AMR Seminar #54 – Short Summary of Cases:

Case 1: A 51-year-old female presented with a right renal mass with thrombus extending into the atrium to the inferior vena cava.

Case 2: Incidental finding in a liver biopsy in an 80-year-old man.

Case 3: A male baby was born with a very large tumor involving the face and scalp.

Case 4: An infant female was delivered by C-section at 38 weeks to a 37-year-old G2P1001 mother. MRI showed a large 5x4x3 cm heterogeneous mass in the region of the left atrium.

Case 5: A 78-year-old man underwent a 3rd operative ERCP for recurrent stones; during the endoscopic procedure a spontaneous biliary-duodenal fistula was seen and a sudden cardiopulmonary arrest occurred. Patient died.

Case 6: A 56-year-old woman presented with a one-year history of recurrent pneumonias. CT showed a mass in the right lower lobe with associated lobar collapse.

Case 7: A 70-year-old female was seen for a tumor of the left posterior tongue.

Case 8: A 46-year-old man is evaluated for a "polyp" of upper respiratory tract.

Case 9: A 46-year-old, gravida 1, para 1, female presented with a month history of abnormal vaginal bleeding. Physical examination revealed a 4 cm, exophytic friable mass in the uterine cervix.

Case 10: A 5-week-old male infant was born at an outside hospital via normal spontaneous vaginal delivery at 39 weeks gestation. Chest X-ray showed increasing bilateral granular opacifications on both lung fields. Open lung biopsy was performed.

Case 11: A 45-year-old female patient complained about an increasing soft tissue swelling in the upper third of the anterior part of the right thigh. Intraoperatively, an intramuscular neoplasm measuring 8 cm in largest diameter was found.

Case 12: A groin nodule in a 62-year-old man was removed.

Case 13: A 66-year-old Caucasian man, nonsmoker, underwent CT scan in May 2008 for increasing thoracic pain. CT scan examination showed a large mass in the posterior mediastinum that was weakly and irregularly positive with PET scan.

Case 14: A 56-year-old woman with unremarkable past medical history presented to the hospital with vaginal bleeding and pelvic swelling. A 23x15 cm ovarian mass was found.

Case 15: A 49-year-old male presented with biliary colic. Clinical work-up, including MRI scan, revealed a cystic lesion in the tail of the pancreas.

Case 16: A 57-year-old female patient underwent excision of a 6X4X4cm tumor of the left ovary.

Case 17: A 47-year-old female presented with vague epigastric discomfort. Upper GI endoscopy revealed an intramural mass, which was then surgically excised.

Case 18: A 62-year-old female with a history of papillary thyroid carcinoma 3 years previously presented with an enlarging mass in the left neck described as being located in the "jugular area".

Case 19: A 56-year-old woman with no significant past history was found to have multiple long, fingerlike, polypoid projections protruding into the lumen of the large bowel at the level of the proximal transverse colon during a routine screening colonoscopy.

AMR SEMINAR #54
CASE 1

Contributed by: Volkan Adsay, M.D.

Short history: 51-year-old female with a right renal mass measuring 11 cm.

History: 51-year-old female presented with a right renal mass with thrombus extending into the atrium to the inferior vena cava. A right radical nephrectomy with inferior vena cava thrombectomy and atrial thrombectomy was performed.

Macroscopic Findings: The nephrectomy specimen demonstrated a heterogeneous, pink –tan, and yellow hemorrhagic mass measuring 11x10.5x8.0 cm. There were also multiple satellite nodules within the normal appearing kidney parenchyma. The tumor was invading the renal sinus and renal vein.

Microscopic Findings: The tumor was composed of highly cellular neoplasm forming solid sheets, focally in a nodular architecture. In addition to sheetlike formation, the cells focally had a vague nested pattern, and in some areas a delicate reticulin network surrounding each cell could be appreciated. There were also rare foci in which the cells were lying individually in a sclerosed stroma. Hemangiopericytoma-like vasculature was evident in some foci. The cells had minimal amount of cytoplasm, and the nuclei were round to ovoid with inconspicuous nucleoli. Nuclear grooves were appreciated in some areas. Mitotic activity was prominent, and necrosis was also noted in some sections.

Immunohistochemical Findings: The neoplastic cells were positive with vimentin and smooth muscle actin. Collagen type 4 showed a reticular pattern surrounding individual cells. Epithelial markers (AE1:AE3, EMA and Cam 5.2) were negative and so were S-100, synaptophysin, CD99 and desmin.

Diagnosis: Malignant Glomus Tumor (Glomangiosarcoma)

Comment: With the overall morphology, the cytologic features, combined with the immunoprofile, we concluded that this is a glomangioma, and the degree of cellularity, mitotic activity and necrosis point to a malignant glomangioma (glomangiosarcoma). Glomus tumor is very rare in the kidney, and glomangiosarcoma is even rarer. Actually I was not able to identify any documented cases of renal glomangiosarcoma in the literature on a cursory review of PubMed. Clear cell sarcoma of the kidney can occasionally exhibit this pattern, and that was also in our differential.

The criteria for malignancy put forth in glomus tumors are deep location with size greater than 2.0 cm or moderate to high nuclear grade with greater than 5 mitotic figures per 50 HPF, and this tumor fulfills all those criteria. The fact that this tumor is large and highly infiltrative also goes along with this impression.

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1. Al-Ahmadie HA, Yilmaz A, Olgac S, Reuter V. Glomus tumor of the kidney: a report of 3 cases involving renal parenchyma and review of the literature. Am J Surg Pathol. 2007 Apr;31(4):585-91
2. Folpe AL, Fanburg-Smith JJ, Miettinen M, Weiss SW. Atypical and Malignant Glomus Tumors: Analysis of 52 Cases, With a Proposal for the Reclassification of Glomus Tumors. Am J Surg Pathol 2001:25(1): 1-12.

AMR SEMINAR #54
CASE 2

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

CLINICAL HISTORY: This liver biopsy was sent as a frozen section in the course of a gastrectomy procedure performed on an 80-year-old man for carcinoma.

PATHOLOGICAL DESCRIPTION: The specimen measured 2.5 cm and contained a well demarcated white nodule measuring 1.2 cm. The frozen section showed a haphazard ductular proliferation which was limited to the nodule and did not penetrate into the liver. The intra-operative diagnosis was bile duct adenoma.

The permanent sections indeed confirmed the diagnosis, showing ducts scattered in the spindle cell stroma that were lined by low columnar cells with eosinophilic cytoplasm and open nuclei with benign features. However in between and alongside them a second epithelial population became apparent, consisting of smaller cuboidal cells arranged in nests with granular basophilic or amphophilic cytoplasm and small compact nuclei. These cells were positive for synaptophysin and chromogranin while the conventionally appearing bile ducts were negative. The gastrectomy showed a typical intestinal type adenocarcinoma of the stomach penetrating into the muscularis propria with multiple lymph node involvement.

DIAGNOSIS: Bile duct adenoma with neuroendocrine proliferation.

DISCUSSION: This phenomena was first described by our colleague Marku Miettinen in paper published in the AJSP in January 1992 (O'Hara et al) which consisted of two cases. The proliferation was compared to tumorlets seen in the lungs. This paper is often cited in textbook discussions of bile duct adenoma. To the best of my knowledge no other cases of this sort have been published since.

On close examination of some of the recuts made for distribution these nests are focally seen underlying the endothelium of a vein and approaching a small nerve (as pointed out by Dr Bernard Portmann of London who was kind enough to review the slides and who essentially agreed with the diagnosis) (see attached images). Given the advanced stage of the stomach tumor debating any potential malignant behavior of this proliferation might be academic at this point. Dr Portmann did bring up the possibility of a metastasis from a different neuroendocrine neoplasm to the bile duct adenoma, which would seem to be a highly unusual and complicated explanation for this finding. However to be honest I did not specifically question the surgeons as to whether the patient was known to have a neuroendocrine tumor elsewhere.

Two additional papers might be of interest with regards to this case. One, by Roskams et al, shows that reactive bile ductular proliferation secondary to cholestasis shows immunohistochemical evidence of neuroendocrine metaplasia. However, these ducts do not show neuroendocrine or carcinoid features on routine histologic examination as is seen in this case. Bhathal et al demonstrated that the ducts seen in bile duct adenomas express antigens similar to those of peribiliary glands. Thus they propose that bile duct adenomas can be considered *peribiliary* gland hamartomas. They were also able to demonstrate mucin positivity in the cells of bile duct adenoma such as is seen in peribiliary glands. However they did not investigate the presence or absence of neuroendocrine differentiation in this setting.
As this phenomenon would seem to be extremely rare as reflected in the small number of cases published it would be very interesting to learn if anyone else in the group has seen this or knows of other cases. I would be especially interested in knowing what feedback Marku Miettinen might have received on this issue following publication of his article.

References:
1. O'Hara BJ et al. Bile duct adenomas with endocrine component: immunohistochemical study and comparison with conventional bile duct adenomas. Am J Surg Path 16: 21-25, 1992.
2. Roskams T et al. Rapid Communication- neuroendocrine features of reactive bile ductules in cholestatic liver disease. Am J Pathol 137: 1019-1025,1990.
3. Bhathal PS et al. The so called bile duct adenoma is a peribiliary gland hamartoma. Am J Surg Path 20: 858-864, 1996.

AMR SEMINAR #54
CASE 3

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

Clinical History: A male Arab baby was born with a tumor on the face and scalp. The baby was born to a 33-year-old mother at 39.5 weeks by Cesarean section due to "suspected large baby", with a birth weight of 3825 gr. and Apgar 8/9. The pregnancy was normal. The family history was normal. The mass on the left face extended from the temporal area and crossed the midline at the nose-bridge. It had a bluish to purple color (see figure). MRI showed a large infiltrative tumor of the left face and scalp which fills the left orbit, elevates the eye globe, pushing it externally (see figure). The optic nerve is deviated. The tumor crosses the midline and involves the margin of the right orbit. The tumor involves the outer plate of the temporal bone and the sphenoid, and pushes the maxilla. The radiologic conclusion was that the tumor may be consistent with a vascular tumor (hemangioma) with a differential diagnosis of angiosarcoma or other sarcoma. PET-CT showed pathologic non-homogenous uptake in the left hemi facial area, extending to the midline. The baby underwent several biopsies, all showing similar histology.

Pathologic Findings: Tumor infiltrating soft tissue and skeletal muscle composed of epithelioid cells with solid-cellular areas and foci of speudoalveolar/pseudovascular architecture. Cells show round nuclei with small nucleoli and eosinophilic cytoplasm, focal intranuclear cytoplasmic inclusions, and focal melanin pigment. Very rare mitoses. Tumor cells show diffuse strong staining for S100, MelanA and HMB45. They are negative for desmin, myogenin, synaptophysin, chromogranin, NSE, cytokeratin. Ki67 index is low (less than 5% of the cells). We also received a small superficial biopsy which showed scattered, isolated epithelioid melanocytes in the dermis with no atypia and no mitoses.

DIAGNOSIS: Congenital melanocytic tumor of the face, scalp and orbit

Comments and Follow-up: When we received the first biopsy, the maxillofacial surgeon wrote "tumor of the zygomatic arch". Initially, due to the melanin pigment, we considered the diagnosis of melanotic neuroectodermal tumor of infancy, but the histology and immunohistochemical stains were in favor of malignant melanoma, which was our diagnosis. A few days later, our dermatopathologist, who knew the patient's cutaneous lesion, looked at the slides and considered the possibility of an unusual variant of congenital nevus. Once we had a doubt, we looked again at the slides and due to lack of severe atypia and mitoses, in spite of the horrible clinical extension of the tumor, we sent it for consultation. We asked two well-known expert surgical pathologists whether the tumor is a peculiar/atypical congenital nevus or a melanoma (low-grade?) arising in a congenital nevus. Both experts favored malignant melanoma arising in congenital nevus. One of them suggested further biopsies and added "given the extensively destructive nature of the lesion, I would not regard this as a low grade lesion". The second expert added "it is recognized that the behavior of lesions with the morphologic attributes of melanoma, when occurring in young infants as in this patient, is highly unpredictable. While some behave aggressively, it appears that others may show a process of maturation and ultimately turn into neurotised (neurofibroma-like) lesions. Unfortunately, there is no way of making this prediction on morphologic grounds. Nevertheless, particularly given the remarkable extent of this small infant's lesion, I think that it is illogical to label this as anything other than melanoma, acknowledging that the outcome may be good".

The baby was presented to several surgeons in the country and all were reluctant to operate him (huge tumor with involved large vessels). A couple of weeks later, Dr. Bernard Ackerman from New-York visited our dermatology department. He saw the baby and the histologic slides, and favored a diagnosis of nevus. He also said that further deep biopsies may disclose a melanoma, but he did not see evidence for it in the current slides. A deeper biopsy from the lateral wall of the left maxillary sinus at another hospital showed similar histology to the current slide. An expert neuroradiologist refused trying to embolize the tumor.

Recent follow-up of just over 3 years from diagnosis shows no further local growth and no distant spread of the tumor. The oncologist who follows the child informed me that "the tumor grows along with the child (not faster than the child)" and that the child conducts a normal life and goes daily to a kindergarten. I suppose that most consultants were right. The tumor did not progress. Thus, is it a non-progressive melanoma of infants? Is it an unusual infiltrating type of congenital nevus?

Concerning the literature of congenital melanoma, they are of course rare tumors, "and their incidence is difficult to determine, given the small number of reported cases and problems associated with diagnosis" (1). There are 3 groups of congenital melanomas: 1. The very rare transplacental spread of melanoma from the mother, 2. Melanomas arising in medium and large/giant congenital nevi, and 3. Melanomas arising de novo. The latest review (2) found 4 transplacental

cases (3 with follow-up died), 11 arising in congenital nevus (5 of 10 with follow-up died) and 12 de novo cases (2 of 11 with follow-up died). The other review (1) (of almost the same literature) detailed 13 cases arising in congenital nevi, 6 of 12 with follow-up died, and in 5 of the 13 the lesion involved the scalp.

I would be glad to have your opinion.

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AMR SEMINAR #54
CASE 4

Contributed by: Gerald Berry, M.D.

Clinical History: This infant female was delivered by C-section at 38 weeks to a 37-year-old G2P1001 mother. The pregnancy was uncomplicated. The infant was tachypneic after birth with grunting and hypoxemia. MRI showed a large 5x4x3 cm heterogeneous mass in the region of the left atrium. An incisional biopsy followed by attempted resection was performed. At surgery, the mass was located in the left atrium and not the pericardium. According to the OR note, this large lobulated mass involved the LA and region of the LCA and extended into the AV groove and superiorly to the aorta. It also involved the region of the RCA. Biventricular failure developed intraoperatively and the infant could not be weaned from the bypass pump.

Pathological Findings: The resected mass measured 5.3x4.5x3.0 cm and weighed 36 gm. It was lobulated and contained solid and cystic areas. Microscopic sections showed a cardiac teratoma composed of both mature and immature elements.

Diagnosis: Intracardiac teratoma (left atrium).

Comment: I thought the members would enjoy this rare example for their teaching files. Larry may remember this case as I dug it up from our files from 1987!

Primary pediatric cardiac tumors are rare and the most common lesions are hamatomas rather than true neoplasms (rhabdomyoma and cardiac fibroma). Cardiac teratomas are rare neoplasms and usually present in infancy or childhood. Most are intrapericardial and are surgically excised after careful dissection of the vascular attachment to the aorta or pulmonary artery. The intramyocardial type is less common still and are technically more challenging to resect. They range in size from 2-9 cm and commonly causes heart failure symptoms on account of their mass effect. As in this case, they do not have a clear plane of dissection and vascular compromise is common.

References:
1. Uzun O, Wilson DG, Vujanic GM, et al. Cardiac tumors in children. Orphanet J Rare Dis 2007; 2:11.

2. Burke A. & Virmani R. Pediatric heart tumors. Cardiovasc Pathol. Epub ahead of print.

AMR SEMINAR #54
CASE 5

Contributed by: Michele Bisceglia, M.D.

Clinical History: A 78-year-old male, who many years previously had undergone both gastroduodenal resection for duodenal ulcer and cholecystectomy for gallstones, was admitted for recurrent ascending cholangitis secondary to stones. While undergoing endoscopic sphincterotomy and 2 endoscopic retrograde cholangiopacreatography (ERCP) procedures for the removal of bile duct stones, he was also diagnosed with chronic lymphocytic leukemia. After 3 months, he underwent a 3rd operative ERCP for recurrent stones: during the endoscopic procedure a spontaneous biliary-duodenal fistula was seen and a sudden cardiopulmonary arrest occurred. Imaging studies (CT scan –performed in emergency) demonstrated abundant air in the pulmonary artery, right heart (with air-fluid level), and tributary veins of both superior and inferior vena cava, as well as in some intraparenchymal suprahepatic vein radicles of liver and several biliary ducts (the latter also containing contrast medium). Air was seen even in the cerebrocortical veins of the right hemisphere and in the ipsilateral smaller veins of the inner capsule and caudate nucleus, and in the superior ophthalmic veins bilaterally. (**Image 1 in the web**). Autopsy was performed.

Autopsy Findings:
- *Pulmonary artery and right heart air embolism were confirmed according to appropriate techniques acted in the autopsy room.*
- *The spontaneous bilio-digestive fistula (through which a lot of gas likely entered the intrahepatic biliary tree) was found while opening lengthwise the descending portion of duodenum.***(Image 2 in the web).**
- *Veno-biliary fistulas were demonstrated according to the following technique: the liver was taken out en-bloc and investigated with both anterograde portography and retrograde suprahepatic venography via 3 suprahepatic veins. Bench radiographs, performed in the radiological operating room, revealed reflux-extravasation of the contrast medium into the biliary tree, where some tufts of cotton wool had been positioned, which were then radiographed separately.* **(Images 3-4-5 in the web)**. *The contrast medium absorbed by the cotton tufts provided evidence for the presence of small veno-biliary fistulas at both the portal and systemic radicle level.*
- *In the cut-up room on sectioning the liver surface appeared as punctuated by many parenchymal micro-abscesses containing impacted biliary sand and minute stones.***(Image 6 in the web).**
- *Histologically air bubbles were easily seen in the mist of inspissated bile and in abscesses of the inflamed portal tracts (***Image 7 in the web**, *and* **2 histological glass slides** *enclosed:* **Au-7-3-A**, **Au-7-3-B***). Air bubbles were also present in some blood clots incidentally included in the histology samples. Some small veins histologically seen in the perihepatic soft tissue also showed air embolism.*

Diagnosis: Fatal systemic venous air embolism following endoscopic retrograde cholangiopacreatography (ERCP).

Discussion: Air embolism is a rare complication of gastrointestinal endoscopy, resulting from penetration of gas into the portal veins. Risk factors associated with air embolism in this setting include situations where the mucosa is damaged or where high pressures are generated in the gastrointestinal tract.   Air embolism is a complication that can be seen in the context of various pathologies, including acute mesenteric ischemia, chronic inflammatory gastrointestinal diseases, gastrointestinal infections, acute gastric dilatation, caustic ingestion, superior mesenteric artery syndrome with duodenal dilatation, ileus, blunt abdominal trauma, duodeno-caval fistulas, and invasive diagnostic procedures, such as double-contrast barium enema, endoscopic sphincterotomy, and ERCP.

The likely mechanism, by which endoscopic sphincterotomy and ERCP may cause air embolism, is the intramural dissection of insufflated air into the portal venous system via venous duodenal radicles which are inadvertently injured or transected during the procedure. Air embolism is an ominous sign and may be fatal (mortality rate of 75%), but may also be reversible or cured by surgery depending on the underlying causes. The first case of fatal air embolism due to endoscopic sphincterotomy was described in 1988 (1), and the first fatal case of systemic air embolism due to ERCP was reported in 1997 (2). So far less than 10 cases of air embolism after ERCP have been reported. This case has to be added to the series of these rare, but dramatic and unfortunate events, occasionally fatal, possibly occurring during endoscopic procedures.

Conclusions: The air was thought to have entered the portal venous system via intrahepatic radicles of both the suprahepatic and portal veins, which might have undergone perforation on the background of chronic ischemic damage secondary to prolonged impaction and infection of the involved ducts.

- Insufflation which is given during perduodenal cholangioscopy created the gradient pressure that made air penetrate -through the spontaneous bilio-duodenal fistula- into portal and suprahepatic vein radicles, resulting in portal gas and air embolism.
- Spontaneous bilio-duodenal fistula likely derived from decubitus pressure of a bile duct stone which was either previously removed during one of the former ERCPs or passed through into the bowel.

References:
1. Simmons TC. Hepatic portal venous gas due to endoscopic sphincterotomy. Am J Gastroenterol 1988; 83: 326-328.
2. Kennedy C, et al. Fatal hepatic air embolism following ERCP. Gastrointest Endosc 1997; 45: 187-188.

AMR SEMINAR #54
CASE 6

Case contributed by TV Colby, M.D.

History: (TV08-16). A 56-year-old woman presented with a one-year history of recurrent pneumonias. CT showed a mass in the right lower lobe with associated lobar collapse. Bronchoscopic biopsies were nondiagnostic. PET scan showed increased uptake in the right lower lobe mass as well as increased uptake in hilar, mediastinal, and supraclavicular lymph nodes. A mediastinal lymph node biopsy was interpreted as reactive hyperplasia. Lung biopsies were taken.

Histologic Findings: The most dramatic aspect of this case from a lung pathologist's point of view is the extensive mononuclear cell infiltrate involving airways, arteries, and veins. There is extensive transmural infiltration in some of these vessels without associated necrosis and without granulomatous features. The infiltrate is rich in plasma cells and does include some histiocytes. There is also an inflammatory process involving the pleura. A few eosinophils are present. There are large numbers of plasma cells and in many high power fields greater than 30 IgG4 positive plasma were confirmed immunohistochemically. The plasma cells did not show light restriction with kappa and lambda staining. CD3 and CD20 showed that most of the small lymphocytes were T cells with only occasional CD20 positive (non plasma cell) B cells. S-100 did not show features suggestive of Rosai-Dorfman diagnosis. An occasional lymphoid follicle with a reactive germinal center is present.

Diagnosis: Histologic changes consistent with so-called hyper IgG4 disease.

Follow-up: She had had an orbital "pseudotumor" resected 1 year earlier. By description it sounds similar to the lung. I am getting the slides and hope to IgG4 stains and will give the group follow up. The lung showed preliminary response to steroids.

Discussion: As members of the group well know, there are some predictable events that occur when a new disease is described. Recently, autoimmune pancreatitis has been recognized and many of the cases are associated with increased numbers of IgG4 staining plasma cells and elevations of IgG4 in the serum. Along with the recognition of this condition in the pancreas, a number of other sites in the body are now being reported and I as a lung pathologist have to put in my two cents worth.

Approximately 2% of resected pancreatic masses turn out to be inflammatory with a marked lymphoplasmacytic infiltrate ("autoimmune pancreatitis"). Most patients are between 55 and 65 and many have raised serum levels of IgG4 and increases in IgG4 containing plasma cells in the tissue, usually more than 20/hpf. From a clinical point of view, the patients typically show narrowing of the main pancreatic duct, enlargement of the pancreas, the presence of auto antibodies or elevations of serum IgG4, and histologically there is a marked lymphoplasmacytic infiltrate with large numbers of IgG4 containing cells. The precise number of cells required for the diagnosis is not clear and an increase in IgG4 positive cells is not entirely specific. In the study from MGH (see Deshpande reference), IgG4 positive plasma cells could be identified in appreciable numbers of cases of chronic nonspecific pancreatitis and ductal adenocarcinoma of the pancreas but their numbers were significantly less than in cases of autoimmune IgG4 associated pancreatitis. The clinical group at Mayo Clinic Rochester (see Chari ref) has identified the five cardinal features of this condition in the pancreas:

1) Histology showing sclerosing lymphoplasmacytic infiltrate with numerous IgG4 positive plasma cells.
2) Characteristic imaging with diffuse sausage-shaped enlargement of the gland on CT scanning or magnetic resonance imaging with delayed peripheral (rim) enhancement. Pancreatography shows diffusely irregular narrow pancreatic duct however focal masses are also recognized.
3) Serology with elevated titers of gamma globulins, IgG, and a variety of antibodies including ANA, RF, and to carbonic anhydrase and lactoferrin. Elevation of IgG4 is also recognized.
4) Other organ involvement including a number of other disorders such as PSC, Sjogren's syndrome with salivary gland involvement, et. al.
5) Response to therapy. The pancreatic, biliary, and salivary gland diseases that are associated with an infiltration of numerous IgG4 positive plasma cells often show a dramatic response to steroid therapy, whereas mimics do not.

Involvement of the biliary tract is not surprising but concomitant involvement of salivary glands, orbit, lung, gallbladder, kidney, prostate, aorta, and retroperitoneum have all been described. I am sure more sites will be described.

Thus, we are in the midst of a new disease that has been defined and its footprint of involvement in the body is now being clarified. I am not sure there is sufficient information available yet to know how often increased numbers of IgG4 positive plasma cells are as background cells found in a variety of sites in other conditions; i.e. we don't have a good baseline. There is some data on their frequency in pancreatic lesions but there is insufficient data for lung lesions.

I present this case to the group because we did not really have a good name for this prior to identifying the increased numbers of IgG4 positive plasma cells. In the occasional cases of lung involvement of hyper IgG4 disease that are described, there is notable infiltration of airways and vessels by large numbers of inflammatory cells, particularly plasma cells and the case presented would seem to show that quite nicely. Some cases have described prominent eosinophils and germinal centers. I have 4 or 5 somewhat similar cases. A couple of them had some S-100 positive histiocytes containing inflammatory cells (emperipolesis) and I have tried to sell one or two to Juan Rosai as consistent with Rosai-Dorfman disease.

The clinical and radiologic findings of reported IgG4 related conditions in the lung span a spectrum from localized masses (many of them called inflammatory pseudotumor or plasma cell granuloma) to zones of consolidation (like the case described) to diffuse disease and some cases have been interpreted as bronchiolitis obliterans organizing pneumonia (BOOP) or nonspecific interstitial pneumonia (NSIP).

Over the next few years we will see how many cases we have called inflammatory pseudotumor or some sort of interstitial pneumonia actually fit into this condition.

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AMR SEMINAR #54
CASE 7

Contributed by: Göran Elmberger, M.D.

Originally contributed by Robert Cameron Lund.

Clinical History: 70-year-old female with a tumor of the left posterior tongue. No metastases. Operated with left hemiglossectomy, tonsillectomy, resection of floor of mouth and left neck resection region II-III.

Morphological Findings: Grossly a 30 x 30 mm sized diffusely circumscribed tumor was seen. Epicentre of tumor at the junction of the anterior two-thirds and the posterior one-third of the dorsal tongue around papillae circumvallate. Tumor extended under intact surface epithelium and was present at resection margins. Microscopically, the distributed section reveals covering squamous epithelium from tongue with a suggestive circumvallate papillae. At the base of the surrounding furrow there are accessory minor salivary glands. A small group of salivary glands have a rather peculiar morphology and a strict serous differentiation. This group of glands may well represent remnants of Ebner's glands. Beneath the intact surface epithelium the tumor is characterized by infiltration of small cuboidal cells arranged in small ducts, cords and sometimes small cysts. In some deeper parts a morphea-like or Indian-file-like cell infiltration is present. Tadpole-like formations are seen but cribriform differentiation is not present. The infiltrating tumor ducts are in close apposition with covering surface epithelium and small accessory salivary glands at the papillae furrow but no obvious precursor lesion can be observed. Beneath the surface epithelium a vague squamoid differentiation including solid nests with prominent intercellular bridges is seen. Well-developed keratocysts or features of follicular differentiation are not seen.

The tumor cells are small with hyperchromatic round or oval nuclei. Some nuclei show prominent nucleoli but generally pleomorphism is not marked. The cytoplasm is pale eosinophilic sometimes with a granulated or microvacuolated character. Mitoses are rare. No necrosis or apoptosis is seen. The stroma is dense and collagenous but sometimes shows more desmoplastic and inflamed reaction. Often the stroma is arranged in a concentric onion peel pattern around tumor ducts. The tumor is deeply invasive and extends into the striated muscle of the tongue. Extensive perineural and intraneural growth is present. Furthermore a peculiar focal chronic lymphocytic response is seen.

Results of Ancillary Studies:
PAS-positive diastase-resistant granular material is seen within ducts and cysts but intracytoplasmic mucin is not seen. IHC high-lights a biphenotypic differentiation with a peripheral basal cell phenotype and a central luminal epithelial differentiation. The peripheral cell type is positive for p63 but more specific myoepithelial markers, such as smooth muscle myosin heavy chain and actin were negative. The luminal cells are positive for CEA, EMA, CK7, CK low MW, and BerEp4. All tumor cells are positive for MNF116, CK high MW, CK5, CK18 and CD 138. CK20, TTF-1, bcl-2, p53 and p21 were all negative. Proliferation rate is approximately 2-4 % (MIB1).

Diagnosis: Microcystic adnexal carcinoma of the tongue (MAC): A tumor derived from Ebner's glands

Follow-up: Recent diagnosis.

Differential Diagnosis: Generally, other intraoral primary tumors such as other salivary gland carcinomas, adenosquamous carcinoma, thyreoglossal duct derived tumors as well as metastases must be differentiated from the rare occurrence of MAC of the tongue.

Another adnexal-like tumor that shows strict similarity with present case is syringoid eccrine carcinoma. The absence of keratocysts and the relative absence of maturation-zonation in the present case might advocate rather for this subtype diagnosis. As far as I can understand from reading standard texts, the delineation from microcystic adnexal carcinoma is at least somewhat unclear and since the latter terminology seems to be the preferred one by latest WHO volume on skin I have rather arbitrarily chosen to stick to this terminology.

At the higher end of the malignancy spectrum, the MAC needs to be separated from adenoidcystic carcinoma. The absence of cribriform structures, definitive myoepithelial differentiation and the lower cell proliferation in present case favour a diagnosis of MAC.
Adenosquamous carcinoma of low-grade has occasionally been described intraorally and in tongue. Typically this tumor is cytologically high-grade and show definitive squamous component. Mucoepidermoid carcinoma also reveals bidirectional

differentiation but absence of mucocytes and intermediate cells favour MAC diagnosis. The diagnosis of adenocarcinoma NOS G I/III could be discussed but the bidirectional differentiation of luminal and basal cells does not fit.

Discussion: With the exception of adenosquamous carcinoma most primary tongue adenocarcinomas are considered being of salivary gland type. The most common types are mucoepidermoid carcinoma, adenocarcinoma NOS, adenoidcystic carcinoma and clear cell carcinoma. As far as I could find there is only one report by Schipper et al 1993 on adnexal adenocarcinoma similar to the one circulated here. These authors suggested the classification as MAC derived from Ebner\s glands. The suggestion was based on histological and immunohistochemical similarities as well as on the resemblance of Ebner\s glands to the eccrine adnexal glands of the skin. These two tumours both are characterized by partly vertically oriented superficial tubules opening into the spaces between a papilla and a partial squamous differentiation occurring close to the surface. Likewise the stroma in the previous case was described as sclerotic.
The Ebner\s glands are seemingly unique among the intraoral minor salivary glands in being strictly serous. They are only located in association with the circumvallate papillae in the posterior part of the tongue and their function is not fully known. They show a histological and immunohistochemical resemblance to eccrine glands of the skin and hypothetically they can give rise to adnexal tumours of eccrine type. Some functions attributed to the circumvallate papillae von Ebner gland complex are lipase secretion, detection of lipophilic pheromones, and a simple washout role preparing the circumvallate taste buds for new stimuli.

Question: I wonder if members of AMR would accept suggested diagnosis in this rare case. Other suggestions?

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AMR SEMINAR #54
CASE 8

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

A 46-year-old man is evaluated for a "polyp" of upper respiratory tract. On direct inspection the tumor fills the nasal sinuses and has a broad implant over the respiratory mucosa. There is no instrumental evidence of bony invasion. Polypectomy ("piece-meal") is carried out. Several grey-tan fragments are received.

Tissue sections show an unencapsulated spindle cell tumor covered by unremarkable respiratory epithelium. The neoplastic cells are enmeshed in a variably collagenized ground substance. The nuclei are elongated to oval. Pallizading of nuclei is frequently noticed, sometimes with Verocay body formation. There are a few mitoses, none atypical. Myxoid changes with formation of Antoni B areas may be also noticed. Tumor cells are strongly positive for S100 and negative for keratins, EMA, actins, bcl2, desmin. CD34 is also focally positive. All melanoma markers (including melan A, Hmb45, mift, and thyrosinase) were negative. The ki67 proliferative rate is 5%.

Diagnosis: Sinonasal Schwannoma.

I think this is benign, nevertheless because of size, instrumental features, lack of encapsulation and a likely incomplete resection I have advised a close follow-up.

I am submitting this case since I do not have recent memory of peripheral nerve sheath tumor arising within the upper respiratory tract, including the nasal cavity. An origin from branches of the trigeminal nerve is postulated. The differential diagnoses we have considered include extra cranial fibrous meningioma and solitary fibrous tumor

It seems that peripheral nerve sheath tumors of sinonasal tract represent an under-reported topic, with lesions of different biologic potential published either as single case reports or mini-series. Recurrence potential is low for sinonasal schwannomas.

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AMR SEMINAR #54
CASE 9

Contributed by: Masaharu Fukunaga, M.D. (S07-2148)

History: A 46-year-old, gravida 1, para 1, female presented with a month history of abnormal vaginal bleeding. Physical examination revealed a 4 cm, exophytic friable mass in the uterine cervix. A cervical biopsy was performed and the initial pathologic diagnosis was endometrioid adenocarcinoma. She underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy and omentectomy. The patient is alive with no evidence of disease at 10 months after the surgery.

Macroscopic features (Figure): A 4 cm, exophytic, almost circumferential, whitish yellow, friable mass.

Immunohistochemical studies: CK7, CAM5.2, EMA, calretinin: (+). Vimentin, CEA, ER and PgR receptors, CD10 (-).

Diagnosis: Mesonephric adenocarcinoma of the uterine cervix with mesonephric hyperplasia.

Comments: This slide shows three components, mesonephric adenocarcinoma, atypical mesonephric hyperplasia (cystically dilated glandular elements with atypia) and typical mesonephric hyperplasia. Mesonephric adenocarcinoma exhibits varying morphologies; ductal, tubular, papillary and cystic patterns. Spindle cells or heterologous (rhabdomyosarcoma or cartilage) elements were sometimes observed. A lobular or diffuse mesonephric hyperplasia was observed adjacent to mesonephric adenocarcinoma of the uterine cervix in almost all reported cases. The mesonephric adenocarcinoma presented here is considered arising from the mesonephric hyperplasia based on the overall histology, the presence of atypical hyperplasia and immunohistochemical features. Mesonephric adenocarcinoma may be more common than what is suggested by the previously reported cases owing to their morphologic diversity and potential misclassification as a Mullerian tumors or florid mesonephric hyperplasia. The present tumor was limited in the uterine cervix. Sage I mesonephric adenocarcinoma seems to have a more indolent behavior than their Mullerian counterparts. I hope that members enjoy this typical case of mesonephric adenocarcinoma.

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AMR SEMINAR #54
CASE 10

Contributed by: Thomas Krausz, M.D.   (ID number: A08-26)

Clinical History: A 5-week-old male infant was born at an outside hospital via normal spontaneous vaginal delivery at 39 weeks gestation to a 17-year-old G2P1 female. Apgars of 6 at one minute and 9 at five minutes, weak cry, poor tone, and blue color, requiring intubation. Chest X-ray showed increasing bilateral granular opacifications on both lung fields. The infant was transferred to the University of Chicago Medical Center for continued management of progressive respiratory failure. Severe pulmonary hypertension was also noted. There was no clinical evidence of an infectious or a reversible disease process and genetic studies for surfactant protein B mutation were negative. Open lung biopsy was performed. Because the diagnosis of the lung biopsy suggested a disease of poor prognosis, care was withdrawn and the patient expired. At autopsy the lungs were overweight for the patient's age and grossly congested. The submitted histological slide is from the autopsy; however, the features are similar to those seen in the previous open lung biopsy.

Pathology: Histologically there is "chronic pneumonitis of infancy" with a combination of morphologic features of non-specific interstitial pneumonia, desquamative interstitial pneumonia and focal alveolar proteinosis. Accordingly, there is thickening of alveolar septa, marked hyperplasia of type II pneumocytes, filling of many alveolar spaces with macrophages and focally by proteinaceous material. Alveoli lined by type I pneumocytes are virtually absent. No significant inflammatory process is seen. Such histologic features are suspicious for a genetic disorder of surfactant protein deficiency.

Immunohistochemistry for surfactant protein-A and protein-B showed strong immunoreactivity in the cytoplasm of the type II pneumocytes. The intraalveolar proteinaceous material seen in rare alveoli was also positive.

Ultrastructural study revealed morphologically abnormal lamellar bodies in the cytoplasm of type II pneumocytes. Instead of the regular lamellar bodies there were abnormal forms with distinct electron dense material surrounded by tightly packed concentric membranes (see attached digital image). The finding of the electron dense inclusions within the lamellar bodies is highly suggestive of one of the genetic disorders of surfactant proteins: *ABCA3* gene mutation.

Diagnosis: Chronic pneumonitis of infancy due to *abca3* gene mutation.

Comments: Pulmonary function at birth and later in life depends on the normal regulation of synthesis and secretion of surfactant proteins for normal lung function. These proteins are synthesized and packaged with surfactant phospholipids in lamellar bodies of type II pneumocytes and is secreted into the alveoli by exocytosis. Normal lamellar body formation in the type II pneumocytes requires surfactant protein-B and ABCA3. ABCA3 is a member   of the ABC (ATP-binding cassette) family of ATP-dependent membrane-associated transport proteins. Mutations in *SFTPB, SFTPC* and *ABCA3* genes block type II pneumocyte function and cause serious abnormalities in surfactant homeostasis. Homozygous loss-of-function mutations in gene encoding the hydrophobic surfactant protein B (*SFTPB*) results in fatal surfactant deficiency in full-term newborns. When deficiency of surfactant protein B is excluded, like in the case submitted, other gene mutations like *ABCA3* mutations should be considered. In patients with *ABCA3* gene mutations, abnormal processing of surfactant protein-B has been reported. Expression of surfactant protein-B, –C, and ABCA3 are co-regulated during late gestation by TTF1 and forkhead box a2.

The histological findings of "chronic pneumonitis of infancy" (alveolar septal thickening, striking type II pneumocyte hyperplasia and intraalveolar accumulation of macrophages with some granular proteinaceous material) have been described in infants with *ABCA3* gene mutation. However, these histologic features have been described not only in *ABCA3* mutations but also in infants with *SFTPB* and *SFTPC* gene mutations. While the H&E findings are overlapping, the ultrastructural features of the surfactant lamellar bodies differ between the genetic disorders. Electron-dense inclusions in the lamellar bodies ("fried-egg" appearance) signal *ABCA3* gene mutation. The importance of EM studies in the diagnosis of congenital surfactant deficiencies has been emphasized by the Children's Interstitial Lung Disease Pathology Co-operative Group in the protocol for handling of tissue obtained by operative lung biopsy. Ultrastructural examination should be part of the evaluation of an infant with unexplained severe respiratory failure who undergoes a lung biopsy, or in the autopsy of a full-term infant who dies from hypoxic failure of unknown cause.

ABCA3 gene mutations are inherited in an autosomal recessive manner and involve the gene encoding the ABC transporter A3. ABC transporters are a superfamily of highly conserved membrane proteins that transport a broad variety of substrates across cell membranes and 14 ABC genes have been associated with distinct genetic diseases in humans.

The gene encoding ABC transporter 1 (*ABCA1*) is mutated in Tangier disease, a disorder involving the accumulation of cholesterol in macrophages and peripheral tissues as well as deficiency of high-density lipoproteins. The *ABCA4* gene is expressed in photoreceptors and encodes a protein that has been implicated in transporting retinal-phophatidylethanolamine complexes in the photoreceptor membrane disks of rods causing diseases like retinal degeneration, macular dystrophy due to Stargardt's disease, and retinitis pigmentosa. The *ABCAG5* and *ABCAG8* genes are expressed in the liver and intestine and are mutated in patients with sitosterolemia, a disorder involving accumulation of cholesterol and other sterols.

The *ABCA3* gene is located on chromosome 16p13.3 and encodes a 1704 aminoacid protein highly expressed in the lung. It has been localized to the limiting membrane of surfactant lamellar bodies. ABCA3 transporter is suggested to be involved in the traffic of specific lipids essential for the formation of mature lamellar bodies. The clinical consequences of *ABCA3* mutation depends on the codon affected. The mechanism of the surfactant deficiencies is classified into two categories: type I (abnormal intracellular trafficking) and type II (normal intracellular trafficking). Patients with type I/type II compound heterozygous *ABCA3* mutations died of surfactant deficiency during the neonatal period. However, type II *ABCA3* mutations on one allele do not result in fatal surfactant deficiency. Homozygous type II mutations have not been reported. *ABCA3* mutations in codon 292 have been found to cause milder form of the disease with survival into young childhood.   *ABCA3* gene mutation in the case presented has been confirmed not only by ultrastructural study demonstrating the "fried-egg" appearance of the surfactant lamellar bodies but also by mutational analysis.

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AMR SEMINAR #53
CASE 11

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

History: A 45-year-old female patient complained about an increasing soft tissue swelling in the upper third of the anterior part of the right thigh within three months. Ultrasound investigations showed an intramuscular, lobular lipogenic lesion, and an atypical lipoma was suspected. Intraoperatively, an intramuscular neoplasm measuring 8 cm in largest diameter was found and marginally excised, and after the diagnosis was established a wide tumor excision with tumor free margins was performed.

Pathology: Grossly, a heterogeneous neoplasm with myxoid, gelatinous areas irregularly associated with lipomatous areas was seen. Histologically, two irregularly admixed components were found. Lipomatous tumor areas did not show lobulation and were composed of mature appearing adipocytic cells showing considerable variations in size and shape. In addition cells with slightly enlarged and hyperchromatic nuclei as well as scattered lipoblasts in perivascular location were found. The tumor stroma contained numerous dilated vessels with slightly fibrosed walls and revealed focal myxoid changes. Immunohistochemically, no clear nuclear expression of MDM2 and CDK4 respectively was present, but molecular analysis by FISH-technique showed a *MDM2* amplifiation in 21 out of 53 analysed nuclei, and a *CDK4* amplification in 14 out of 61 analysed nuclei. The myxoid tumor component was composed of small, undifferentiated mesenchymal cells associated with uni- and multivacuolated lipoblasts set in a prominent myxoid stroma with mucin pools and a prominent network of thin-walled and branching capillaries. Molecular analysis by FISH-technique showed a translocation the *CHOP* gene in 21 out of 53 analysed nuclei, and a translocation of the *FUS* gene in 23 out of 62 analysed nuclei

Diagnosis: Liposarcoma, mixed type.

Comment: This case is a rare example of mixed type liposarcoma, in which the presence of two components was confirmed by molecular analysis. Mixed-type liposarcoma is defined as a liposarcoma showing either features of combined myxoid/round cell liposarcoma and atypical lipomatous tumor/well-differentiated liposarcoma/dedifferentiated liposarcoma or of myxoid/round cell liposarcoma and pleomorphic liposarcoma. There is only one case of true mixed-type liposarcoma arising in subcutaneous tissue of the thigh in 29-year-old male patient, that metastasized to the supraclavicular region, in which a mixed genotype corresponding to atypical lipomatous tumor/well-differentiated liposarcoma and myxoid liposarcoma had been illustrated in the primary neoplasm as well as in the metastasis. There are a number of cases of so-called mixed-type liposarcoma in the literature, in which no molecular evidence of the two tumor components was given. However, at least some of these cases most likely represent examples of atypical lipomatous tumor/well-differentiated liposarcoma or of dedifferentiated liposarcoma with focal prominent myxoid changes, what represents a well recognized phenomenon especially in long standing lipogenic neoplasms in retroperitoneal and intra-abdominal locations.

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AMR SEMINAR #54
CASE 12

Contributed by: Elizabeth Montgomery, M.D.

History: Groin nodule in a 62-year-old man.

Diagnosis: [?] Ectopic Ependymoma

Comment: This case came to me as a consult a few years ago and I thought it looked like an ependymoma but the clinical presentation was so peculiar that I was insecure. It had only focal GFAP but no S100 protein, CD34, keratin, actin, or desmin. Unfortunately I did not do an EMA. I had Peter Burger look at it at the time and he thought ependymoma was a reasonable diagnosis but that he had some reluctance based on the peculiar presentation. As far as I know the patient has done well and no spinal cord lesion was detected. For me, the differential diagnosis is with palisaded myofibroblastoma of lymph node, nerve sheath tumors, and hyalinizing spindle cell tumor with rosettes but it does not really strike me as any of those things. Ependymomas have been reported in peculiar locations but usually closer to the spinal cord area [as well as ovary and liver].

AMR SEMINAR #54
CASE 13

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

Patient's History and Gross Pathology: A 66-year-old Caucasian man, nonsmoker, underwent CT scan in May 2008 for increasing thoracic pain. The medical and family past history was unremarkable. CT scan examination showed a large mass in the posterior mediastinum that was weakly and irregularly positive with PET scan. The patient underwent thoracotomy, and a large tumor mass was excised measuring 16 cm in its greatest dimension. The mass adhered to the tracheal carina and the esophagus wall too, but did not infiltrate these structures or other mediastinal organs. Grossly, the lesion was solid and cystic in the cut section, whitish to yellow, with cystic spaces being filled with gelatinous, jelly-like fluid.

Microscopic Pathology: tumor was supplied with a well-formed fibrous capsule that adhered closely to the esophagus wall (a portion of this muscular wall was excised too) without infiltrating it. The growth pattern was predominantly of Antoni B type with loose-textured, cobweb-like network of elongated, spindled tumor cells admixed with chronic inflammation. Extensive stromal and vascular degenerative changes were visible, including widespread hyalinization, edema and hemosiderin accumulation along with marked nuclear pleomorphism and hyperchromasia and ganglion-like cells provided with more abundant eosinophilic cytoplasm, but mitotic activity or necrosis was absent. Moreover, there was formation of pseudocysts with an epithelium-like lining of tumor cells. Immunohistochemically, tumor cells were strongly and diffusely positive for S-100 protein and this positivity was also seen in the pseudoepithelial lining of cystic spaces but all tumor cells were negative for cytokeratin AE1-AE3 pool, synaptophysin and smooth muscle actin.

Diagnosis: Neurinoma with extensive regressive changes including pseudocystic spaces (ancient Schwannoma).

Comment: Although I feel that all AMR members have been often faced with this type of lesion, this is an interesting tumor that may be found in the mediastinum or retroperitoneum under the assumption that it has been present for a very long time also in the light of the large size of tumor mass. It is well known that one of the most treacherous and disturbing aspects of this lesion type is the nuclear atypia encountered in tumor cells including pleomorphism and hyperchromasia, which is regarded as a purely degenerative change also taking into account the fact that mitotic figures were absent.

AMR SEMINAR #54
CASE 14

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

Clinical Data: A 56-year-old woman with unremarkable past medical history presented to the hospital with vaginal bleeding and pelvic swelling. A 23x15 cm ovarian mass was found and surgically removed with difficulty due to "adhesions". A frozen section was requested during the procedure. The Pathologist describes an ovarian mass with irregular borders and red discoloration. The cut surface consisted of cystic spaces filled with blood and extense necrosis involving approximately 80% of the tumor. A section was frozen and a preliminary diagnosis was given of "Spindle cell tumor with no clear signs of atypia", a definitive diagnosis was deferred to permanent paraffin sections.
The surgeons decided to follow an ovarian cancer protocol based on the adhesions and the necrosis.

Pathology: A proliferation of pleomorphic spindle cells was observed with areas of storiform pattern. These cells showed hyperchromatic nuclei, scant cytoplasm and ill-defined margins. More than 10 mitoses were found per 10 HPF. Some bizarre and giant cells were present interspersed in the tissue. IHC: Vimentin +, Ki 67 + in > 60% of the cells. CK, CD 117 (c-kit), SMA and H-caldesmon were all negative. Complementary surgical specimens were not involved by the neoplasm.

Diagnosis: Primary Ovarian Fibrosarcoma.

Comment: Primary ovarian fibrosarcoma is an extremely rare entity that originates from direct malignant transformation of stromal cells around the sex cord of ovarian follicles or from malignant transformation of a fibroma. Can occur at any age with increased incidence in menopausal and post-menopausal women, usually patients present with rapidly progressing abdominal swelling.

Diagnosis is difficult and can be specially challenging in frozen section. Histologically, they look as fibrosarcomas from other locations with cellular pleomorphism and 4 or more mitoses per 10 HPF. There are no specific IHC or molecular studies for this entity. Trisomy 12 or 18 have been reported in some cases. Can be associated with Maffucci or nevoid basal cell carcinoma syndromes.

Before making a diagnosis of primary ovarian fibrosarcoma, other spindle cell neoplasms should be ruled-out.
This entity should be differentiated from a mitotically active fibroma, which would have less than 4 mitoses per HPF, no cytologic atypia, necrosis or infiltrative margins, however there is a lot of overlapping between the two entities and despite the poor prognosis that primary ovarian fibrosarcomas carry, in some series, cases that meet the criteria for fibrosarcoma morphologically, have showed good unexpected survival, what shows that we still don't have accurate criteria to differentiate both processes. More studies will be necessary to find biological predictive factors of behavior.

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AMR SEMINAR #54
CASE 15

Contributed by: Joshua Sickel, M.D.

Clinical History: A 49-year-old male presented with biliary colic. Clinical work-up, including MRI scan, revealed a cystic lesion in the tail of the pancreas. Fine needle aspiration was performed showing scant cellularity. Cyst fluid analysis revealed the following results: CA 19-9: 789 U/mL and CEA: 45,617 ng/mL. Because of the clinical suspicion for malignancy, a distal pancreatectomy was performed.

Gross Exam: Cut section of the distal pancreas revealed an accessory spleen measuring 3 cm in diameter. Further sectioning of the accessory spleen demonstrated a cystic lesion containing thick bloody fluid. Cyst lining had a trabeculated appearance (see enclosed photograph). Adjacent tissue contained a second accessory spleen measuring 1.2 cm.

Microscopic Exam: Sections show a "true" epithelial cyst arising within intrapancreatic accessory splenic tissue. The cyst lining is composed of stratified non-keratinizing squamous epithelium with scattered mucin positive goblet cells. Immunohistochemistry shows positive staining for CK5/6 and CEA-p. CA19-9 was unavailable, but I suspect this would also have been positive.

Diagnosis: True epithelial "mucoepidermoid" cyst arising within an intrapancreatic accessory spleen.

Comments: Non-parasitic splenic cysts are classified as "true" (epithelial) or "false" (pseudocysts). The most common epithelial cysts are typically classified as epidermoid type, lined by stratified squamous epithelium. Suggested pathogenesis has ranged from developmental displacement of epithelial tissue to squamous metaplasia of invaginated mesothelial lining. Several reports have described an association between splenic epithelial cysts and significantly elevated CA 19-9 and CEA in the serum and cyst fluid. Not surprisingly, immunohistochemical studies have revealed positive staining of the cyst wall with CA 19-9 and CEA.

To be honest, I was completely unaware of this association. As you might have predicted, epidermoid cysts have also been described within intrapancreatic accessory spleens, however, this phenomenon is extraordinarily rare (less than 10 cases in the world literature). The additional presence of goblet cells further adds to the unique nature of this lesion (I haven't found features described before). It seems that all clinical departments involved with the care of this patient (radiology, gastroenterology, surgery, pathology) learned something new and different from this instructive case. Have any other club members encountered a similar lesion?

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AMR SEMINAR #54
CASE 16

Contributed by: Elvio G. Silva, M.D.

CLINICAL HISTORY: A 57-year-old female patient underwent excision of a 6X4X4cm tumor of the left ovary. There is no history of another neoplasm.

SPECIAL STUDIES: The tumor cells are positive for keratin 7 and focally positive for WT1 and ER. They are negative for keratin 20.

DIAGNOSIS: Primary ovarian carcinoma, microcystic type.

COMMENTS: This patient has an unusual primary ovarian carcinoma that I believe it represents a microcystic carcinoma. Low power examination of the slide is very important because in addition to the small groups of cells there are cystic spaces lined by the same type of cells forming the small groups. Also in several areas of the tumor there is a background of a fibroma. These two features are enough to recognize the tumor as a primary ovarian malignancy. It is important when we examine this type of case not to go to the groups of cells immediately because these cells do not have any specific features of an ovarian type of carcinoma and in addition, in several areas they have clear vacuols in the cytoplasm giving the appearance of signet-ring cells. Some of these signet-ring cells also have an eosinophilic deposit in the lumen creating the appearance of a target type of change. If we consider the possibility of a metastasis and we obtain mucin stains the signet-ring cells and the cells with target appearance will be positive for alcian blue, mucicarmin, and PAS. Frequently, like many ovarian carcinomas, this lesion is bilateral. The main feature to distinguish this primary ovarian carcinoma from a metastasis is that in most cases this lesion is not pure, therefore review of additional material usual shows other patterns predominantly papillary serous carcinoma.

In the rare case, like the one presented here that the tumor is pure, is very important to note that the tumor arose in association with an adenofibroma (because of the fibromatose background in different areas), that there are multiple cystic spaces lined by the same cells that form the groups, and that the signet-ring cells are only found in the groups of cells. A significant difference with metastases is that the signet-ring cells are never seen in a pool of mucin or as individual cells in the stroma.

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AMR SEMINAR #54
CASE 17

Contributed by: Dominic Spagnolo, M.D. (Accession Q08B17959B)

Case History: A 47-year-old female presented with vague epigastric discomfort. Upper GI endoscopy revealed an intramural mass, which was then surgically excised. No history of NF1 or NF2.

Macroscopic specimen: The partial gastrectomy revealed a partly intra-, and partly extra-mural ovoid mass 30mm in maximal dimension. It had a sharply circumscribed but unencapsulated peripheral border, and extended on a smooth front into subserosal tissue and omental fat. The mucosa was not ulcerated. The mass was of rubbery consistency and had a solid, vaguely whorled, pale tan/yellow cut surface (see image).

Microscopic: There is a bland spindle cell proliferation growing in fascicles, whorls and focally storiform patterns. The stroma is variably collagenous and myxoid. There are prominent numbers of lymphocytes and few plasma cells in the lesion, and distinctively at its periphery there is abundant lymphoid tissue including reactive follicles, mimicking the appearance of lymph node. **There** are no mitoses, at least in the original sections studied.

Immunostaining: (see selected images)
Positive: S-100 protein, GFAP, pericellular laminin and collagen IV. MIB-1<1%.
Negative EMA, desmin, pan-muscle actin, alpha-smooth muscle actin, smooth muscle myosin, calponin, caldesmon, CD34, CD117, neurofilament protein.

Ultrastructure: Typical features of Schwann cells, with long, multilayered processes, cellular interleavings, pericellular basal lamina, and intermediate junctions.

DIAGNOSIS: Gastric schwannoma.

COMMENT: This lesion does not pose any diagnostic problem. It is a very uncommon tumor, and I thought colleagues might enjoy seeing it. I have attached some images of the gross and immunos. Of all GIT schwannomas, gastric lesions are the most common, followed by colorectal tumors. Gastric schwannoma differs from its peripheral counterpart in lacking encapsulation; Antoni A and B areas and Verocay bodies are often absent; the hyalinised vasculature and secondary degenerative features are often absent; stromal inflammatory cells are common and a peripheral cuff of lymphoid tissue with or without follicles and germinal centres is typical. Unusual morphological variants have been published - signet ring schwannoma (by Saul Suster and colleagues), and microcystic/reticular schwannoma (by Chris Fletcher and colleagues). Rare melanotic examples may also occur.

These tumors are nearly always benign. Malignancy is based on an assessment of cellularity, pleomorphism, mitotic activity and tumor necrosis, but data are scant. From what I could glean, these rare malignant examples, with or without NF association, are published as case reports and not in mainstream pathology journals, but I have not done an exhaustive search.

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AMR SEMINAR #54
CASE 18

Contributed by: Bruce Wenig, M.D.

Clinical History: A 62-year-old female presented with an enlarging mass in the left neck initially described as in the "jugular area". The mass was freely mobile and not attached/connected to any structures such as salivary glands. The patient has a history of thyroid papillary carcinoma diagnosed 3 years ago, which was 1 cm in size, encapsulated and completely confined to the thyroid gland. Metastatic work-up now was negative for other mass lesions and/or disseminated disease. The neck mass was excised.

Histology: Lymph node within which is a cellular proliferation characterized by cells with prominent oncocytic cytoplasm, as well as intermixed cells with clear appearing cytoplasm. Overall, the cellular proliferation is bland lacking significant pleomorphism without evidence of increased mitotic activity and/or necrosis. There is not evidence of normal salivary gland parenchyma. Given the fact that the oncocytic cell proliferation is localized to within a lymph node and clinically there were no identifiable lesions in major salivary glands or in other organ sites, the possibility of metastatic disease was considered. Review of the prior thyroid-based carcinoma showed a completely different morphology than that of the intranodal oncocytic lesion.

Histochemical Stains: Non-contributory.

Immunohistochemical Staining: Lesional cells were reactive for cytokeratins (AE1AE3, CAM5.2, CK7) and p63 but without reactivity for calponin, thyroglobulin, thyroid transcription factor 1, BRST2, mammoglobin, CD10, renal cell marker, S100 protein, melan A, inhibin and WT1. There was negligible proliferation activity as seen by Ki67 (MIB1) staining.

Despite the localization to a lymph node, based on the light microscopic features and IHC findings, I did not feel this lesion represented a metastasis from an occult primary neoplasm. My primary consideration was that this lesion represented a salivary gland neoplasm. Embryologically, the parotid gland develops prior to regional lymph nodes and cervical lymph nodes may commonly incorporate normal salivary gland parenchyma. The latter in turn may give rise to all types of salivary gland lesions/neoplasms in the absence of a primary mass within the salivary gland itself. Given the pathologic findings in this case coupled to the absence of a mass lesion elsewhere, it is my view that this oncocytic lesion is of intranodal salivary gland origin despite the absence of finding normal salivary gland parenchyma. The overall features in this case were not those of a malignant neoplasm (e.g., oncocytic adenocarcinoma, oncocytic variants of mucoepidermoid carcinoma, acinic cell adenocarcinoma, others). The findings are not those of oncocytosis. All in all, I favored a diagnosis of an oncocytoma and recommended a conservative "watch and wait" approach.

Diagnosis: Oncocytoma likely arising from intranodal salivary gland parenchyma.

This case was submitted to me in consultation from a local hospital. About 3 weeks after I received the case, I got a phone call from a local head and neck surgeon. He was seeing the patient in consultation and informed me that the mass was at the level of the hyoid bone, a location that raised questions relative to origin from intranodal salivary gland tissue. At his request, we performed additional IHC staining to exclude other diagnostic possibilities, including a neuroendocrine neoplasm (even though the morphology was not particularly indicative of a neuroendocrine lesion); calcitonin, chromogranin and synaptophysin were negative. He later informed me that serum calcitonin, calcium and parathyroid hormone levels were all negative. I still feel this lesion is best classified as an oncocytoma of likely intranodal salivary gland parenchymal origin even if located in a lymph node well away (anatomically) from the usual locations were such a lesions/neoplasms occur. Does anyone have any other opinions relative to this case?

AMR SEMINAR #54
CASE 19

Contributed by: Saul Suster, M.D.

Clinical History: A 56-year-old woman with no significant past history was found to have multiple long, fingerlike, polypoid projections protruding into the lumen of the large bowel at the level of the proximal transverse colon during a routine screening colonoscopy. The patient relates no history of inflammatory bowel disease or other intestinal ailment. The lesions endoscopically were said to resemble "long worms" attached to the colonic mucosa and dancing freely in the lumen.

Histology: The lesions are completely lined by normal colonic mucosa without any evidence of dysplastic features. There is chronic active inflammation of the mucosa with focal ulceration of glands and crypt abscess formation. There is also intense eosinophilia. The cores of the polyps show prominent vessels with minimal smooth muscle hyperplasia and prominent clusters of ganglion cells. A few small lymphoid follicles are also seen in the submucosa.

Diagnosis: Filiform polyposis of the colon.

Comment: This is the first time I have seen this rare type of polyp in the colon. When we first saw it here we wondered if we were not witnessing some type of hamartomatous process (due to the prominent ganglion cell hyperplasia, proliferation of vessels, etc). Filiform polyposis is thought to represent a variant of inflammatory polyp most often encountered in the setting of inflammatory bowel disease. There is one case published documenting similar lesions in a patient without history of IBD that resembled familiar adenomatous polyposis. In that paper, the authors also describe neuromuscular and fibrovascular hyperplasia with disarray in the submucosa of the polyps. These authors also suggested the possibility of a hamartomatous process for their lesions.

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