

AMR Seminar #52 – Short Summary of Cases:

Case 1: A 52-year-old-female presented with a gastric mass.

Case 2: A 21 year old male presented with multifocal lymphadenopathy of the head and neck region, along with constitutional symptoms (night sweats, weakness).

Case 3: A 25 year old woman was found to have a slow-growing renal mass which was followed radiographically for 7 years. A partial nephrectomy was performed.

Case 4: A 4 1/2-year old male toddler presented in late July 2007 with neck swelling causing breathing difficulties. His family practitioner found cervical adenopathy and tonsillar enlargement. He did not respond to antibiotics and tonsillectomy was performed.

Case 5: A 17 year-old Italian girl presented with a twisted pedunculated liver mass, 11 cm in size, which was surgically resected in an emergency procedure.

Case 6: A 26-year-old woman with cystic fibrosis underwent a right upper lobectomy for what was described as a chronic abscess.

Case 7: A 38 year-old woman first presented with a right thyroid nodule 4 years previously. The nodule had been slowly growing and measured now approximately 3 cm. A right thyroid lobectomy was done.

Case 8: A 30 year-old lady had a long history of breast lump that increased in size during the past few months. A lumpectomy was done.

Case 9: A 47-year-old Japanese woman presented with a circumscribed yellowish white mass measuring 30 mm in greatest diameter in the uterine cervix.

Case 10: A 46 year-old woman underwent a cholecystectomy for abdominal pain. Peritoneal "implants" were biopsied during the procedure that was diagnosed as well-differentiated papillary mesothelioma. A few weeks later the patient underwent additional removal of several omental and peritoneal nodules.

Case 11: A 66-year-old female patient developed an indurated 9cm. subcutaneous lesion on the right hip.

Case 12: A 38 year old woman had a neck mass impinging on the base of her skull removed.

Case 13: A 76-year-old man, former smoker for 30 years underwent left upper lobectomy for Aspergillus infection in 1980. In May 2007, the patient began to complain of hemoptysis again and a chest X-ray showed a 6-7 cm tumor mass in the right upper lobe. A right upper lobectomy was performed.

Case 14: A 44-year-old man was seen for a 4x5x5-cm, expansive, but circumscribed lesion in the left frontoparietal region. The lesion was removed.

Case 15: A 55 year-old woman was admitted for symptoms compatible with Guillain-Barré syndrome. Shortly after admission the patient arrested and died. An autopsy was performed. The sections for review are from the heart.

Case 16: A 17 year-old female presented with irregular PV bleeding for 14 months and right iliac fossa pain. Taking combined oral contraceptives. No features to suggest estrogenic or androgenic hyperfunction. Pelvic ultrasound showed a 24mm right ovarian cyst.

Case 17: A 63-year old woman was seen for an 8 cm. mass adherent to the serosa of the sigmoid colon. The mass showed gray, firm solid areas admixed with cystic spaces containing thick, gelatinous material. The patient had undergone a TAH+BSO for simple cysts of the ovary three months previously.

Quiz Case 1: A 55-year old woman with no significant past history was seen for a 5 cm. soft tissue mass in her right upper arm of 8 months evolution. The mass had recently started to grow rapidly. The lesion was completely excised.

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CASE 1

Contributed by: Volkan Adsay, M.D.

History: A 52-year-old-female presented with a gastric mass and underwent subtotal gastrectomy. The slide is from this specimen. 2.5 years after the original diagnosis, the patient experienced recurrences in the celiac region, involving perigastric soft tissues as well as lymph nodes.

Macroscopic findings: There was a 3.0 cm tumor on the wall of the stomach, covered by normal mucosa, and forming a subserosal bulge. The tumor appeared to be relatively well demarcated on gross examination. Cut surfaces appeared fleshy and homogenous.

Microscopic findings: The tumor was composed of round to ovoid epithelioid cells forming sheets, and focally also vague nests, which had led to the erroneous diagnosis of carcinoid on frozen section in the outside institution. The tumor appeared subtly infiltrative at the peripheral edges. The intervening stroma had desmoplastic quality. Nuclei were relatively uniform, but focally showed mild irregularities with occasional grooves. Chromatin was fine, pale and vesicular, and nucleoli were prominent. Although the cells were epithelioid, the ovoid appearance of the nuclei and the degree of overlapping were more in keeping with a mesenchymal process. Moreover, the cells did not appear to be sharply demarcated from the stroma, which was also in favor of a mesenchymal process. One of the striking cytologic features was that the cytoplasm was fairly abundant, and focally had clear quality to it. Especially in the areas with more nested (almost zellballen) pattern, this finding was more prominent. In these areas, the cytoplasmic borders were also distinct.

Overall appearance of the tumor was that of a mesenchymal neoplasm, with the possibility of gastrointestinal stromal tumor (GIST). However, the tumor cells were negative for c-kit (CD117) and PDGFR, as well as for CD34, actin and desmin. Lymphoma markers CD45, CD30, CD138 and epithelial markers (wide-spectrum keratins) were also negative. S-100 protein was strongly positive, while other melanoma markers (HMB45, Mart-1 and microphthalmia factor) were negative. Fluorescent in-situ hybridization disclosed the presence of EWS-CREB1 fusion transcript.

Diagnosis: Gastrointestinal-type clear cell sarcoma.

Comment: The main differential diagnosis in this case was a GIST. GISTs are often epithelioid, they may have clear cells, and they may appear monotonous as in this case. In fact, if it were not to the c-kit negativity, I wonder if this case would have been taken under further scrutiny that has led to the current diagnosis. I suspect it would probably have been signed out as a GIST. However, it appears that the gastrointestinal clear cell sarcomas, as described by Antonescu et al, are probably a distinct clinicopathologic entity that is closely related to but at the same time quite different from either GIST or clear cell sarcoma of soft parts.

Gastrointestinal clear cell sarcomas are similar to GISTs both by morphology and location. However, they show subtle but important cytologic differences as described above. Furthermore, they lack c-kit and PDGFR mutation. In a tumor like this, once c-kit is negative, and S100 strongly positive, then the main differential is clear cell sarcoma of soft parts. However, unlike the clear cell sarcoma of soft parts, in the gastrointestinal-type clear cell sarcomas, melanocytic differentiation is not evident. Melanoma markers, HMB45, Mart-1 and microphthalmia factor are typically negative, and ultrastructural evidence of melanocytic differentiation, such as melanosomes are also lacking. The molecular-genetic alteration that characterizes CCS of the GI-tract is also similar but at the same time distinct from that of its counterpart in the soft tissues. CCS of soft parts show the fusion of EWSR1 and ATF1, whereas CCS of GI tract shows fusion of EWSR1with CREB1, which is closely related but different from ATF1.

In summary, this case illustrates a nice example of clear cell sarcoma occurring in the gastrointestinal tract. The information on these tumors is somewhat limited. But they appear to form clinicopathologic entity distinct from both GIST and CCS of soft parts.

Reference: Antonescu et al. EWS-CREB1: A recurrent variant in clear cell sarcoma- association with gastrointestinal location and absence of melanocytic differentiation. *Clinical Cancer Research* 12(18): 5346-5362, September 15th, 2006.

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CASE 2

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

Clinical History: A 21 year old male presented with multifocal lymphadenopathy of the head and neck region, along with constitutional symptoms (night sweats, weakness). A lymph node was excised and sent for examination with the clinical diagnosis of lymphoma.

Pathological Findings: The gross appearance of the specimen was rather dramatic as it showed multiple foci of softening very reminiscent of tuberculous granulomas. As the patient belongs to an ethnic group in which this disease is not uncommon, I was sure that this was the diagnosis and in fact ran downstairs to the microbiology lab with a sample for culturing. In the meantime I had a touch imprint stained which showed to my great surprise histiocytic cells with the classical indented, folded, grooved nuclear features characteristic of Langerhans cells. In addition, numerous eosinophils were seen in the background.

Subsequently, I received histological sections showing extensive replacement of the lymph node architecture by sheets of the aforementioned cells, accompanied by dense eosinophilic infiltrates with abscess formation, geographic areas of necrosis containing eosinophilic debris and cell detritus, and Charcot-Leyden crystals. These cells stained positively for S100 and for CD1a, confirming the diagnosis of Langerhans cell histiocytosis presenting as multifocal lymphadenopathy. The cells were also positive with the new marker langerin (courtesy of Dr. John Chan).

Diagnosis: Langerhans cell histiocytosis of lymph node.

Discussion: Though on cytological grounds, the diagnosis here is obvious, I thought that the histology of this case was dramatic and demonstrative enough that the other members of the group would find it interesting. As is well known, systemic Langerhans cell histiocytosis is characteristically a multifocal disease appearing in children and involving multiple organ systems, which can include lymph nodes. Lymph node involvement in this circumstance can also be secondary to drainage of another involved focus, say in a bone. Outside the context of Langerhans cell histiocytosis as a disease process, Langerhans cell proliferations can also be an incidental finding in lymph nodes involved by lymphoma. Dr. Rosai also mentions the possibility of finding Langerhans cell proliferations in lymph nodes draining papillary carcinoma of the thyroid. The involvement is often referred to, at least at the onset, as sinusoidal.

Fortuitously in searching for literature on this topic, I found the very recent and relevant manuscript by Saul and Cesar Moran, which is as of this writing available on the Human Pathology web site as an e-publication ahead of the formal publication in that journal. This review encompasses twenty cases of Langerhans cell histiocytosis limited to the lymph nodes, which were collected from the archives of their respective institutions (as of the time the material was put together) and their own personal consultation files. The patient ages were spread across the spectrum, including some young children, but with many young adults and elderly patients, and in most of their cases, the cervical lymph nodes were involved (as in my case). While sinusoidal involvement is present in all cases and has been stressed in previous articles and standard textbook descriptions, Saul and Cesar emphasize the degree of extension of the process into the parenchyma; as in this case, most of theirs showed subtotal effacement of the architecture with some showing total replacement. Other features noted in the article include eosinophilic abscesses or geographic necrosis and the presence of giant cells (this latter finding not seen in this case). Given the extent of involvement by the process in this case, I don't think there is any differential diagnosis; when there is only focal sinusoidal involvement other conditions specified in the article (Hodgkin disease, Kimura's disease, dermatopathic lymphadenopathy) should be taken into consideration.

Another wrinkle on this situation is provided by a case from Singapore published last year by Tan et al. in the Journal of Clinical Pathology (59: 248-249). This article describes a 30 year-old man with cervical lymphadenopathy on one side whose lymph node biopsy showed multiple foci of eosinophilic necrosis surrounded by granulomas; it was only on more careful scrutiny that the presence of Langerhans cells surrounding the granulomas was discerned. They also mentioned the presence of Charcot-Leyden crystals as I found in my case (see above). In my own case on careful histological review, I wasn't impressed by granuloma formation, but CD68 identified many scattered single cells, which at least in one focus congregated around one portion of the perimeter of a site of necrosis suggestive of partial granuloma formation. The development of granulomas is considered by the authors to be reactive to the necrosis in the same way that Saul and Cesar explained the presence of the osteoclastic giant cells in their cases. The presence of true granulomas and eosinophilic abscesses makes the differential with Churg-Strauss disease very real and requires careful examination of the slide to pick up the Langerhans cell proliferation which was not apparent at first. Though this wasn't mentioned explicitly,

no other sites of disease were specified by the authors and presumably this patient's disease was also limited to the lymph nodes.

Apparently the prognosis in cases such as this where Langerhans disease is limited to lymph nodes is excellent and the disease can be self-limiting (though the Singapore patient was given chemotherapy). The patient whose slide I am submitting, in fact, was not followed in our hospital, and I don't have any information regarding further workup possibly performed elsewhere so I can't be totally certain whether the disease was truly limited to the lymph nodes. Suffice it so say that whatever clinical examination performed by the ENT surgeon and other ancillary tests performed preparatory to surgery (including chest radiology which may have shown possible evidence of lung involvement) did not turn up any other salient features, and no other complaints by the patient (for example bone pain) were recorded.

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CASE 3

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

Clinical History: Renal tumor of a 32 year-old woman which was found radiographically 7 years ago when she was 25 years old. Follow-up since then revealed very slow-growth of the tumor. Thus, needle biopsy was performed followed by resection of the tumor (partial nephrectomy).

Pathologic Findings: We received a 3.8 cm tumor partially surrounded by a small rim of renal tissue. Cut sections show elastic gray-pink tissue. Histologic sections show predominantly various-sized follicles containing densely eosinophilic material (colloid-like), some tubuli with obliterated lumen, focal complex interanastomoses between follicles, and focal-rare pleomorphic nuclei. No clear cells, no necrosis, no mitoses. A tiny subtle focus of papillae which is present in this slide was very rare, and not seen in the other 5 paraffin blocks.

Immunostains: Negative for TTF1 and Thyroglobulin. CK-7 strong diffuse positive, CK-19 and HMWCK (34BE12): positive, AMACR (p504) and EMA: focal positive. CD10: mostly negative. RCC: negative. C-KIT: negative. WT1: negative.

Diagnosis: Thyroid follicular carcinoma-like tumor of the kidney (or thyroid-like follicular variant of papillary carcinoma?).

Comment: I received the case from a dear colleague, who phoned me when she first saw the slides to ask me if I know of a "renal tumor which looks like thyroid". I did not know any. Only when I received the slides and showed them to another colleague, he quickly found in Pubmed the seminal paper of Jung and Ro (Jung et al: Thyroid follicular carcinoma-like tumor of the kidney. A case report with morphologic, immunohistochemical and genetic analysis. Am J Surg Pathol 30:411-15, 2006). So good to have friends.

I did not see the previous needle biopsy that was performed at another hospital, and that was sent to a well-known uropathologist in the U.S. who performed stains for TTF1 and Thyroglobulin, which were negative and called the tumor "renal cell carcinoma, unclassifiable".

The seminal paper mentions 3 other similar tumors which were presented at the 2004 annual meeting of USCAP (Amin MB, Michal M et al: Primary thyroid-like follicular carcinoma of the kidney: A histologically distinctive primary renal epithelial tumor (Abstract). Mod. Pathol. 17:136A, 2004).

These tumors have in common the "thyroid-like" histology and the lack of clear cells, papillae, chromophobe cells. However, Jung's case showed necrosis, high-mitotic rate and high nuclear grade, while Amin's cases lacked necrosis. Three of the four cases had no recurrence (at 6,36 and 54 months follow-up), while one of Amin's cases had metastases to renal hilar lymph-nodes. The current case shows features of a low-grade tumor, both clinically (slow enlargement during 7 years of follow-up), and pathologically (including low KI67 index).

In addition to focal very rare papillae in our case, the immunohistochemical phenotype is similar to papillary renal cell carcinoma (diffuse positive CK-7, positive CK-19, focal positive AMACR, negative RCC, mostly negative CD10, negative C-KIT). The stains in Jung's case were different (negative cytokeratin 7 and 19, diffuse positive CD10). Amin's cases had variable results, but all were CK-7 positive and RCC negative. The specific chromosomal changes in Jung's case, dissimilar to other renal tumors, suggest that this is a separate entity among renal tumors. However, the somewhat variable histologic features, lack of concordant immunostains and the paucity of reported cases warrant further studies to decide if this is really a unique-separate renal tumor or a histologic pattern of several other renal tumors.

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CASE 4

Contributed by: Gerald Berry, M.D.

Clinical History: This 4 1/2-year old male toddler presented in late July 2007 with neck swelling causing breathing difficulties. His family practitioner found cervical adenopathy and tonsillar enlargement. Rapid Strept study and throat cultures were negative but EBV IgM was elevated. Because of upper airway obstruction he received IV, antibiotics, and IV Decadron. He did not improve, and he was taken to the OR for tonsillectomy and adenoidectomy. Lab values from his work-up: ESR 138, WBC 18k, 56% lymphocytes, PMNs 32%, 1% bands, 10% monocytes. On the day of discharge, his serum EBV PCR was reported at 60,000 copies/mL.

Microscopic Findings: We received both tonsils and adenoids (your slide is from the adenoidal tissue). There is marked effacement of the normal adenoid architecture with only occasional residual but distorted germinal centers. The low power appearance is mottled. There is a prominent immunoblastic proliferation throughout the expanded interfollicular areas. Many of the immunoblastic cells display plasmacytoid features. The accompanying image highlights the paucity of CD20 positive germinal centers with numerous CD3+ T-cells. There is a CD8/CD4 predominance. The proliferation marker, Ki-67 shows a high proliferation rate 60-70%. In situ hybridization for EBER demonstrates many EBV-positive cells.

Diagnosis: Acute mononucleosis, tonsil.

Comment: This is a nice example of acute mononucleosis involving the tonsils and adenoids. It is uncommon to see surgical specimens these days and the surgical indication in this case was upper airway obstruction. Historically, the architecture of lymph nodes or extranodal tissues ranges from minimal changes to florid effacement. The histologic picture depends, in part, on the timing of the biopsy. The follicles are preserved in the early stages and become less distinct as the paracortical expansion proceeds. The paracortical proliferation produces a mottled appearance composed of immunoblasts and variable numbers of small lymphocytes and plasma cells. In some cases, the immunoblasts retain RS-like features causing confusion for Hodgkin lymphoma. The distinction from immunoblastic lymphoma is aided by the clinical history, immunohistochemistry and in situ studies.

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CASE 5

Contributed by: Michele Bisceglia, M.D.

Clinical History: In March 1999 a 17 year-old Italian girl presented with a twisted pedunculated liver mass, 11 cm in size, which was surgically resected in an emergency procedure. No significant previous clinical manifestations were recorded, in particular no history of oral contraception, Fanconi anemia, glycogen storage disease, familial adenomatous polyposis or diabetes mellitus.

Pathological findings: On cut surface a seeming central scar was grossly apparent along with some hemorrhagic foci and a small blood filled cavity sized. On histology (slides labeled 88903-99), I diagnosed this mass as consistent with Focal Nodular Hyperplasia (FNH) based on the presence of what was interpreted as a "central scar", abnormal vessels, and patchy ductular reaction, which was subtle but visible here and there at the interface between the fibrous septa of the "central scar" and the tumor parenchyma. Peliotic, hemorrhagic and infarction changes (not shown in the submitted sections, although some degree of focal sinusoidal ectasia and early peliosis-like hemorrhagic foci can even be seen) were ascribed to and considered secondary to the torsion. (Enclosed slides A and B; images submitted for the web show the following findings: a typical peliosis-like telangiectatic hemorrhage, a focus of peliosis hepatis, and the bile ductular reaction recently highlighted with immunostaining for CK7).

At surgery another 3 cm liver mass located on the dome of the liver was noted (of which I was not aware at that time). This second lesion was left alone till the end of 2006, followed-up with ultrasound investigations. By September 2006, this lesion had grown to 7 cm, when I was consulted again and fully involved. (Obviously, I was concerned since at the time of the primary diagnosis I too considered in the differential both hepatocellular adenoma and well differentiated hepatocellular carcinoma). Given the clinical context of progressive enlargement of the second nodule and the risk of bleeding, surgical excision was considered the best therapeutic option. While planning the second surgical intervention, many slides of the 1st lesion (14 HEs and 9 unstained) were sent in consultation to 7 specialized international liver centers, resulting in diverse diagnoses, ranging from classic FNH to hepatocellular adenoma of telangiectatic type, to classical hepatocellular adenoma. Suspicion of a well-differentiated hepatocellular carcinoma was also expressed in the differential diagnoses by 2 of those who diagnosed hepatocellular adenoma classic type. Concern was also expressed with regards to the new lesion by the same 2 consultants. All the consultants expressed their brisk interest in what the second lesion would turn out to be.

The second tumor was resected in another institution in December 2006, of which I got several representative blocks thanks to the courtesy of the local pathologist who also was very interested in the opinions from the above mentioned referral centers even on this second lesion. The excised lesion was 11 cm sized, with no visible central scar on sectioning. The lesion was poorly-delimited with some zonation of clear ballooned hepatocytes, steatosis around thin-walled venules alternating with smaller eosinophilic cells disposed along arterial branches was present; bile ducts and ductules were well noted, much better than in the former lesion; multiple minute hyperplastic nodular foci of clear/steatotic hepatocytes were also seen in the adjacent host liver. (Enclosed slide C – labeled MB-316).

Slides from the second lesion were sent to 5 of the previous centers: the diagnoses received from 3 were classic hepatocellular adenoma, hepatocellular adenoma with CK7+ biliary ductules, and liver cell adenomatous hyperplasia (excluding hepatocellular adenoma due to the presence of ductules), respectively; (no answer was received from the other two centers). One of the consultants who diagnosed hepatocellular adenoma also underlined the concept that the satellite peripheral nodules, which were present in this second liver lesion, were similar to those of the nodular regenerative hyperplasia and that some cases of liver cell adenomatosis which had previously been published as such in the literature actually may have been examples of nodular regenerative hyperplasia (viz. adenomatous hyperplasia). As the consultants, who diagnosed hepatocellular adenoma, were aware of the previous history of hepatocellular adenoma, they also suggested for this case the condition of multiple adenomas or adenomatosis.

Finally, two more pathologists reviewed the entire case at the same time, one of these was voluntarily consulted by one of the centers to which I primarily sent the slides. These final revisions resulted in the following diagnoses "adenomatosis with different types of hepatocellular adenomas" (hepatocellular adenoma of telangiectatic-FNH type as for the first liver mass, and hepatocellular adenoma(s) steatotic-type* as for the second liver mass), and "multiple hepatocellular adenomas with ductal differentiation" (equivalent to hepatocellular adenomas progressive FNH-type), respectively. Of interest, one of these latter consultants interpreted the "central scar" of the first tumor as the result of so called "congestive hepatopathy". (*Steatotic-type hepatocellular adenoma corresponds to the variant-1 of the new classification of hepatocellular adenomas [ref. 6]).

Malignancy was excluded based on morphology (absence of atypia, intact reticulin framework, and regular disposition of 1-2 thick-layered trabeculae) and immunostainings (Glypican3 was negative, CD34 showed only minimal sinusoidal staining, and MIB-1 labeled very occasional nuclei – *Glypican3 was tested in one of the consulted centers*).

Discussion: Focal nodular hyperplasia (FNH) and hepatocellular adenoma are benign liver tumors, and both may be multiple, and occasionally even pedunculated. FNH is characterized by a central scar containing abnormal arteries (hypertrophied muscular media and intimal proliferation) and lymphoid inflammatory and ductular reaction. However, some cases of FNH with lack of, or with inconspicuous, or with only some of the key diagnostic features may also occur. Classic hepatocellular adenoma has been traditionally defined as composed of benign hepatocytes arranged in liver cell plates up to 3 cell thick (thickened cell plates alternating with normal ones) with thin-walled arteries scattered throughout the tumor, in absence of acinar architecture. In hepatocellular adenoma, there are no portal triads or central veins, and there is no connection with the biliary system, with bile ducts typically absent and no ductular reaction.

In December 1999, after an extensive study of 305 surgically resected lesions, two categories of FNH were proposed and popularized: the **classical type** (~80%, i.e. 245 lesions) and the **non-classical type** (~20%, i.e. 60 lesions). Only a proportion (153 lesions) of FNH of the classical type in that study showed one to three gross central scars (~63%), while others (i.e. 92 lesions) did not (~37%). All the cases with gross central scar histologically showed architectural nodular distortion, malformed arterial vessels, and bile ductular reaction; 43 cases of the total 92 without gross central scar also microscopically showed the same features, with evidence of fibrous septa, architectural nodularity, and ductular reaction; the remaining 49 cases of the total 92 cases without gross central scar (~20% of the entire category of classical FNH), usually small nodules, “also had the classical characteristics, but on a subtle scale” (ref. 1), with only vague nodular aspect, arteries only moderately abnormal, and only discrete bile ductular proliferation visible at high magnification.

FNH of the non-classical type was defined as lacking nodular architecture or malformed vessels, but always presenting some degree of interlobular bile ductular proliferation, viz. the hallmark of the lesion (ref. 1). FNH of the non-classical type was further sub-divided into telangiectatic FNH* (TFNH) (~15%, i.e. 47 cases of the total 305 from the study), mixed hyperplastic and adenomatous FNH (1-2%), and FNH with cytologic atypia (2-3%) (ref. 1). *The denomination of telangiectatic FNH was introduced for the first time in 1989 in the publication of a series of 13 cases of syndromic FNH [ref. 2] as opposed to the usual “solid” type of FNH (which notoriously is pale on cut surface, “paler” than the surrounding liver). TFNH was so defined based on its telangiectatic appearance; with diffusely tan to brown coloured cut surface, congestive red areas, and possibly hemorrhagic cavities. Microscopically, the center of TFNH contain portal tracts with numerous irregular vascular channels connected with abnormal arteries and draining into dilated and telangiectatic sinusoids (well demonstrated here in slide A). It has been hypothesized that the telangiectatic FNH has incompetent precapillary sphincters allowing transmission of higher pressure to the sinusoids (in contrast to the “solid” type of FNH which has competent precapillary sphincters) (ref. 2).

In 2004 molecular studies showed that TFNH is closer to hepatocellular adenoma than to FNH and the term telangiectatic hepatocellular adenoma (HCA-TFNH type) was suggested (ref. 3). This latter conception was soon corroborated by others (ref. 4, 5), and TFNH is now included in the monoclonal spectrum of hepatocellular adenoma as a separate entity (hepatocellular adenoma variant), due to its peculiar morphology and –unlike other types of hepatocellular adenoma– to the absence of a known gene mutation.

This year new diagnostic criteria came out with regard to hepatocellular adenoma, and 4 variants have been delineated in addition to the classical one (ref. 6). Thus, five variants of hepatocellular adenoma have been delineated: the archetypal (monoclonal), variant-1 (with HNF1 α mutation and marked steatosis/clear cells), variant-2 (with β -catenin mutation and cytological atypia, also called “HCA/HCC borderline lesion”), variant-3 (no known mutation, which may contain CK7+ ductules), and variant-4 (no known mutation with no specific morphologic trait) (ref. 6). Hepatocellular adenoma variant-3 (with or without inflammatory infiltrates) corresponds to TFNH (which some people also called “progressive FNH” [ref. 7]). Hepatocellular adenoma variant-3 may contain CK7+ bile ductules (“adenoma with ductal differentiation”) (ref. 6). The other types of non-classical FNH have been incorporated into these new variants of HCA (ref. 6), and FNH is now represented by the classical or solid form only (ref. 4). However, also in the 2007 “Bordeaux update” on the new diagnostic criteria distinguishing hepatocellular adenomas and FNH (ref. 6), cases of FNH with “lack of, inconspicuous or only some of the diagnostic features” of the “archetypal” type are allowed in the category, and these must be coincidental with that minority of FNH cases “without a central scar” which microscopically “have the classical characteristics, but on a subtle scale” (ref. 1: see above at the beginning of this discussion).

Diagnosis and Conclusions: Given the absence of any specific clinical context, the final diagnosis in this case was “spontaneous” multiple adenomas” (spontaneous adenomatosis). The clinical management of adenomatosis is difficult, but requires regular follow up: removal of larger tumors at risk of bleeding is recommended.

Comment: The diagnosis of hepatocellular adenoma is problematic for the following reasons: a) the overlapping features existing among the several variants, which have to date been recognized; b) the new developing molecular studies; c) the recently changed criteria of classification and terms of denomination; and d) some histological overlaps with (classical) FNH. At this regard, the case, herein presented, seems to be paradigmatic.

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CASE 6

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

History (TV07-40): A 26-year-old woman with cystic fibrosis underwent a right upper lobectomy for what was described as a chronic abscess.

Pathologic Findings: There was gross evidence of extensive inflammation with some bronchiectasis and marked acute and chronic inflammation. Peculiar amorphous material was identified in pulmonary vessels, airways, lymphatics, and in regional lymph nodes (see digital images below*). This was associated with a giant cell reaction.

Follow-up: Subsequently, it was determined that this patient had a history of hemoptysis and had undergone therapeutic embolization on multiple occasions by multiple operators with a variety of agents, not all of which could be identified; probably polyvinyl alcohol (PVA) and tris-acryl gelatin microspheres; possibly also cyanoacrylate.

Discussion: The case is presented as an extremely unusual finding, unique to the experience of the presenter, illustrating the patterns that may be encountered with embolized material and showing the very unusual phenomenon of this material getting into regional lymph nodes. The attached discussion is taken verbatim from Dr. Kelly Butnor's discussion of this phenomenon at the Pulmonary Evening Session at the 2007 USCAP meeting.

*Images on web site show degenerating material in the node with an associated giant cell reaction as well as embolic material in the lymphatics entering the lymph node capsule.

Dr. Butnor's discussion:

Iatrogenic Causes of Pulmonary Emboli

Perhaps the most familiar type of iatrogenic pulmonary embolus is bone marrow emboli seen at autopsy following cardiopulmonary resuscitation or rarely in thoracotomy specimens. Such emboli typically lodge in small-caliber arteries and are considered incidental. Clinically significant pulmonary bone marrow emboli have been reported as a complication of various orthopedic surgical procedures. [4, 5]

Iatrogenic embolization of fat to the pulmonary circulation is becoming an increasingly recognized complication of body sculpting (lipoplasty) procedures, the detection of which relies on a high index of suspicion and appropriate fixation and histochemical staining techniques. [6] Bile is another endogenous substance that can embolize to the lungs. This rare and sometimes disastrous complication has been reported in a variety of hepatobiliary procedures, including percutaneous liver biopsy and ERCP. [7, 8]

In addition to its accepted role in certain cosmetic surgical procedures, injectable liquid silicone (polydimethylsiloxane) is also being used by non-licensed practitioners for illicit breast augmentation and other aesthetic procedures. Rare instances of pulmonary embolization of liquid silicone, sometimes resulting in death, have been recorded. [9] On routine H&E stain, liquid silicone pulmonary emboli appear as vacuolated globules. Vascular leakage of polymethylmethacrylate (PMMA) cement, a substance used during vertebroplasties to stabilize fractures, also occasionally results in clinically significant pulmonary emboli. [10] Barium sulfate or other agents are added to most bone cements to make them radiopaque, which impart a characteristic gray-green granular appearance on histologic examination. In many cases, however, pulmonary emboli secondary to vertebroplasty are comprised of fat and/or bone marrow elements.

Air and other gaseous pulmonary emboli can result from craniotomy, Caesarean section, surgeries that involve mechanical insufflation such as laparoscopy, and the insertion of intravenous catheters. [11] Diagnosis is usually based on clinical grounds and can sometimes be confirmed by imaging.

Synthetic medical devices that have unintentionally embolized to the lungs include fractured intravenous catheters of various types and radioactive prostate brachytherapy seeds. While a broad range of sequelae have been reported with catheter emboli, radioactive seed emboli appear to have a remarkably low incidence of adverse clinical effects. [12, 13, 14]

Transcatheter embolization therapy is a method used to treat vascular abnormalities such cerebral and pulmonary AVMs and certain hepatic malignancies. The array of embolotherapy agents includes absorbable Gelfoam, polyvinyl alcohol particles, and permanent occlusive devices. [15] Inadvertent migration to the lungs occasionally results in pulmonary infarction or death. [16, 17]

Iatrogenic Causes of Pulmonary Emboli

Type of Embolus	Inciting Causes	Histologic features
Endogenous Bone marrow Fat Bile Air	CPR, orthopedic surgeries Liposuction, orthopedic surgeries Liver biopsy, ERCP Craniotomy, laproscopy, catheters	Marrow and fat elements Oil Red O-positive globules Golden-green pigment Difficult to detect
Foreign Material Liquid silicone Methylmethacrylate cement Radioactive implant seeds	Cosmetic procedures Arthroplasty, vertebroplasty Prostate carcinoma brachytherapy	Vacuolated globules Green-gray granular material (rarely) ± fat and/or bone marrow
Intravenous catheters	Mechanical disruption	
Embolotherapy agents Polyvinyl alcohol particles Tris-acryl gelatin microspheres Lipidol (iodized oil) Vascular occlusion devices Detachable balloons Metallic coils (e.g. Gianturco, Nester)	Treatment of hepatic malignancies Cerebral and pulmonary AVMs	Black-gray particles ± calcification Purple-pink homogenous particles May see coil-associated synthetic fibers (e.g. Dacron, nylon)

Pulmonary Manifestations of Hereditary Hemorrhagic Telangiectasia

Although no obvious mucocutaneous stigmata of hereditary hemorrhagic telangiectasia (HHT), as known as Osler-Weber-Rendu, were apparent in the present case, the patient had two smaller pulmonary AVMs in addition to the large embolized lesion.

It is estimated that over 80% pulmonary AVMs are congenital and of these, 80-90% are associated with HHT. [18, 19] As many as 15-35% of individuals with HHT have pulmonary AVMs, which are often multiple and typically involve the lower lobes near visceral pleural or outer third of the parenchyma. [18, 19, 20] Although two separate genetic alterations have been identified on chromosomes 9q34 and 12q, the former of which encodes endoglin, a binding membrane glycoprotein on vascular endothelial cells, the exact pathogenesis of pulmonary AVMs in HHT remains uncertain. [21] Individuals with HHT often experience hypoxia and/or dyspnea due to left-to-right shunting. Severe complications include massive hemoptysis and neurologic sequelae such as stroke.

Embolotherapy of Pulmonary Arteriovenous Malformations

Left untreated, pulmonary AVMs are associated with 11% mortality, therefore treatment of even asymptomatic lesions is recommended when the diameter of the feeding vessel(s) exceeds 3 mm. [20, 21] Embolotherapy using vascular occlusive devices, such as detachable balloons or metallic stainless steel or platinum coils invested with synthetic fibers, such as Dacron polyester, to enhance thrombogenicity is the currently preferred method of treatment. Deployment into the AVM feeder vessel(s) is performed under radiologic guidance and post-deployment angiography is used to exclude continued perfusion. [20] Although usually safe and effective, occasional complications include fever, air emboli, and pleuritic chest pain, with pulmonary infarction occurring after as many as 5% of procedures. [20, 21, 22]

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AMR SEMINAR #52

CASE 7

Contributed by: Göran Elmberger, M.D.

Clinical history: A 38 year-old woman first presented with a right thyroid nodule 4 years previously. The nodule had been slowly growing and measured now approximately 3 cm. Previous attempts at diagnosis utilizing FNA x 6 rendered suggestions of colloid nodules and lateral neck cyst. Previous medical history included resection of ACTH producing hypophyseal adenoma at 29 years age and levaxin substituted hypothyreosis at 31 years of age. Ultrasonographic examination of the neck showed a corresponding intraglandular hypoechogenic tumor but were otherwise unremarkable. No signs of neck node metastases. CT thorax and abdomen were unremarkable. A right sided thyroid lobectomy was performed.

FNA findings: In retrospect, upon review of FNA's a fairly characteristic mixture of three diagnostic cell types were seen; mucocytes, intermediate cells and a few mature squamous cells. Focally slight cytological atypia was present. The background revealed debris, minor component of mucus, crystalloids and lymphocytes. Macrophages including multinucleated giant cells were also seen.

Pathological findings: Grossly a 30 mm well circumscribed and encapsulated tumor and a smaller mahogany brown, solid 6 mm tumor were seen. Microscopical analyses of the larger tumor revealed a partly cystic biphenotypic neoplastic proliferation with glandular and epidermoid components. The epidermoid part consisted mainly of intermediate cells partly with clear cell differentiation but focally well formed mature squamous pearls were seen. The clear cells contained PAS+ material sensitive to diastase treatment consistent with glycogen. The cystic spaces were lined by intermediate cells with interspersed mucocytes. Intraglandular secretion was of mucoid character showing PAS+/- diastase +, Alcian blue pH 2.5+ and negative IHC for thyroglobulin. Tumor cell nuclei showed only mild pleomorphism and minor nucleoli. The tumor was further characterized by a sclerotic stroma richly infiltrated eosinophils, lymphocytes and plasma cells. Histiocytic giant cell reaction was seen in association with squamous pearls and glandular cholesterol type of crystalloids. No destructive infiltrative growth could be demonstrated. No perineural or LVI could be detected. The tumor cells showed a rather complex immunophenotype partly highlighting the dual morphological differentiation. All tumor cells were positive for TTF-1, CK high MW, CK5, CK18, CK19, CD138 and prohibitin. The epidermoid component was also positive for p63. The glandular component was additionally positive for low MWCK, BERE4, CK7, secretory component, sialyl transferase (mucocytes) and EMA. Tumor cells were negative for thyroglobulin, calcitonin, chromogranin A, CK20, HER2 and S-100. Proliferative fraction 1% (MIB1). No evidence for p53 mutation. The background thyroid showed Hashimoto thyroiditis with fibrosis and minor foci of squamous and oncocytic cell metaplasia as well as a nodular oncocytic proliferation most likely representing an oncocytic adenoma.

Diagnosis:

1. Thyroid sclerosing mucoepidermoid carcinoma with eosinophilia.
2. Hashimoto thyroiditis.
3. Oncocytic adenoma/adenomatoid oncocytic nodule.

Follow-up: At 4 year control no signs of local recurrence or distant spread.

Discussion: Sclerosing mucoepidermoid carcinoma with eosinophilia of the thyroid (SMECE) was first described by Chan et al in 1991¹ as a new distinctive low-grade carcinoma of the thyroid gland generally occurring in a background of Hashimoto's thyroiditis. Since this initial report, approximately 25 additional cases have been described²⁻⁹. Most cases manifested a relatively indolent clinical course. Metastasis has been described as an unusual manifestation of this clinical entity. The average age of patients in the literature was 53 years with the majority of the patients being women.

SMECE of the thyroid gland are rare tumors that can present diagnostic difficulties to the cytopathologist and pathologist due to the unusual cytopathological and histologic features. In FNA, the findings are rather characteristic than pathognomonic^{10,11}. The overall picture seems more important than individual elements in recognizing this rare entity cytologically, since the predominant type of malignant cells has a deceptively bland appearance. The differential diagnoses include other primary thyroid malignancies, Hashimoto's thyroiditis, metastasis and lateral branchiogenic cyst of lymphoepithelial type. In our present case, the reason for not making the diagnosis with FNA is probably the low probability of the diagnosis since the features of the smears in retrospect were quite characteristic. Ultrasonographic guidance is to my personal experience very helpful not only to assure representative material but also in cases like this to ascertain the thyroid intraglandular location of the lesion.

The etiology and histogenesis of these tumors has been debated in the literature, with some authors believing that the tumors arise from remnants of the ultimobranchial body (UBB, solid cell nests)¹² and others proposing that they arise from follicular epithelium derived metaplastic squamous cells occurring in a background of Hashimoto thyroiditis^{1,13,13}.

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AMR SEMINAR #52

CASE 8

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

Clinical history: The patient is a 30 year-old lady with a long history of breast lump that increased in size during the past few months.

Gross: The specimen shows a 3 cm, lobulated mass having a fasciculated cut surface. No necrotic or hemorrhagic features are noted on gross inspection.

Microscopic description: This is basically a complex fibroepithelial lesion with orderly admixed hyperplastic tubuloglandular units with apical snouts set against a cellular, spindle and pleomorphic stromal component. There seems to be a fair proportion between the epithelial and stromal component. The latter have bizarre or irregular multiple nuclei with uneven chromatin and often prominent nucleoli. There are scattered mitoses, some atypical. Mitotic figures range from 2 to 4 per 10 HPF. The mitotic rate evaluated by means of the MIB-1 antibody is comparable. Immuno is not specific. Stains are positive where they are expected to be (epithelial units are +ve for keratins). The stromal cells are negative for most antibodies (including keratins and muscle markers) except diffuse CD34. Complete excision with adequate clear margins has been achieved.

Diagnosis: Cellular fibroepithelial tumor with malignant stroma (? Adenosarcoma; ? atypical phylloides tumor)

Comment: I do not have a good name for this tumor. Clearly, it belongs to the family of cellular fibroadenoma/fibroepithelial lesions, but nuclear atypia of the mesenchymal component is "too much" even for the most bizarre example of fibroadenoma. Likewise, it does not have convincing features for either phyllodes tumor or periductal stromal tumor. I reviewed this case with Janez Lamovec, who has agreed with this assessment although a precise label is difficult to choose. Likely, the patient does not need additional surgical therapy.

AMR SEMINAR #52

CASE 9

Contributed by: Masaharu Fukunaga, M.D. (S06-2838-A2)

History: A 47-year-old, gravida 2, para 2, Japanese woman presented with abnormal vaginal bleeding and a PAP of the uterine cervix was positive (adenocarcinoma, most likely). A total abdominal hysterectomy, bilateral salpingo-oophorectomy and lymph node dissections were performed. Macroscopically, there was a circumscribed yellowish white mass measuring 30 mm in greatest diameter in the uterine cervix.

Immunohistochemical studies: CAM 5.2, CK 7, MNF 116: +. CK20:-

Diagnosis: Papillary squamotransitional cell carcinoma of the uterine cervix.

Histology and Comments: The tumor consisted of predominantly a papillary proliferation of urothelial cell-like cells with fibrovascular cores, resembling urothelial cell carcinoma, grade 2 or 3. Features of squamous cell carcinoma and prominent lymphatic invasions were observed in the deeper portion of the tumor. Other slides showed the endometrial extension of the tumor, bilateral ovarian and lymph node metastasis. There would be diagnostic problems if only surface of the lesion was taken for the biopsy. Squamotransitional carcinoma is listed in the uterine cancer in the WHO classification. Squamotransitional carcinoma of the uterine cervix is substantially identical to squamous cell carcinoma in the many aspects, including immunoprofiles, HPT type 16, chromosomal and molecular analyses. There is no relationship between the tumor and transitional cell metaplasia. The biological behavior of this cancer, especially difference between this type of tumor, papillary squamous cell carcinoma and pure transitional cell carcinoma, has not been understood well. I would very much appreciate hearing from you regarding your diagnosis.

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AMR SEMINAR #52

CASE 10

Contributed by: Thomas Krausz, M.D.

History: A 46 year-old female presented with abdominal pain six month ago. During cholecystectomy, peritoneal "implants" were biopsied which were diagnosed as well-differentiated papillary mesothelioma. A few weeks later the patient underwent a hysterectomy bilateral salpingo-oophorectomy, omentectomy and removal of several peritoneal nodules. There were nodules on both the parietal and visceral peritoneum, omentum, and on the sigmoid colon. The nodules measured between 0.4 – 1.2 cm.

Pathology: The submitted sections (A and B) represent two different omental nodules. These and all the other nodules show mesothelial proliferations with extensive papillary growth pattern, but there are also tubulopapillary and solid areas (section B). Nuclear grade is low and nucleoli are not prominent. Mitotic figures are very rare. A focus of convincing superficial infiltration to adipose tissue was observed in one block (not submitted). Immunohistochemical study confirmed mesothelial lineage.

Preferred Diagnosis: Epithelioid malignant mesothelioma, low nuclear grade, with prominent papillary pattern.

Comments: This is a consult case with a referral diagnosis of well-differentiated papillary mesothelioma, which was taken by the oncologist to mean a benign disease requiring no further therapy. The prominent papillary growth pattern combined with low nuclear grade, less than one mitosis/10 HPFs and absence of convincing invasion in most blocks, can cause hesitation in making a malignant diagnosis. The mesothelial proliferation clearly does not meet the histologic criteria of a benign papillary mesothelioma, and we can argue in view of the architectural complexity with branching tubules, cords and solid areas especially on slide B whether it still fits within the spectrum of well-differentiated papillary mesothelioma (I do not think so). Dr. Rosai discusses well-differentiated papillary mesothelioma under the heading of malignant mesothelioma.

Historically, the term "benign papillary mesothelioma" was limited to incidental, small solitary lesions with broad fibrovascular cores lined by a monolayer of bland mesothelial cells. In subsequent literature, the "benign papillary mesothelioma" term was swallowed by "well-differentiated papillary mesothelioma" with broadened histologic spectrum including lesions with solid areas. Some pathologists even accepted superficial invasion within the spectrum. This group of mesothelial tumors was thought to be an indolent condition, which does not require further treatment. However, subsequently it became clear that some of these did indeed behave in a malignant fashion over a variable period of time, which is not surprising in view of the expanded histologic spectrum.

I agree with Dr. Rosai that the only lesion that can confidently be diagnosed as benign is one that fulfills the original criteria for "benign papillary mesothelioma". All other lesions are potentially malignant, albeit with a variable course. Although repeatedly mentioned in the older literature that no histologic parameters could reliably predict behavior of epithelioid malignant mesothelioma, recent studies suggest that nuclear grade, mitotic activity and complete cytoreductive surgery are helpful in determining prognosis of peritoneal mesothelioma.

The reason for submitting this case is to see how the members would classify these lesions. Would you diagnose this as a well-differentiated papillary mesothelioma or a malignant mesothelioma, epithelioid type with prominent papillary pattern? Would your oncologist understand the malignant potential of some of the former or would they consider it a relatively benign disease requiring no further treatment? Are we ready, similarly to the classification of a number of other neoplasms, to adopt a borderline/intermediate category in the classification of mesothelial tumors?

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AMR SEMINAR #52

CASE 11

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

Clinical Findings: A 66-year-old female patient developed an indurated subcutaneous lesion on the right hip. Clinically, a soft tissue neoplasm was suspected and the lesion was marginally excised. Grossly, a 9 x 5 x 5.5 cm specimen was seen.

Histological Findings: Histologically, a mixed dermal infiltrate with fibrosis and increase of vessels is seen, and in the subcutis a lobular as well as septal cellular infiltrate with fibrosis is noted. The cellular infiltrate contains numerous CD20 positive B-cells, a lower number of CD2 positive T-cells, and numerous plasma cells. The number of CD30 and CD56 positive cells is not increased. The fibrotic stroma contains numerous vessels and ASMA-positive stromal myofibroblasts. Interestingly, small clusters of CD123 positive cells are present, whereas the number of Foxp3 and CD25 positive cells is decreased.

Diagnosis: Lupus panniculitis (Lupus erythematosus profundus).

Comment: This case, which came to us in consultation with the diagnosis of inflammatory liposarcoma, represents in our opinion an unusual example of tumour-like lupus panniculitis. Lupus panniculitis represents a chronic and recurrent panniculitis with predilection for the proximal extremities, the trunk, and the back, and patients complain about subcutaneous nodules or plaques, that tend to be large and painful. Histologically, a prominent lymphocytic infiltrate of the subcutis with paraseptal lymphoid follicles and plasma cells is seen, and myxohyaline as well as sclerotic changes may be present. Interestingly, and this is seen in all forms of lupus erythematoses, an increase of CD123 positive cells is noted whereas the number of CD25 and Foxp3 positive cells is reduced. CD25 and Foxp3 positive cells represent regulatory T-cells (so-called T-regs) and are able to regulate the immune system by inhibition of autoreactive T-cells. These regulatory cells play a key role in the maintenance of immunologic self-tolerance and negative control of a variety of physiological and pathological immune responses. Foxp3 represents a transcription factor and Foxp3 positive cells act as immunosuppressive cells. Complete depletion of Foxp3 expressing natural Tregs activates self reactive T-clones, including severe autoimmune and inflammatory disorders. As a consequence, the number of these regulatory T-cells is reduced in a number of autoimmune disorders, including lupus erythematoses. In contrast subcutaneous panniculitis-like T-cell lymphoma is composed of atypical T-cells with enlarged and hyperchromatic nuclei, and characteristically a rimming of neoplastic cells surrounding individual fat cells is seen.

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AMR SEMINAR #52

CASE 12

Contributed by: Elizabeth Montgomery, M.D.

History: A 38 year old woman with a neck mass impinging on the base of her skull.

Diagnosis: Giant cell angiofibroma (Giant cell rich solitary fibrous tumor).

Comment: The lesion featured spindled cells, haphazard collagen, a "hemangiopericytoma"-type vascular pattern, and many giant cells. On immunohistochemical stains, the neoplasm was immunoreactive for CD34 but not for actin, desmin, and S100. This case was not a particular diagnostic problem, and this entity is certainly well-known to the members of this group (and first described by one of them). It is amazing how much we have all learned about lesions in the SFT and HPC families in the last fifteen years. This particular neoplasm was "shelled out" in December 2006 by one of our head and neck surgeons and there has been no recurrence thus far, although 9 months is not precisely long term follow-up.

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AMR SEMINAR #52

CASE 13

Contributed by: Giuseppe Pelosi, M.D.

Patient's history: A 76-year-old Caucasian man, former smoker since 30 years (previously he smoked 30 cigarettes/day for at least 20 years), underwent left upper lobectomy for Aspergillus infection (fungus ball) in 1980. The patient experienced hemoptysis in 2003, when a granulomatous inflammation was found in the left main bronchus (likely related to the previous surgery) that was treated with LASER therapy. In May 2007, the patient began to complain of hemoptysis again and a chest X-ray examination showed a huge tumor mass in the right upper lobe, measuring 6-7 cm in diameter. A total body CT scan investigation confirmed the presence of this tumor mass in the right upper lobe, sized 67x48x50 mm, which compressed the lobar bronchus and apparently infiltrated the azygos vein but was not associated with pleural effusion or distant metastases. As PET scan examination did not reveal distant metastases, a right upper lobectomy with a complete hilar-mediastinal lymphadenectomy was performed at the end of May 2007. The postoperative clinical course was uneventful, and the patient was discharged ten days later in good general conditions. The patient's past history included diabetes mellitus, urolithiasis, polyp of the vocal cords, cataract, subphrenic abscess after right pneumothorax and anal fissures.

Gross pathology: Tumor measured 7 cm in its greatest dimension and was located in the pulmonary lobe, attained the visceral pleura but did not infiltrate the azygos vein. Cut section showed areas of necrosis and hemorrhage with friable tissue.

Histologic Findings: Histopathologic examination revealed a morphologically biphasic tumor composed of 1) a high-grade neuroendocrine carcinoma component arranged in nests, trabeculae or solid aggregates, sometimes palisading, and supplied with round, ovoid or spindled nuclei, finely granular chromatin, inconspicuous nucleoli and a variable amount of eosinophilic to fairly clear cytoplasm resembling small-cell carcinoma, and 2) a mesenchyma-like spindle to pleomorphic cell component with abundant collagen deposition resembling high-grade sarcoma. The two components were intimately intermingled with each other throughout the tumor mass, but a slight prevalence of the sarcoma-like component was noted (about 55-60% of the entire tumor mass).

The immunohistochemical study revealed a strong and diffuse positivity for cytokeratins (AE1-AE3) in the epithelial-like component, with either cytoplasmic or paranuclear dot-like decoration, and for CD56 in all tumor cells, and a more variable immunoreactivity for S-100 protein, GFAP, synaptophysin, sarcomeric actin, neurofilaments, TTF-1 and CD10, whereas immunostaining for smooth-muscle actin, CD10, calponin, caldesmon, CD10 and CD56 was found to variable extent in the mesenchymal-like spindle cell component. Remarkably, a co-expression of cytokeratins and myogenin was localized in the same aggregates of tumors cells of epithelial type (with a minor contribution of desmin immunostaining that was only seen in scattered tumor cells inside these aggregates), suggesting the occurrence of a dipartite differentiation in epithelial-like tumor cells. Proliferative activity as evaluated with Ki-67 immunoreactivity showed greater amounts of nuclear stained tumor cells in the epithelial-like component (with labeling index being 80 to 90%) than in the sarcoma-like spindle cell population (30 to 40%). Finally, p53 was detected in most tumors cells of both components as a strong nuclear decoration of immunostaining. Pathological examination showed that the tumor did not invade the visceral pleura or the 3 cm-long fragment of azygos vein, but colonized a peribronchial lymph node with the appearance of epithelial-type small cells (out of a total of 51 excised peribronchial, hilar and mediastinal lymph nodes). Final tumor staging was pT2N1M0. I am performing immunohistochemical reactions for myogenin, cytokeratins and desmin in the metastatic lymph node in order to ascertain whether tumor cells shared the same concurrent differentiation as the primary. Currently, the patient is undergoing adjuvant chemotherapy; he is alive and well with no sign of metastatic disease (even though the follow-up time is very short).

Electron microscopy: A detailed electron microscopy study is currently in progress in order to best characterize the unusual findings of this neoplasm. Preliminary data, however, indicate that the spindle cell component exhibits myofibroblastic differentiation with huge deposition of collagen fibers, whereas the epithelial cell-like component shows neuroendocrine epithelial differentiation with paranuclear cytokeratin filaments and dense-core neurosecretory-type granules and, less frequently, bundles of contractile filaments containing abortive Z bands reminiscent of skeletal muscle differentiation. Sometimes, tumor cells seem to show a dipartite differentiation with concurrent rhabdomyoblastic and neuroendocrine differentiation, this representing the ultrastructural counterpart of the immunohistochemical findings of co-localized cytokeratins and myogenin (less constantly desmin) in the same tumor cell aggregates.

Diagnosis: I feel that a diagnosis of combined small-cell carcinoma with skeletal muscle differentiation and spindle cell sarcoma component of myofibroblastic type may be suggested for this case. I wonder if other members of AMR have ever seen similar cases of combined small-cell carcinoma of the lung in their diagnostic practice, and if they would be interested in collecting these cases for publishing a clinicopathologic series.

Discussion: The combined small-cell carcinoma variant makes up about 10 to 15% of all small cell carcinomas of the lung. It refers to the variable admixture of small-cell and non-small cell carcinoma elements, the latter usually including squamous cell carcinoma, adenocarcinoma and/or large-cell carcinoma¹, and much more uncommonly spindle cell^{2,3} or giant cell carcinoma^{4,5}. Other exceedingly rare combinations in the theme of neuroendocrine carcinomas of the lung include associations of atypical carcinoid and rhabdomyosarcoma⁶, small cell carcinoma plus adenocarcinoma and spindle-shaped cell tumor⁷, small cell carcinoma plus squamous cell carcinoma and spindle cell carcinoma⁸, small cell carcinoma plus sarcomatoid carcinoma with either spindle cell or giant cell carcinoma⁹, and carcinoid and adenocarcinoma^{10,11}. Moreover, occurrence of small cell carcinoma with skeletal muscle differentiation has been described in the larynx¹², as well as in the skin, nasal cavity and urinary bladder¹³, and combination of high-grade neuroendocrine carcinoma and alveolar rhabdomyosarcoma is also on record in the anorectal junction¹⁴.

Although intimate intermingling of small cell carcinoma elements with scattered rhabdomyoblastic cells¹³ and even tripartite differentiation in individual cells with concurrent epidermoid, glandular and neuroendocrine features¹⁵ or dipartite differentiation with rhabdomyogenous and cytokeratin expression within the same mesenchymal tumor cells of carcinosarcomas¹⁶ have been described in the literature, the current case is worth of mention because it is dealing with dipartite components of small cell carcinoma and rhabdomyosarcoma within the same tumor cells coexisting with spindle cell sarcoma/carcinoma, probably as a reflection of the plasticity of a common protoepithelial stem cell. This assumption is in keeping with the general contention that the sarcomatous component occurring in lung sarcomatoid carcinomas is derived from carcinoma elements according to a process of sarcomatous metaplasia rather than to be true collision tumors¹⁷. In fact, it has been demonstrated that additional genetic alterations as determined by microdissection-based allelotyping may be found in the mesenchymal component of sarcomatoid carcinomas of the lung, which were lacking in the epithelial one, suggesting mesenchymal transformation during the progression of epithelial carcinogenesis¹⁷. In this respect, it is not surprising that the spindle cell component of our case did not exhibit any epithelial or rhabdomyogenous differentiation, probably as a result of complete myofibroblastic/smooth muscle transdifferentiation of carcinomatous cells or early divergence during the progression of the same ancestor lesion. Mutation analysis for p53 (exon 5 to 8) on microdissected tissue containing all the different lineages of this tumor is currently in progress in our laboratory to get more information on the histogenetic relationships among these different phenotypic components, in particular regarding clonality.

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AMR SEMINAR #52

CASE 14

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

Clinical History: A 44-year-old man presented with loss of strength and speech alterations of several weeks' evolution. Brain magnetic resonance imaging disclosed a 4x5x5-cm, expansive, but circumscribed lesion in the left frontoparietal region, which was hypo- and isodense with considerable contrast uptake due to surrounding edema. The lesion was removed.

Pathologic Findings: A round, well-delimited 5.5x4x3.5-cm tumor mass was remitted to the laboratory. On cross section, it showed hemorrhagic and cystic areas. The remaining tissue had an elastic consistency, pinkish and grayish color, and white nodular areas. Microscopy revealed a pleomorphic and spindle cell proliferation with large necrotic areas and well-defined borders relative to the brain parenchyma. Some areas showed a marked vascular pattern and frequent osteoclastic giant cells.

Immunohistochemistry:

Positive: vimentin, Cd99 (focal), TTF1 (20% and weak), CD10 (focal and at the periphery)

Negative: keratins (CAM 5,2; CK 5,7,7,18,14; EMA; p63; protein S100; HMB45; smooth muscle actin; GFAP)

Diagnosis: Metastasis of sarcoma (see comments).

Follow-up: Four months later, a 4x3-cm mass was detected in the patient's right leg and at the level of the right cardiac atrium. Both tumors were removed and morphological characteristics similar to the brain mass were observed in the leg mass and a large part of the cardiac mass. Notably, areas of bone formation were very evident in the atrial mass, which even showed chondroid differentiation.

Comments: On the basis of the morphological and immunophenotypic characteristics of the brain mass, no specific diagnosis could be established. Once gliosarcomas and sarcomatoid carcinomas had been ruled out, we contemplated the possibility of metastasis of malignant fibrohistiocytic tumor or synovial sarcoma, but a FISH study of synovial translocation was negative. Finally, based on the osseous differentiation in the cardiac tumor, we were inclined toward an osteosarcoma. In fact, reviewing the slides after the diagnosis of the heart tumor, a few areas with some osteoblastic appearance could be observed.

I'm sending the case because of the difficulty we had in establishing a final diagnosis. The biological evolution is also very infrequent in a supposed primary cardiac tumor debuting with metastases in the leg and brain. The pattern of osteoclast-type giant cells bordering pseudo cavities has, however, been described in osteosarcomas and in other sarcomas. Later, we found out that in the patient's prior radiological studies, calcifications had been seen in the cardiac area. So, I await your comments.

AMR SEMINAR #52

CASE 15

Contributed by: Joshua Sickel, M.D.

Clinical history: The patient was a 55 year-old woman who was recently brought to our emergency department with CPR in progress. In March 2007, she started developing increasing numbness and weakness of the lateral left leg, with subsequent left foot drop. She also complained of some numbness and tingling in both hands. She eventually was evaluated by a neurologist, four days prior to admission, who thought these symptoms were clinically compatible with Guillain-Barré syndrome. Four days later, when the visiting nurse went to the patient's home to administer the first treatment of immunoglobulin, the patient was found to be in respiratory distress. During a brief call to the neurologist, the patient stopped breathing and collapsed. The nurse called 911 and started CPR. Paramedics arrived, intubated the patient, continued CPR and brought the patient to the emergency room. Past medical history was significant for asthma, mitral valve prolapse and hypertension. She had previous sinus surgery years ago. Despite aggressive resuscitative measures, the patient was subsequently pronounced dead several minutes after admission. An autopsy was requested by the treating physicians. Sections of the heart are submitted for your examination.

Gross findings: The heart was enlarged and dilated, with moderate coronary atherosclerosis. Both lungs were focally consolidated and heavy. Abdominal organs were generally unremarkable.

Microscopic findings: Histologic sections show massive, transmural infiltration of the myocardium by abundant eosinophils, with extension into epicardial fat. Myocardium shows patchy coagulative necrosis, as well as subendocardial fibrosis. A striking necrotizing vasculitis (small to medium-sized arteries and veins) is present within the myocardium and epicardial tissues. Scattered "allergic" granulomas, consisting of palisading histiocytes surrounding necrotic eosinophils and fibrin, are present. Preliminary sections from the lung show typical features of eosinophilic pneumonia with associated vasculitis and allergic granuloma formation. Sections from the liver, kidney and adrenal also show focal vasculitis with eosinophilic infiltrates.

Diagnosis: Necrotizing eosinophilic myocarditis with associated vasculitis, consistent with Churg-Strauss syndrome.

Discussion: This is a fascinating case because of the unusually fulminant clinical course and the fact that the diagnosis of Churg-Strauss syndrome (CSS) was completely unexpected. Interestingly, a peripheral blood smear was retrieved from the initial neurological workup, which showed a 25% eosinophil count. There are scattered reports in the literature of CSS simulating Guillain-Barré syndrome. This case is a reminder that neurologic involvement in CSS is very common, occurring in close to 70% of patients. Mononeuritis multiplex (often affecting the common peroneal nerve) is the most common manifestation in most reported series. Unfortunately, the delay in diagnosis had catastrophic consequences for our patient.

The cause of death in CSS is most commonly related to severe cardiac involvement, typically manifesting as heart failure or myocardial infarction. Less common causes of mortality include renal failure, cerebral hemorrhage and GI perforation.

In 1990, the American College of Rheumatology proposed a traditional format classification for CSS, comprised of the following: 1) asthma, 2) eosinophil count greater than 10%, 3) mono- or polyneuropathy, 4) non-fixed radiographic pulmonary infiltrates, 5) paranasal sinus abnormalities and 6) biopsy containing a blood vessel with extra-vascular eosinophils. If four of these criteria are met, the diagnosis can be established in 85% of cases, with a specificity of 99.7%.

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AMR SEMINAR #52

CASE 16

Contributed by: Dominic Spagnolo, M.D.
(Accession Q07B28236B; courtesy of Dr. W. Robinson)

Case History: A 17 year-old female presented with irregular PV bleeding for 14 months and right iliac fossa pain. Taking combined oral contraceptives. No features to suggest estrogenic or androgenic hyperfunction. Pelvic ultrasound showed a 24mm right ovarian cyst.

Macroscopic specimen: An ovoid pale orange nodule was removed measuring 22x15x10mm.

Microscopic findings: Distinctly pseudolobulated neoplasm; islands of large, round cells having vacuolated or luteinized cytoplasm; more irregular areas of plump spindle stromal cells; prominent, thin-walled branching vessels; zones of denser fibrous stroma. (Myxoid areas were present in other slides).

Immunostaining: Spindly and round cells: vimentin+, alpha-smooth muscle actin+ (round cells +/-), pan-muscle actin+ (spindle cells only), CD99+ (round cells mainly), PR+.

Round cells: Cam 5.2+, MNF116+, AE1/AE3 patchy +; calretinin+, melan A+, inhibin+ (v. few spindle cells+).

Negative: ER-, S100-, desmin-, EMA-.

Diagnosis: Sclerosing stromal tumor of the ovary.

Comments: We don't see these very often, and I hope those who encounter these more frequently aren't too bored with the case. I have not encountered a case with so many, large vacuolated or luteinized cells. These are uncommon (<5%) benign stromal tumors mostly occurring in the second and third decades. Rare bilateral cases are described. They are typically non-functioning, though functioning estrogenic and androgenic cases are described. Meig's syndrome has been associated in some cases. The morphology is distinctive enough to allow separation from the fibroma-thecoma group, particularly the lobulation and stag-horn vessels. Probably the most important issue is not to confuse these with Krukenberg tumors in cases where signet ring cells are prominent. The vasculature and edema may be related to the expression of VEGF which has been demonstrated in some tumors.

AMR SEMINAR #52

CASE 17

Contributed by: Saul Suster, M.D. (courtesy of Gabriel Groisman, M.D., Department of Pathology, Hillel-Yaffe Medical Center, Haifa, Israel).

Clinical History: A 63-year old woman was seen for an 8 cm. mass adherent to the serosa of the sigmoid colon. The mass showed gray, firm solid areas admixed with cystic spaces containing thick, gelatinous material. The patient had undergone a TAH+BSO for simple cysts of the ovary three months previously. There was no other significant past history.

Pathologic Findings: The tumor is composed of sheets of round to polygonal epithelioid cells with abundant eosinophilic cytoplasm and round, centrally placed nuclei. The nuclei show frequent longitudinal nuclear grooves, nuclear indentations, and occasional rare intranuclear pseudoinclusions. There is no evidence of mitotic activity. The cytoplasm of the cells is rather sharply delimited, with crisp cytoplasmic borders imparting the cells with a somewhat epidermoid appearance. The tumor cells show a striking syncytial arrangement on scanning magnification and are separated by regular islands of fibrovascular stroma with scattered inflammatory elements. Peripheral areas of the lesion show marked stromal sclerosis with irregular strands and cords of tumor cells circumscribing globs of densely eosinophilic material. The tumor appears to be well circumscribed and surrounded by a thin fibrous capsule.

Special stains: A large battery of special stains was performed by the referring pathologist as follows:

Positive stains: Diffuse cytoplasmic stainin was obtained with CK22 (wide spectrum), CK7, CK5/6, mesothelin, bcl-2, claudin-1, D2-40, and S-100 protein. Focal staining was observed with calretinin (~ 40% of cells, cytoplasmic), EMA (20-30% of cells, membranous and cytoplasmic), CA-125 (focal peripheral stain), WT1 (focally in the periphery), and Ki-67 (~5% of cells).

Negative stains: Inhibin, synaptophysin, SMA, desmin, ER, PR, CD34, CEA, CD15, CD99, Melan-A, E-cadherin, c-kit, CA19.9, p63, TTF1 and vimentin (done twice!).

Diagnosis: I don't know – HELP!

Comment: This case was sent to me in consultation with the question of whether this could represent some unusual variant of peritoneal mesothelioma. My reply was that I didn't think so (as I have never seen a mesothelioma that looked quite like this). But I was not able to come up with any other good ideas.

I am sharing this case with the club members out of sheer frustration and with curiosity in the hope that one of you can tell me what this tumor is! This tumor reminds me somewhat of a thymoma with pseudosarcomatous stroma ("metaplastic thymoma" of the WHO), but this is quite far from the thymus.....

Any thoughts??????????

Many thanks!

AMR SEMINAR #52

QUIZ CASE 1

Contributed by: Saul Suster, M.D.

(Case contributed by Dr. Vladimir Osipof, Medical College of Wisconsin).

Clinical History: A 55-year old woman with no significant past history was seen for a 5 cm. soft tissue mass in her right upper arm of 8 months evolution. The mass had recently started to grow rapidly. The mass was superficially located in the subcutaneous tissue beneath the skin. The lesion was excised. The cut surface showed a well-circumscribed, tan white fleshy, homogenous tissue with a small 1 cm eccentric area of discoloration and hemorrhage (see gross image). There is no other evidence of tumor elsewhere on thorough imaging studies.

On pathologic examination, three distinct histologic patterns were identified. The majority of the tumor showed a bland-appearing spindle cell proliferation with focally prominent storiform pattern and scattered mitoses that demonstrated at the edges a lace-like pattern of infiltration of the surrounding adipose tissue (slide A). Certain areas of the tumor, however, showed increased cellularity displaying a tight herringbone pattern with more frequent mitoses (slide B). Sections taken from the eccentric area of discoloration showed foci of immature woven bone circumscribed by the fascicular spindle cell proliferation (slide C).

Immunohistochemical stains were positive in many of the spindle cells for CD34 and CD99. All other markers including S100, desmin, SMA, cytokeratin, H-caldesmon, etc were negative.

Diagnostic opinions ranged from fibrosarcomatous transformation of DFSP with metaplastic bone (or focal "osseous differentiation") to extraskeletal osteosarcoma. The oncologists indicated that if the final diagnosis was extraskeletal osteosarcoma they would treat the patient much more aggressively than if it was diagnosed as fibrosarcomatous transformation of DFSP.