arise in the thorax (mediastinum, pleura or even lung) (Andino et al, 2006), which is sometimes able to simulate other lesions, in particular solitary fibrous tumor or even sarcomas. Recently I have seen another similar case of fibromatosis presenting as a large-sized lesion of the thorax abutting the pleural cavity, and I am wondering if other Members of AMR have been experienced with similar cases in their diagnostic practice in order to publish a clinicopathologic series.

Reference:

Andino L, Cagle PT, Murer B, Lu L, Popper HH, Galateau-Salle F, Sienko AE, Barrios R, Zander DS. Pleuropulmonary desmoid tumors. Immunohistochemical comparison with solitary fibrous tumors and assessment of beta-catenin and cyclin D1 expression. Arch Pathol Lab Med. 2006;130:1503–1509.

AMR SEMINAR #56
CASE 15

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

Clinical History: A 79-year-old lady with a 25 mm mass in right breast. No significant past medical history. Needle biopsy followed by lumpectomy were performed.

Pathology: The macroscopic evaluation of the specimen showed a 20 x 15 x 10 mm irregular, hard mass with a white discoloration and multiple microcysts filled with hematic and mucoid content present less than 0.1 cm from the closest resection margin.

Histologically, the lesion consisted of a neoplasm formed by irregular dilated glands lined by pleomorphic cylindrical epithelial cells with moderate and severe atypia with abundant intra and extraglandular mucinous component, surrounded by areas of DCIS.

IHC profile: Positive for: CK7 , Negative for: ER, PR, HER2, p53 and CK 20.

Diagnosis: Primary Mucinous Cystadenocarcinoma of the Breast.

Comments: I decided to send this case because we have had two recent cases in our institution with this diagnosis.

Primary mucinous adenocarcinoma of breast are rare tumors within the wider group of mucinous carcinomas of breast. There were initially described by Tavassoli in 1998 ,and currently there are only eight cases reported in the literature.

They should be considered low grade tumors since the prognosis is generally good. No deaths have been reported and only two cases have presented with lymph node involvement. Median age at presentation is 67.9 years. They can present as big, palpable masses and are usually negative for ER, PR and HER2, and can be viewed as a variant of triple negative tumors of good prognosis. The diagnostic differential is with other mucinous lesions and with metastatic disease, mainly pancreatic or ovarian cystadenocarcinoma. The presence of concomitant DCIS and the immunostaining pattern: CK7+, CK20-, CEA-, MUC5AC- , help to favor a primary origin. However, extensive radiologic work-up should always be considered due to the striking similarities of this entity with primary ovarian and pancreatic neoplasms.

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AMR SEMINAR #56
CASE 16

Contributed by: Joshua Sickel, M.D.

Clinical History: 74-year-old male with a 12 cm renal mass.

Histologic Findings: Most of the tumor showed characteristic features of chromophobe renal cell carcinoma, grade 2-3. Immunostains for e-cadherin and CD-117 were both positive. Sections taken from a 2 cm focus with gritty consistency on cut section, show abrupt transition to a high grade sarcomatoid neoplasm with osseous differentiation. Metastatic chromophobe cell carcinoma was found in 2 peri-nephric lymph nodes.

Diagnosis: De-differentiated chromophobe renal cell carcinoma with osteosarcomatous differentiation

Discussion: This is a rare tumor which has been recently described in the pathology literature. The phenomenon of "de-differentiation" to a high grade sarcomatoid neoplasm is more common in chromophobe tumors than in other types of renal cell carcinoma. I was struck by the sharp transition between the two histologies. Have any club members encountered this unusual tumor in your practice?

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AMR SEMINAR #56
CASE 17

Contributed by: Dominic Spagnolo, M.D. (Accession Q08B20982L).

Case seen in consultation courtesy of Dr. V Ojeda, Western Diagnostic Pathology (08-2755065).

Case History: Splenectomy from a non-smoking female 31 years-of-age with a complex history of fluctuating, often massive splenomegaly over a period of about 43 months, following an acute viral-like illness for which she received no specific treatment until coming to splenectomy.

She was first referred to a clinical hematologist in November 2004 following an acute viral - like illness, commencing as 2 days of diarrhoea, vomiting and tiredness, followed about 2 weeks later with severe sore throat, fever, sweats, loss of appetite, abdominal discomfort and weight loss. There was no arthritis or skin rashes. She was not taking any medication or other drugs. In retrospect she volunteered a history of tiredness over several months and easy bruising. There was no other significant past history nor family history of any blood disorders (her name suggested an Italian background); there was no haemolysis. Examination showed an inflamed throat with surface exudate, bilateral tender cervical adenopathy and 2cm of non-tender mild splenomegaly. There was no hepatomegaly or other adenopathy. She was mildly pancytopenic. All serological tests were negative (EBV, CMV, parvovirus, others; autoimmune screen, etc); LFTs normal. Marrow trephine showed an active cellular marrow without specific features; flow cytometry on marrow did not show any abnormal lymphoid population. Apart from antibiotics in the acute phase, she received no specific treatment. The adenopathy resolved completely.

For the next almost 4 years she remained in excellent health, had 2 normal pregnancies and deliveries, but continued to have waxing and waning, often massive splenomegaly (measuring up to 19cm on CT scanning), with intervening periods of complete clinical resolution. Following delivery of her second normal child, because of increasing splenomegaly yet again and patient anxiety, she proceeded to diagnostic splenectomy (about 43 months after original presentation).

Latest follow-up obtained on 30 April 2009 (about 52 months after presentation) shows her to be in excellent health, into her 3d pregnancy, with no evidence of disease, minor post-splenectomy changes in the blood and mild thrombocytopenia.

Pathological Changes: The spleen weighed 773 gms and measured 210 x 132 x 74mm. The gross description read as follows "No focal lesions are identifiable. The splenic capsule is unremarkable. The splenic parenchyma shows a diffuse miliary infiltrate instead of normal white pulp." The outside pathologist has kindly provided a gross photograph (see attached) which shows nicely the relatively uniform, miliary, nodular expansion of the white pulp, typically the nodules measuring less than 2mm. Microscopically, there is relatively uniform expansion of the white pulp consisting of pronounced widening of the marginal zones (individual nodules vary in the number of layers of marginal zone cells). Mantle zones of varying width are discernible, are often largely replaced, while only rare follicles have residual, mildly hyperplastic residual germinal centers (highlighted in the BCL-6 stain). The expanded marginal zone cells have small to medium-sized round or oval nuclei and a modest amount of pale staining cytoplasm. At the margins of the nodules, these cells trail off minimally into the surrounding red pulp, which is not significantly expanded. The red pulp contains moderate numbers of polyclonal plasma cells, and cordal histiocytes are not particularly prominent. There is no hemophagocytosis. Small collections of lymphocytes are present in the red pulp and there are moderate numbers of mature plasma cells. There are no granulomata or significant extramedullary hematopoieses (I noted some isolated collections of normoblast-like cells only).

Immunostaining confirms that the white pulp is expanded and consists largely of CD20+, IgM+, IgD-, CD21+, BCL2+, BCL6-, CD10-, CD43-, cyclin D1-, EBER-, polyclonal marginal zone B lymphocytes (clear-cut kappa and lambda positivity without predominance of either).

Small splenic hilar lymph nodes (sections not submitted) show a preserved architecture with widely patent sinuses and atrophic white pulp consisting mainly of primary follicles. Surrounding some of these primary follicles, and also in a patchy parasinusoidal distribution, there are bland "marginal zone" like cells similar to those in the spleen. Again, immunoglobulin light chain stains do not show any light chain restriction.

Flow cytometry on splenic lymphocytes did not reveal any monoclonal B-cell population.

DNA was extracted from a paraffin block of spleen and a hilar node, and also from the frozen splenic tissue. PCR assays using consensus primers (FR1, FR2A and FR3A forward primers) were used to assess the rearrangement status of the IgH gene. Only polyclonal IgH gene rearrangements were found in all assays in spleen and node, with no suggestion of a monoclonal rearrangement.

Karyotyping (G-banding) revealed metaphases having a normal karyotype (whether these were from normal cells or not cannot be determined). Interphase FISH studies carried out on paraffin sections of spleen using break apart probes did not show any disruption of the IgH or MALT1 loci, nor was any IgH/BCL2 fusion detected.

Diagnosis: Florid marginal zone hyperplasia of the spleen, causing pronounced splenomegaly, producing macroscopically visible splenic miliary nodules and mimicking splenic marginal zone lymphoma.

Discussion: I am submitting this case because I, and everyone to whom I have shown the case including experienced hematopathologists, all favored a splenic marginal zone lymphoma, despite the clearly unusual, and inappropriate clinical setting and evolution.

The clinical context and evolution, and the constellation of morphological, immunophenotypic, molecular and cytogenetic features indicate that this is a reactive process, though close and continuing follow-up is mandated. It is important to note that, unlike reactive monocytoid B cells, normal/reactive marginal zone cells are BCL2 positive. In hindsight, the repetitively miliary pattern and uniform size of the nodules is unlike the few cases of early splenic marginal zone lymphoma (causing only mild splenomegaly) that I have seen, where even in those early cases, the nodules are more heterogeneous in terms of their size. Such an extreme form of marginal zone hyperplasia causing pronounced splenomegaly is unusual and I have not seen this phenomenon to this degree before.

Of course, there is no definition of what constitutes marginal zone hyperplasia (let alone mantle hyperplasia which is also bandied about), and in the scant literature available, arbitrary definitions of 3 or more, or 12 or more cell layers have been used. I assume that in normal practice it is based on the "gestalt" combination of an enlarged spleen, lack of florid follicular hyperplasia and red pulp changes to account for the splenomegaly, and "prominent" marginal zones. Such marginal zone expansion is well recognized in various auto-immune and post-infective conditions, and is also seen in spleens removed for spontaneous or traumatic rupture, though splenomegaly to this degree typically does not occur. There is nothing in this patient's history or laboratory findings to suggest an underlying autoimmune disorder or a congenital immunodeficiency, and while the initial presentation strongly suggests a viral infection, none was ever proven, and the subsequently wildly fluctuating splenomegaly from significant proportions to periods of complete clinical resolution would be most unusual (?even for EBV infection, which seems to be have been reliably excluded).

Questions:

1. Am I right?
2. What have I not considered?
3. Has anyone encountered this to this degree before, let alone in this clinical context?
4.

Opinions and any advice will be gratefully received.

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