AMR Seminar #55 – Short Summary of Cases:

Case 1: Patient with a subcutaneous mass in the buttock at the site of injection 20 years ago.

Case 2: F.71 with soft tissue mass in left iliac space.

Case 3: F.52 with a pubic soft tissue mass.

Case 4: M.54 with a renal mass with solid and cystic components.

Case 5: F.56 with a 5.0 x 4.5 x 3.5 cm spherical tumor attached to the jejunum.

Case 6: F.46 with painful, large soft tissue mass in her thigh.

Case 7: M.24 with anal atresia and a long history of complications and a colostomy. During the last procedure remnants of the rectum were excised and he had drainage of a presacral abscesses.

Case 8: F.26 with fever of one week duration, cervical lymphadenopathy and left enlarged tonsil.

Case 9: F.47 with 2 cm. nodule at the ventral base of the tongue.

Case 10: M.56 developed pain, swelling and bruising in the flexor surface of the forearm at the site of a surgically constructed arteriovenous fistula placed for hemodialysis.

Case 11: M.41 presented with a 2-year history of firm irregular scrotal swelling.

Case 12: F.31 presented with a tumor of the left iliac bone.

Case 13: M.32 with large abdominal and hepatic masses.

Case 14: M.80 with an anterior mediastinal mass.

Case 15: F.86 presented with a large ulcerated tumor of the skin and subcutaneous tissue of breast.

Case 16: F.56 with tumor in the adrenal gland.

Case 17: M.52 with a 2 cm in diameter tumor of the hypophysis.

Case 18: M.31 with large mass attached to small bowel.

Case 19: M.81 presented with a right retroperitoneal mass on CT scan.

Case 20: F.57 was examined for a large palpable thyroid nodule of her right lobe.

Case 21: M.53 who presented with left distal tibia pain with no history of trauma. A tumor was found.

Case 22: F.56 presented with a 6-month history of increasing left leg pain. A tumor in the left tibia was found.

Case 23: M.47 with hepatosplenomegaly. Splenectomy was performed.

Quiz Case 1: M.8 with mural tumor in the gastric wall.

Quiz Case 2: Elderly man with 2 cm. coin lesion in the lung (no slides; web-images only).

Quiz Case 3: Man with periapical abscess and maxillary osteomyelitis (no slides; web-images only).

Quiz Case 4: F.63 with tumor of the thyroid involving surrounding soft tissue.

AMR SEMINAR #55
CASE 1

Contributed by: Philip Allen, M.D., Flinders Medical Centre, South Australia (Case #FMC 08/S03050)

History: The patient presented with a recently growing mass in the subcutis of the left buttock, and a high CRP and white cell count. A CT scan showed a lesion near the left hip and the differential diagnosis on radiological grounds was abscess versus haematoma. No disseminated disease was identified. At surgery, the mass was solid and was arising superficial to the gluteus maximus and appeared to be a tumour rather than an abscess. Additional information from the patient's GP revealed that the patient had injections into the buttock at the tumor site more than 20 years ago and that a firm nodule has been present there ever since. The nature of the injections is not known. Over the two weeks preceding surgery, the nodule changed and a CT scan showed a mass suspicious of an abscess or hematoma. The specimen consisted of a firm, well circumscribed multinodular mass measuring 130 x 70 x 85 mm. with adherent fat and some skeletal muscle. There was no overlying skin. On cutting the specimen, there were three contiguous adherent nodules, the largest 100 x 50 x 50 mm, the smallest 20 mm in diameter, both focally calcified and centrally necrotic, and the third, a fleshy haemorrhagic mass 55 x 25 x 25.

Diagnosis: Injection site high grade angiosarcoma, subcutis, left buttock region, associated with hemosiderin and large calcified masses of old fat necrosis, presumably secondary to subcutaneous iron injections 20 years previously.

Caption for Illustration: The cut surface of the specimen showing three contiguous masses. On the left, there are two well circumscribed, mutually adherent yellowish necrotic nodules the largest measuring 50 in diameter and 100 mm long; The smaller at the top of the photo, is a spherical nodule measuring 20 mm in diameter. They both exhibit white fibrous capsules as well as several small white fleshy areas in the central yellow necrotic areas. Calcification was palpable in each of these two masses. On the right of the photograph, there is a fleshy haemorrhagic mass measuring approximately 55 x 20 x 25 mm with an entirely different appearance. The thick white capsule is impregnated with brownish yellow nodules.

Sections of the fleshy haemorrhagic mass showed a high-grade angiosarcoma with numerous mitoses (approximately 20 per 10 high power fields), including atypical forms, but no necrosis. However, the proliferative index, as assessed by Mib-1 staining, is estimated at only around 1%. The tumour cells stained positively for the endothelial markers CD31 and to a lesser extent, for factor VIII, but not for CD34. Very occasional malignant cells were positive for the epithelial markers, AE1/AE3 and Cam 5.2, an occasional finding in angiosarcomas, but were negative for melanoma markers. The cells were also positive for the mesenchymal marker, vimentin. The fleshy tumour was located in the subcutaneous fat, superficial to the few voluntary muscle fibres at the edges of the sections and was surrounded for the most part by a capsule of dense fibrous tissue which was heavily infiltrated by hemosiderophages. Hemosiderophages were very scanty within the fleshy tumour, except for a few areas where fibrous septae in continuity with the capsule divided it into poorly defined nodules. Sections of the yellow necrotic nodules (blocks A, D and E) showed a fibrous capsule with scattered hemosiderophages, foamy macrophages, cholesterol clefts and clumps of calcification, some of which was iron positive, surrounding necrotic material with numerous cholesterol clefts as well as the ghost outlines of focally calcified necrotic fat cells with thick eosinophilic membranous undulating walls (membranous fat necrosis), yellowish-brown pigment, presumably bilirubin, and a few groups of angiosarcoma cells at the periphery. The hemosiderophages also extended out into the surrounding fat.

COMMENT: There seems to be little doubt that this high grade angiosarcoma arose at an injection site and that the injected material was probably an iron product. The patient had indicated that there was a mass at the injection site(s) which had been stationary for a latent interval of approximately 20 years until some recent growth. The gross specimen consisted of two confluent calcified nodules of fat necrosis with heavy peripheral impregnation of hemosiderin, consistent with more than one injection into the area. The tumour had apparently arisen in a third contiguous mass which invaded parts of the nodules of fat necrosis.

Injection site sarcoma is well recognized in cats (1) but the evidence suggests that sarcomas arising in injection sites of iron compounds in humans are extremely rare (2), although sarcomas arising at prosthesis sites (3) and prosthetic vascular grafts (4) are perhaps less rare and are now well recognized. Nevertheless, there is no recorded history of injection of iron compounds in any of the 80 cases of angiosarcoma of soft tissue reported by the Kindbloms (4). The abstracts of the quoted articles, one of which includes prognostic details(4), are included below.

References:

1. Immunohistochemical detection of tumor suppressor gene p53 protein in feline injection site-associated sarcomas. Vet Pathol (United States), Mar 2001, 38(2) p236-8. Nambiar PR; Jackson ML; Ellis JA; Chelack BJ; Kidney BA; Haines DM.

ABSTRACT: Sarcomas associated with injection sites are a rare but important problem in cats. Immunohistochemical detection of p53 protein may correlate to mutation of the p53 tumor suppressor gene, a gene known to be important in oncogenesis. The expression of nuclear p53 protein in 40 feline injection site-associated sarcomas was examined by immunohistochemical staining. In 42.5% (17/40), tumor cell nuclei were stained darkly; in 20% (8/40), tumor cell nuclei were stained palely; and in 37.5% (15/40), tumor cell nuclei were unstained. Immunohistochemical detection of p53 protein in a proportion of injection site-associated sarcomas suggests that mutation of the p53 gene may play a role in the pathogenesis of these tumors.

2. Intramuscular injections of iron compounds and oncogenesis in man. BMJ 1978,1:683-685. Weinbren K, Salm R, Greenberg G.

SUMMARY AND CONCLUSIONS: To evaluate the evidence for iron compounds as local carcinogens in man, histological material and clinical reports have been reviewed in seven of the eight published cases of tumors developing at the site of intramuscular injections. The microscopical appearances suggested benign lesions in two cases and a variety of tumors in the other five. In only two cases (a rhabdomyosarcoma and a fibrosarcoma) was the interval between injections and tumour development longer than six years. Of the remaining three tumors, one was considered to be a rather slowly growing haemangiopericytoma (with an interval of two years), one appeared to be a subcutaneous lymphoma with no evidence of having arisen in the gluteal muscles, and one was a pleomorphic sarcoma with a possible five-year interval. Sarcomas induced experimentally by iron compounds differ in being less variable in type and in containing abundant iron-containing macrophages, which were negligible in these human tumors. Although the total number of patients who have received intramuscular injections of iron compounds is not known, the present findings, in contrast to experimental work, do not support the view that such treatment carries a strong risk of tumour development.

3. Prosthetic implant associated sarcomas: a case report emphasizing surface evaluation and spectroscopic trace metal analysis. Ann Diagn Pathol (United States), Feb 2003, 7(1) p35-46. Adams JE; Jaffe KA; Lemons JE; Siegal GP.

ABSTRACT: Advances with implantation of synthetic biomaterials in the setting of orthopedic surgery have clearly resulted in improvements in patient outcomes. However, all implants have been shown to have associated risks. For example, ionic and particulate debris from implants have been shown to engage in biological interactions with the native tissue, and have been associated with a wide range of metabolic, bacteriologic, immunologic, and oncogenic effects. The propensity of synthetic biomaterials to undergo degradation, producing an inflammatory reaction or other sequelae, has been well recognized. The use of porous implants, which allow for a greater interface area between native tissue and the prosthesis, may magnify the interaction between biologically active tissue and synthetic devices in some situations, giving rise to new and intriguing issues concerning biocorrosion and biocompatibility. In this article, we report the case of a high-grade conventional osteosarcoma occurring at the site of a modular porous-surfaced titanium and cobalt alloy total hip prosthesis 3 years after device implantation. Detailed spectroscopic trace metal analysis was performed and elevated levels of both vanadium and chromium, but not aluminum, nickel, or titanium were identified in the tumor. (Includes tabular literature review).

4. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol (United States), Jun 1998, 22(6) p683-97. Meis-Kindblom JM; Kindblom LG

ABSTRACT: The clinicopathologic, immunohistochemical, and ultrastructural features of soft tissue angiosarcomas are not well defined. Eighty cases of angiosarcoma that involved the deep subcutis, skeletal muscle, retroperitoneum, mesentery, and mediastinum are reported. The lesions occurred in 50 male and 30 female patients who were 5-97 years of age; the peak incidence was in the seventh decade of life. A variety of associated conditions were documented in 20 of these cases, including a history of other neoplasms (some irradiated), synthetic vessel grafts, heritable conditions, and prior trauma or surgery. The angiosarcomas occurred in the extremities (n = 43 cases), trunk (n = 28), and the head and neck (n = 9) regions, with the thigh and the retroperitoneum being the most common sites. They often were characterized as enlarging, painful masses of several weeks' duration and were occasionally associated with acute hemorrhage, anemia, or a coagulopathy. The tumors measured 1-15 cm in diameter (median 5 cm) and frequently were hemorrhagic and multinodular. There was a wide morphologic spectrum within and between cases, including areas similar to cavernous and capillary hemangioma, Dabska tumor, spindle cell and epithelioid hemangioendothelioma, various spindle cell sarcomas, or carcinoma. Histologically, epithelioid angiosarcoma was the most frequently observed pattern; 70% of cases had epithelioid cells that were arranged in nests, clusters, papillae, and gaping vascular channels. Hemorrhage tended to obscure the diagnosis in several cases and often was associated with papillary endothelial hyperplasia-like areas. All 42 cases studied immunohistochemically stained at least focally for Factor VIII-related antigen, and nearly all stained strongly for vimentin, which accentuated the endothelial cells and vessel lumen formation. CD34 antigen was detected in 74% of cases, BNH9 in 72%, and cytokeratins in 35%. Epithelial membrane antigen, S-100 protein, and HMB45 were not detected. Fifty-five percent of the tumors had intracytoplasmic aggregates of laminin. Immunostains for alpha-smooth muscle actin demonstrated a prominent pericytic component in several tumors (24%). Ki67 immunostains with MIB1 indicated high proliferative activity (> or =10%) in 72% of cases. p53 immunoreactivity (>20% nuclear staining) was observed in 20% of cases. Ultrastructural studies performed on poorly differentiated areas of 12 cases showed groups of cells, which were frequently epithelioid, surrounded by basal lamina, and closely associated with pericytes, along with intercellular and intracellular lumina with or without red blood cells. Whorls of abundant intermediate filaments, occasional tonofilamentlike structures, and pinocytotic vesicles also were noted. In contrast to the findings of others, Weibel-Palade bodies were not seen. Follow-up in 49 cases (61%) showed that 53% of patients were dead of disease at a median interval of 11 months, whereas 31% had no evidence of disease at a median interval of 46 months. The remaining patients were either alive with disease (14%) or alive but disease status was unknown (2%). There were local recurrences in 20% of cases and distant metastases in 49%, most frequently to the lungs, followed by the lymph nodes, soft tissues, bone, liver, and other sites. These results indicate that angiosarcoma of soft tissue is a high-grade sarcoma. Older patient age, tumor location in the retroperitoneum, and larger tumor size as well as detection of MIB1 in > or =10% of the tumor cell population were all associated with a poorer prognosis.

AMR SEMINAR #55
CASE 2

Contributed by: Carlos E. Bacchi, M.D.

Clinical History: In April, 2008, this 71-year-old white female had a history of well-tolerated anemia and presented with abdominal discomfort and pain. Physical examination revealed marked hepatomegaly and a large tumor mass that was palpated at the right iliac space. At surgical exploration, the surgeon described the presence of multiple nodules attached to the wall of stomach, small intestine, colon and gallbladder besides the presence of the large tumor in the iliac space. The H&E slides sent to the AMR slide seminar are from the tumor of the iliac space.

Pathology Findings: Microscopically, the mass-like lesion show scattered large atypical cells with trilinear hematopoietic elements, including megakaryocytes (actually, dysmorphic megakaryocytes). In addition, there was a predominantly myxoid and fibrotic stroma that is admixed with small amounts of mature adipose tissue. Immunohistochemistry study showed expression of factor VIII in the large atypical cells (megakaryocytes) and myeloperoxidase in the granulocytic lineage cells. Cytokeratin, S-100 protein and desmin/smooth muscle actin were all negative in the large atypical cell population.

Diagnosis: Sclerosing extramedullary hematopoietic tumor (SEMHT) associated with chronic idiopathic myelofibrosis.

Comments: After we contacted the physician with our diagnosis of SEMHT, we learned that the patient had undergone splenomegaly in 2004 due to a clinical diagnosis of hypersplenism with pathological diagnosis of myeloid metaplasia. The patient's bone marrow biopsy from 2004 revealed diffuse and extensive fibrosis with sinusoidal dilatation and clustering of dysmorphic megakaryocytes, identical to the ones seen in this lesion, which was consistent with chronic idiopathic myelofibrosis. The cytogenetic analyses showed normal karyotype (46XX); bcr-abl test was negative. Currently, the patient is being followed up for 8 months without any major symptoms. She is being treated with blood cell transfusions once every two weeks.

Chronic myeloproliferative disorders are clonal stem cell disorders characterized by the proliferation of one or more myeloid cell lines. These disorders include chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, and chronic idiopathic myelofibrosis or agnogenic myeloid metaplasia. Chronic idiopathic myelofibrosis, as in this case, is characterized by bone marrow fibrosis that is often associated with extramedullary hematopoietic tumor (EMH). SEMHT may be single or multiple and most commonly affects the peritoneal or retroperitoneal areas. They rarely occur in the breast, kidney, lymph node and skin.

I believe that SEMHT has already being presented at one of the AMR slide seminars in the past but as this type of lesion can be misinterpreted for several types of neoplasms, including Hodgkin lymphoma, myelolipoma and pleomorphic sarcomas, it is worthwhile to discuss this lesion once more.

References:

Kwon, Y., E. Yu, et al. (2004). Sclerosing extramedullary hematopoietic tumor involving lesser omentum and ligamentum teres in liver explant. Ann Diagn Pathol 8(4): 227-32.

Lane, J. E., A. N. Walker, et al. (2002). Cutaneous sclerosing extramedullary hematopoietic tumor in chronic myelogenous leukemia. J Cutan Pathol 29(10): 608-12.

Yang, X., T. Bhuiya, et al. (2002). Sclerosing extramedullary hematopoietic tumor. Ann Diagn Pathol 6(3): 183-7.

Remstein, E. D., P. J. Kurtin, et al. (2000). Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative disorders Am J Surg Pathol 24(1): 51-5.

AMR SEMINAR #55
CASE 3

Contributed by: Ira Bleiweiss, M.D.

Brief Clinical History: 52-year-old woman with pubic mass.

Case History: 52 year old woman with pubic mass- Yes, I said pubic. This mass measured 14.5 x 11 cm and weighed in at 518 grams. It was removed along with an axillary mass also measuring 14 x 14 cm and weighing 664 grams. Both were identical microscopically.

Diagnosis: Ectopic breast tissue (lots of it)

Comment: This is not a histologic challenge. I thought everyone might like something easy for a change. I send it only because of the clinical situation: This woman first came to our attention in 2000 when she had a 3.5 cm breast mass removed showing nodular pseudoangiomatous stromal hyperplasia (PASH). Then both of her breasts began to grow dramatically and, in the surgeon's words, grotesquely, to the point where she had severe back pain and was becoming debilitated. She then had bilateral simple mastectomies (weights: left 3700 grams, right 2900 grams) which, of course, showed the usual fibrocystic changes, normal breast, and areas of PASH, but not nodules of it. Three months later a 3 cm area of breast tissue was removed from her mons pubis. Seven years later she now has pubic and axillary breast tissue again removed. The slides you received are from her current surgical procedure and to me show relatively normal breast tissue containing perhaps fewer lobules than I would expect and the nonspecific PASH areas.

This woman has had extensive endocrinologic workups with every conceivable test coming out as normal, and we are mystified as to why she keeps growing breasts, at least along the milk line. Has anyone seen or heard of such a situation before?

AMR SEMINAR #55
CASE 4

Contributed by: John Chan, M.D. (Case #J98-08)

History: This 54-year-old man had a renal mass with solid and cystic components.

Diagnosis: Kidney – Tubulocystic carcinoma

Comment: This case illustrates the typical morphology of tubulocystic carcinoma, a recently characterized tumor type of the kidney. There are variable-sized tubules, some cystically dilated, separated by a hypocellular fibrous stroma. The lining cells are cuboidal, flat or hobnailed, with abundant eosinophilic granular cytoplasm and distinct nucleoli. In this case, there is also a minor component of papillary renal cell carcinoma (not included in the circulated slide). FISH studies show trisomy 17 but no trisomy 7, in both the tubulocystic carcinoma and papillary carcinoma components.

Tubulocystic carcinoma, an uncommon tumor, was previously considered a low grade collecting carcinoma. Recent studies have clearly shown that this is a distinctive tumor type of the kidney (and thus the list of renal cell neoplasms is getting longer and longer everyday……..). In the report of Yang et al, a proportion of cases have a component of papillary carcinoma like this case, suggesting perhaps a relationship with papillary carcinoma.

References

Yang XJ, et al. Tubulocystic carcinoma of the kidney: clinicopathologic and molecular characterization. Am J Surg Pathol 2008;32:177-187.

Amin MB, et al. Tubulocystic carcinoma of the kidney: clinicopathologic analysis of 31 cases of a distinctive rare subtype of renal cell carcinoma. Am J Surg Pathol [Epub ahead of print]

AMR SEMINAR #55
CASE 5

Contributed by: Kum Cooper, M.D.

Clinical History: This 5.0 x 4.5 x 3.5 cm spherical tumor was attached to the jejunum and removed en bloc with ileum and cecum from a 56-year-old woman.

February 2002
Significant past history: She presented with a (17.0 cm, mitotically active 20/10 HPF, large areas of necrosis) malignant GIST (CD117/CD34+) arising from the wall of the small bowel. The morphology was largely spindled with focal areas of epithelioid growth pattern.

March 2006
Recurrent malignant spindled GIST (7.0 cm, mitoses ~26/10 HPF, large areas of necrosis) with focal CD117 and diffuse CD34 immunoreactivity with sigmoid colon and small bowel resection. A second (1.8 cm) hyalinized, less cellular (spindled and epithelioid), minimally mitotic active tumor was strongly CD117 and CD34 positive. The second lesion was consistent with post-imatinib therapy.

November 2006
A soft tissue periumbilical tumor (3.0 cm) subcutaneous metastatic spindled malignant GIST (28 mitoses/10 HPF) was excised.

June 2008
Submitted slide from recurrent (5.0 cm) malignant GIST; status post imatinib; status post sunitinib. Diffuse CD117/CD34 positive; mitoses 16/10 HPF; areas of necrosis.

Diagnosis: Recurrent malignant GIST with diffuse rhabdoid morphology.

Discussion: Given the recent literature on morphological changes of post-therapy GIST, secondary mutations and heterologous differentiation in treated GIST (largely from our soft tissue experts in the AMR Club). I thought the rest of the members would enjoy the peculiar morphology of this case.

For an excellent referenced review on the subject, I would refer to Thomas Krausz's write-up from the Mexico City AMR Meeting in June 2008.

I look forward to comments from members.

AMR SEMINAR #55
CASE 6

Case contributed by: Ivan Damjanov, M.D.

Short History: A painful palpable mass in the thigh of an obese 46 year-old woman. Radiologic examination revealed an indistinctly demarcated soft tissue mass measuring 14x6x5 cm extending from the subcutaneous fat tissue into the muscle fascia. The MRI examination suggested that this inhomogeneous soft tissue mass is most likely an "inflammatory desmo-fibrous tumors" (whatever that was meant to be!). On frozen sections we saw fibrotic tissue replacing the fat with a lot of spindle cells that did not belong there, aggregates of lymphocytes and numerous scattered plasma cells. We could not exclude a neoplasm and thus the surgeon resected the lesion with 1-2 cm margins and the overlying skin.

On permanent sections we excluded the possibility of malignancy and concluded that this is an inflammatory lesion. We considered deep lupus erythematosus, but the patient was ANA negative. John Chan was kind to help us out with formulating the final diagnosis, for which we thank him. I was so impressed with his reasoning that I decided to quote directly from his e-mail:

The subcutaneous fat shows patchy fibrosis by strands of collagen fibers. Interspersed in the fat and in the fibrous areas are collections of plasma cells and lymphocytes. Plasma cells are also somewhat more abundant than the usual panniculitis. On going back to low power, there are paler or pink areas alternating with dark-staining aggregates of plasma cells -- this is a pattern I will always raise the possibility of Rosai-Dorfman disease. On closer analysis of the paler or fibrous areas, there are indeed large cells (not a lot) with round nuclei, vesicular chromatin, central nucleoli and an appreciable amount of pale cytoplasm, highly suggestive of Rosai-Dorfman histiocytes.

On immunostaining for S100, these cells are indeed highlighted -- the larger nuclei and the broad cell bodies with cell processes are well highlighted. Within the cytoplasm, there are some non-staining nuclei representing the phagocytosed cells.

Thus I believe a diagnosis of ROSAI-DORFMAN DISEASE can be substantiated. I believe this lesion has been there for quite some time, and thus some regressive changes have occurred, accompanied by a reduction in the number of diagnostic histiocytes.

Diagnosis: Rosai-Dorfman disease.

Epicrisis:
1. I learned a lot from this case courtesy of John Chan. In retrospect I thought that we did not diagnose it because the regressive changes partially masked the typical features of RDD. More importantly we did not even think of RDD- an S100 IHC stain would have sent us in the right direction (maybe!).
2. We "discovered" that RDD can occur in soft tissues.
3. Reading about this, I found out that several members of the AMR club have written about this topic. I hope that they will agree with the diagnosis and possibly add something else that was not mentioned above.

References:

1. Montgomery EA, Meis JM, Frizzera G. Rosai-Dorfman disease of soft tissue. Am J Surg Pathol. 1992, 16(2):122-9.

2. Bisceglia M, Spagnolo D, Galliani C, Fisher C, Suster S, Kazakov DV, Cooper K, Michal M. Tumoral, quasitumoral and pseudotumoral lesions of the superficial and somatic soft tissue: new entities and new variants of old entities recorded during the last 25 years. Part XII: appendix.
Pathologica. 2006;98(4):239-98.

3. Govender D, Chetty R. Inflammatory pseudotumour and Rosai-Dorfman disease of soft tissue: a histological continuum? J Clin Pathol. 1997;50(1):79-81.

4. Young PM, Kransdorf MJ, Temple HT, Mousavi F, Robinson PG. Rosai-Dorfman disease presenting as multiple soft tissue masses. Skeletal Radiol. 2005;34(10):665-9.

AMR SEMINAR #55
CASE 7

Contributed by: Otto Dietze, M.D.

Clinical History: A 24-year-old male patient with anal atresia and a long history of complications and a colostomy. Within the last procedure remnants of the rectum were excised and he had drainage of praesacral abscesses.

Histology: The remnants from the rectum show diffuse inflammatory changes with pronounced lymphoid hyperplasia. The infiltrate does not affect the muscular wall and there is only minor crypt distortion if compared with ulcerative colitis.

Diagnosis: Diversion colitis.

Comment: We usually have to deal with small biopsies and it may be difficult sometimes to differentiate diversion colitis from a relapse of inflammatory bowel disease. In this patient there is no evidence of CU or Crohn´s disease and I wanted to take the opportunity to share this case with a larger resection specimen.

Reference:

Geraghty JM , Talbot IC. Diversion colitis: histological features in the colon and rectum after defunctioning colostomy. Gut 1991, 32, 1020-23

AMR SEMINAR #55
CASE 8

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

Clinical History: A 26-year-old female developed fever of one week duration. On exploration, large cervical lymph nodes were palpable and growth of the left tonsil was detected. A lymphoma was suspected and the tonsil removed. One week after surgery the fever and lymphadenopathy disappeared.

Gross Findings: The tonsil measured 3 cm, on section, the tissue had a soft friable consistency with pale apparently necrotic areas.

Microscopic Findings: The architecture is partly preserved, some crypts are ulcerated with total loss of the epithelium, around the crypts there are areas of geographic necrosis surrounded by a band of atypical lymphoid cells including immunoblasts and Reed-Sternberg-like cells with prominent nucleoli. Many mitotic figures (up to 20 x 10 HPF) are seen. Eosinophils and plasma cells are scanty.

Immunohistochemical Findings:
The large cells are positive for: CD20, CD30, and LMP-1, Ki67 (60% of cells), and OCT-2. Reactive cells were positive for CD3 and CD45RO. Negative for: ALK-1, CD15 and CD68.

Diagnosis: Infectious mononucleosis tonsillitis with geographic necrosis.

Discussion: The histological picture differs from the one presented by Gerald Berry (AMR #52- case 4), because there is extensive necrosis and many R-S like cells. The spectrum of histological changes in IM may simulate lymphoma. Massive necrosis is unusual and considered a sign of fatal IM, however it may occur in non fatal cases. It is important to be aware of this change to avoid over-diagnosis of lymphoma.

Reference:

Kojima M, et al . Lymph node lesion in infectious mononucleosis showing geographic necrosis containing cytologically atypically B-cells. Pathol Res Pract 2004;200:53-57

AMR SEMINAR #55
CASE 9

Contributed by: Vincenzo Eusebi, M.D.

Clinical History: A 47- year-old lady complained of a nodule at the ventral base of the tongue, which had been noticed (felt) 20 days earlier. No other symptoms whatsoever. Bone scan is normal. The nodule was excised. It measured 2 cm in its greatest axis and was yellowish in colour.

Pathologic Findings: Histologically there is florid pseudoepitheliomatous hyperplasia of the epithelium , but the bulk of the lesion is constituted by large cells with indented irregular nuclei, frequently binucleated with large eosinophilic cytoplasm. The neoplastic cells are intermingled with inflammatory cells of which eosinophils are predominant.
Keratins are negative as well as melanoma markers, but vimentin, CD 68, S-100 protein are strongly positive. CD1a shows patchy but strong definite positivity.

Diagnosis: In view of the atypical features of the large eosinophilic cells, the diagnosis of Langerhans cell sarcoma was made, although I was aware that this condition is widespread at the moment of the diagnosis, and in addition no oral site has been recorded yet to my knowledge.

ADDENDUM: at the moment of sending off the present slides for the seminar I am informed that the patient has noticed an enlargement of a laterocervical lymph node. I will let you know what happens.

AMR SEMINAR #55
CASE 10

Contributed by: Cyril Fisher, M.D., Royal Marsden Hospital, London, UK.

Clinical History: A 56-year-old male developed pain, swelling and bruising in the flexor surface of the forearm at the site of a surgically constructed arteriovenous fistula placed for hemodialysis, which became disused two years earlier following renal transplantation. The lesion was biopsied then excised, and an above-elbow amputation was subsequently performed.

Pathologic Findings: There was extensive thrombosis in the large vessels of the subcutaneous AV shunt, extending to adjacent vessels. Adjacent tissue (Fig 1) contained separate deposits of tumor, which formed raised skin nodules. This section is from a thrombosed vessel proximal to the shunt. Microscopically there is organized thrombus and adjacent recent hemorrhage containing a tumor composed of atypical polygonal cells, some lining vascular channels. At one edge of the section there is a more solid epithelioid proliferation, with prominent nucleoli and atypical mitoses. In another block of this case (from which sufficient sections for distribution could not be obtained) there is tumor within lumen and wall of vessel, adjacent to suture material (Figs 2-4). The tumor cells are immunoreactive for CD34, CD31, FVIIIRAg, FLI1 and INI1, and negative for HHV8, cytokeratins, EMA, CD30, CD45 and S100 protein.

Diagnosis: Angiosarcoma arising in AV fistula previously used for dialysis in renal transplant recipient.

Comment: Angiosarcoma arising at any site in immunosuppressed renal transplant recipients is rare, with fewer than 20 reports. Development of angiosarcoma in a nonfunctioning arteriovenous fistula accounts for about 7 of these[1-8] (one case was reported twice[1, 4]). It is presumably related to immunosuppression following the renal transplant, in an altered vascular environment.[9] The time interval between transplantation and development of the angiosarcoma varies between two and ten years, and is usually more than five years. The presence of satellite nodules and the (at least focal) epithelioid morphology are typical. This is an aggressive neoplasm; initial treatment can include amputation, and reported cases have developed local recurrences and pulmonary metastases.

1. Byers RJ, McMahon RF, Freemont AJ et al. Epithelioid angiosarcoma arising in an arteriovenous fistula. Histopathology 1992;21;87-89.
2. Conlon PJ, Daly T, Doyle G et al. Angiosarcoma at the site of a ligated arteriovenous fistula in a renal transplant recipient. Nephrol Dial Transplant 1993;8;259-262.
3. Keane MM, Carney DN. Angiosarcoma arising from a defunctionalized arteriovenous fistula. J Urol 1993;149;364-365.
4. Parrott NR, Scott PD, Freemont AJ et al. Angiosarcoma in an arteriovenous fistula following successful renal transplantation--a case report. Transplantation 1993;55;676-677.
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AMR SEMINAR #53
CASE 11

Contributed by: Christopher Fletcher, M.D. (Case #CFST 2145)

Clinical history: A 41 year old man presented with a 2-year history of firm irregular scrotal swelling. A piece of scrotal skin measuring 20 cm^2 was excised, beneath which there was a poorly marginated, gelatinous mass measuring 18x16x5 cm.

Diagnosis: Scrotal lymphoedema (with smooth muscle hyperplasia).

Comment: It seems that most examples of massive scrotal lymphoedema such as this are idiopathic and there is no clear association with morbid obesity that has been documented. We have seen two or three such cases over the years and a striking feature is the presence of quite substantial smooth muscle hyperplasia (remember that the entire 5 cm thickness of this large mass had similar appearances to those in this slide). There have only been occasional accounts of this phenomenon in the literature – (see Van Kooten et al. *J Cutan Pathol* 2004; 31:388-392). In truth, this is simply a poorly understood curiosity which I thought might be of some interest to this group.

AMR SEMINAR #55
CASE 12

Contributed by: Andrew Folpe, M.D.

Case History: A 31-year-old woman at 3 months of pregnancy presented with analgesic-resistant pelvic pain and functional disability of the left leg. Her previous medical history was unremarkable. A CT scan showed a 5cm intra-osseous lesion of the left iliac bone adjacent to the acetabulum, with cortical destruction. Following a biopsy, a left internal hemipelvectomy with immediate reconstruction was performed. The patient is currently disease free, 6 months following surgery.

Macroscopic Findings: A large, destructive, partially calcified tumor was present within the iliac bone, with extensive cortical destruction.

Microscopic Findings: Sections from the initial biopsy and the subsequent resection showed identical findings. At scanning magnification, the tumor consisted of sheets of epithelioid cells in association with a hyalinized to calcified matrix. The tumor cells were relatively monomorphic, with moderate amounts of eosinophilic cytoplasm, hyperchromatic, irregular nuclei, and occasional prominent nucleoli. Occasional cells displayed greater nuclear pleomorphism and rhabdoid morphology, with eccentrically placed nuclei and "glassy"-appearing eosinophilic cytoplasm. Mitotic activity, small foci of necrosis, and intralesional hemorrhage were present. In areas the hyalinized matrix surrounding the tumor cells calcified in a peculiar "chickenwire" pattern, reminiscent of chondroblastoma, and incited an osteoclastic giant cell reaction.

Immunohistochemical Findings: The tumor was strongly positive for cytokeratins, EMA, vimentin, and CD34. INI-1 protein expression was entirely lost. CD31 and FLI-1 protein were negative.

Molecular Findings: Fluorescent in situ hybridization studies showed homozygous deletion of *INI1* gene located at 22q11.23.

Diagnosis: Primary epithelioid sarcoma of bone.

Comment: Epithelioid sarcoma, described by Enzinger in 1970 (1), classically occurs in the soft tissues of the distal extremities of young patients (2, 3). Morphologically, classical epithelioid sarcoma consists of an infiltrative proliferation of relatively bland epithelioid to spindled cells, often with a pseudogranulomatous pattern of necrosis. The so-called "proximal variant" of epithelioid sarcoma, characterized by proximal soft tissue location, pleomorphism and rhabdoid morphology, tends to occur somewhat older patients, and appears to have a worse prognosis than does classical epithelioid sarcoma (4, 5).

Although epithelioid sarcoma has been reported in a very wide range of soft tissue locations, I am not aware of a prior report of a primary epithelioid sarcoma of bone. In this case, this diagnosis is substantiated by the very characteristic morphology of the tumor, showing mixed features of classical and proximal-type epithelioid sarcoma, as well as by its essentially diagnostic immunophenotype, with co-expression of epithelial markers, vimentin and CD34, and absent expression of INI1 protein (reflecting a homozygous loss of *INI1*). INI1 protein, the product of the *hSNF5/INI1/SMARCB1/BAF47* gene, is a tumor suppressor involved in ATP-dependent chromatin remodeling, cell cycle control and regulation of the cytoskeleton (6-8). Loss of INI1 expression, though initially to be the molecular hallmark of pediatric rhabdoid tumors of the kidney and central nervous system (9), has recently been shown be a relatively specific marker of epithelioid sarcoma (9-13).

Given the epithelioid morphology of the tumor cells and the prominent matrix calcification, the differential diagnosis for this case included epithelioid tumors of bone, including metastatic epithelioid sarcoma of soft tissue, metastatic carcinoma and epithelioid angiosarcoma, as well as matrix-producing bone tumors, including chondroblastoma and osteosarcoma. Although it is difficult to absolutely exclude a metastasis from an entirely occult or previously excised epithelioid sarcoma of soft tissue, a detailed history and an extensive clinical and radiographic examination were entirely negative. Immunohistochemistry is of great value in the distinction of epithelioid sarcoma from carcinoma, inasmuch as expression of CD34 is seen in 50-60% of epithelioid sarcomas but in <2% of carcinomas (4, 14-16), and loss of INI1 expression is seen in >90% of epithelioid sarcomas, but not in carcinomas (with the exception of medullary carcinoma of the kidney) (9, 11-13, 17, 18). There was also no clinical evidence of a carcinoma elsewhere.

Although epithelioid angiosarcomas may express cytokeratins and CD34, they usually show at least small areas of more typical vasoformative growth, lack rhabdoid cells and matrix calcification, and express in most instances CD31 and FLI-1 protein, markers absent in epithelioid sarcoma (19, 20). Additionally, recent data shows INI1 expression to be uniformly retained in epithelioid angiosarcomas (12). Chondroblastomas typically occur in the epiphyses of the long bones, rather than in the iliac bone (a flat bone, without an epiphysis or epiphyseal equivalent), and lack the high-grade cytological features and epithelial marker expression shown by the present case. Although osteosarcomas may show a wide variety of histologic appearances, occur in essentially any bone, and show limited expression of cytokeratins (21), they would not be expected to show diffuse cytokeratin and CD34 expression. INI1 expression has not been studied in osteosarcoma. Calcified matrix may be seen in a minority of classical epithelioid sarcomas of soft tissue (3).

A final diagnostic consideration is so-called “extrarenal rhabdoid tumor”, a controversial entity considered by some to be identical to proximal-type epithelioid sarcoma (4). Histologically, proximal-type epithelioid sarcoma and extrarenal rhabdoid tumor are essentially identical. Immunohistochemically, both tumors share co-expression of epithelial markers (e.g., cytokeratins and EMA) and vimentin, and show absent expression of INI1 protein (5, 22, 23). It has been suggested that expression of CD34, as seen in the present case, helps to distinguish proximal-type epithelioid sarcoma (positive in 50-60% of cases) from extrarenal rhabdoid tumor (usually negative), although relatively few extrarenal rhabdoid tumors have been examined for CD34 expression (22). Recent molecular genetic data, from Kohashi and colleagues, also suggests differences between epithelioid sarcoma and extrarenal rhabdoid tumor, with homozygous *INI1* gene deletions noted in 10 % of epithelioid sarcomas (all of proximal type), as compared with 86% of extrarenal rhabdoid tumors (5, 23). It has also been suggested that expression of dysadherin, seen in proximal-type epithelioid sarcoma but not in extrarenal rhabdoid tumor, may be of value in this differential diagnosis (24). In the present case, I believe the predominantly non-rhabdoid morphology and the presence of strong CD34 expression to support the diagnosis of epithelioid sarcoma, rather than extrarenal rhabdoid tumor, although I recognize that this distinction may be somewhat arbitrary. In any event, I am not aware of a report of an extrarenal rhabdoid tumor arising primarily in bone, although occasional cases have been reported as secondarily involving bone (25, 26).

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AMR SEMINAR #55
CASE 13

Contributed by: Jerónimo Forteza Vila, M.D.

Clinical history: The patient was a 32-year-old man with big abdominal and hepatic masses. His significant previous history is summarized next:

-12.06: presented to the Emergency Department with asthenia, anorexia, painful mass in left iliac fossa (LIF), and 8 kg weight loss. HBV and HCV negative
-1.07: at the General and Digestive Surgery, abdomen-pelvis computed tomography examination was made and shows an hepatic and pelvic masses. At the beginning of the illness pelvic and hepatic masses were observed in the CT scan, whereas no infiltration in the pancreas was observed at that moment
-3.07: GNAB Biopsy revealed hepatoid morphology, certainly malignant with mitosis. Immunohistochemistry studies revealed expression for hepatocyte, focal CEA, and AFP, what gives support to the hepatocarcinoma diagnosis. The case was reported as well-differentiated hepatocarcinoma
-4.07: started therapy with Sorafenib and Gemox. The patient responded to the treatment and the control CT scan (figure 1) one month and a half after initiating the treatment shows reduced hepatic and pelvis masses. A year and three months later he was admitted as a matter of urgency with a medical profile of high digestive haemorrhage and intestinal sub-occlusion. The next month exitus occurred and autopsy was requested

Autopsy findings: Regarding the hepatic level, on the liver it is observed a main nodule (figure 2), pigmented, circumscribed, with necropsy areas and little hemorrhagic foci and multiple metastatic satellite nodules. With regard to the pelvis, a mass is identified made up of matted adenopathy that infiltrated the pancreas macro and microscopically. H&E shows in the liver a tumor of hepatoid morphology, where it calls our attention the mucous differentiation, unusual in hepatocarcinoma. Infiltration with the same morphology as that of the liver was observed in the pancreas. Metastasis were also observed in heart, intestinal mucosa, spleen, and scalp.

Special studies: Immunohistochemistry studies revealed expression for: CK7, CK18, CK19, hepatocyte, focal CEA, focal CA19.9, and P53; negativity was found for CK20, AFP, and P16.
Molecular biology: we studied KRAS mutations in exon 2 and 3. No mutations were found in codons 12/13 of exon 2, neither in codon 61 of exon 3.

Diagnosis: Hepatocarcinoma with metastases to lymph nodes, pancreas, spleen, heart, intestinal mucous, scalp.

Discussion: differential diagnosis between hepatocarcinoma and pancreas adenocarcinoma was considered based on the absence of cirrhosis, or positive HBV/HCV, important factors for the predisposition to develope this tumour. Clinical evolution was fast, rare in hepatocarcinomas. Also, mucous differentiation was observed at neoplasia, what is very rare too in hepatocarcinomas. The immunohistochemistry profile was not definitive, being compatible with both possibilities. Pancreas was not radiologically infiltrated at the beginning of the illness, this is an important point and the patient evolved correctly at the beginning of the specific hepatocarcinoma therapeutic. Finally, the KRAS-gene analysis helped us to adopt a decision, since the studied exons are mutated in the 90% of the cases of pancreas adenocarcinoma. It was diagnosed as hepatocarcinoma with metastases to lymph nodes, pancreas, spleen, heart, intestinal mucous and scalp.

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AMR SEMINAR #55
CASE 14

Contributed by: Allen Gown, M.D.

Clinical History: Anterior mediastinal mass in an 80-year-old male.

Histology: The tumor appears to be an undifferentiated carcinoma with some suggestion of squamous differentiation. What about variegated cells?

Diagnosis: Thymic carcinoma.

Discussion: Most patients with thymic carcinomas present, as did this patient, with symptoms related to a mediastinal mass. (Unlike the case with thymoma, there is no association with paraneoplastic syndromes.) There are several histologic patterns that can be associated with primary thymic carcinomas, the most common including squamous cell, lymphoepithelioma-like, sarcomatoid, mucoepidermoid, basaloid, and clear cell variants. The case at hand is the most common variant, squamous cell carcinoma, and as in the case at hand usually poses the clinical differential diagnosis of primary thymic squamous cell carcinoma vs. metastasis or invasion of a squamous cell carcinoma arising in the lung. It is said that some histologic features, including the presence of hyaline stroma and a lobulated growth pattern, favor the diagnosis of primary thymic carcinoma, but as demonstrated in this case primary thymic carcinoma generally shows a unique immunophenotype. While the classic p63-positive, cytokeratin 5-positive immunophenotype characterizes thymic as well as primary lung squamous cell carcinomas (and indeed, squamous carcinomas of all sites), thymic carcinomas are unique in their high incidence of CD117 (c-kit) expression, as was shown in this case. This case also demonstrated a phenomenon noted by Kuo in approximately 40% of thymic carcinomas: the presence of a subset of neuroendocrine cells positive for expression of synaptophysin. This feature also appears to be unique to thymic carcinoma.

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AMR SEMINAR #55
CASE 15

Contributed by: Janez Lamovec, M.D.

History: An 86-year-old woman presented with a large ulcerated tumor of the skin and subcutaneous tissue slightly above the inner upper quadrant of the right breast. She reported to have had a lump in that region for 11 years that had started to enlarge considerably 6 months ago. Tumor was excised in another hospital and the patient referred to our institution.

Pathological findings: Grossly, the specimen was represented by an elliptical excision of skin and subcutaneous tissue that was almost completely replaced by a 7.5 x 7 x 4 cm tumor. Skin overlying it was exulcerated over a large area. Tumor was clearly delineated from peripheral rim of skin and subcutaneous tissue. On cut surface, the neoplastic tissue was solid, moderately firm, white-grey, with scattered yellow areas. Excision margins were grossly free of tumor but close to it.

Histologically, the tumor is composed of solid sheets and alveoli of polygonal neoplastic epithelial cells with abundant finely granular to microvacuolated eosinophilic or clear cytoplasm and large oval, mostly vesicular nuclei with focally prominent nucleoli. Cell borders are focally quite distinct. Mitoses, also atypical, are numerous. No ductal structures are seen. In some areas, most of the tumor cells are finely vacuolated, with clear cytoplasm, similar to sebaceous cells. Many cells in these areas also show large empty intracytoplasmic vacuoles that focally coalesce to form cribriform spaces. There are many necrotic areas, with focal formation of pseudocysts. Stromal septa between sheets and alveoli are relatively thin and delicate, in central part of the tumor the stroma appears hyalinized and focally edematous (shown only in the small part of the submitted slide). Tumor involves the skin and subcutaneous tissue, the former is exulcerated. No breast tissue was identified in numerous sections.

Histochemically, microvacuolated cells showed accumulation of fatty substances demonstrated by Oil red on frozen section, some fat vacuoles were large. In addition, many intracytoplasmic vacuoles and optically clear cribriform spaces were filled either with alcian green or PAS positive mucinous material.
Immunohistochemically, most cell showed strong positive reaction for GCDFP-15 (BRST-2) and many also for CEA; CK5 and p63 were focally positive in a peripheral rim of some tumor alveoli, CK19 was diffusely and strongly positive in practically all tumor cells. More than 80% of tumor nuclei were positive for p53. Neuroendocrine markers were negative, NSE though decorated some 30 to 40 % of cells. ER was strongly positive in around 50 and PR in around 30 % of cells; AR were not performed.

Diagnosis: Apocrine carcinoma of the skin with sebaceous (sebaceous-like) and mucinous differentiation.

Follow-up: At our institution, the reexcision of the tumor site and axillary dissection were performed. Tumor metastases were found in 25 of 37 lymph nodes; they were of the same morphology as primary except for the lack of sebaceous differentiation. Mammography, performed at our institution did not demonstrate any suspicious lesion in the breasts. The patient received postoperative radiotherapy in a total dose of 50 Gy. She is alive and well at 88 years, two and a half year following surgery

Comment: I believe that this is a case of a primary adnexal skin tumor. Although the tumor was close to the breast, mammography did not disclose any suspicious breast lesion and no breast tissue was found in the excision specimen. We can only speculate what could be the tumor of 11 years duration reported by the patient; we did not find any remnants of a possible benign tumor histologically. As to the histological type of the submitted tumor, I think that this is essentially an apocrine skin carcinoma even though the decapitation secretion considered by some to be a prerequisite for a diagnosis was not seen in our tumor. However, this was entirely a solid variant of it with no ductal structures identified where such a secretion should be expected. Another interesting aspect of the presented tumor is a sebaceous or sebaceous-like (" sebocrine" – Tavassoli) differentiation and mucinous secretion by tumor cells (intracellular and into cribriform spaces), demonstrated by fat stain and mucin stains. Focal peripheral rim of cells positive for CK5 and p63 demonstrated some myoepithelial/basaloid cells in otherwise glandular cell type tumor.

I am very interested in comments by other members and their suggestions as to how properly classify this tumor that does not quite fit into the picture of described cases of primary cutaneous apocrine carcinoma (1) or cutaneous sebaceous carcinoma with focal glandular pattern - seboapocrine carcinoma (2).

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AMR SEMINAR #55
CASE 16

Contributed by: Michal Michal, M.D., Czech Republic

History: The patients was a 56-year-old women who presented with signs of highly elevated plasma and urine levels of cortisol and elevation of plasma levels of aldosterone. The concentrations of adrenaline (50x) and noradrenaline (10x) highly exceeded the normal levels. The patient suffered from secondary hypertension associated with hypokalemia, metabolic alkalosis. The patient presented with hirsutism, psychic irritability and weight loss and she complained of gaining weight, muscle weakness, rounded face, purple abdominal striae, edemas of lower extremities and polyuria. All these symptoms disappeared after the surgical excision of the tumors and the patient was well and without recurrences in the second year after the removal of the tumors.

Pathologic Findings: Grossly, the tumor was 6x7x8 in size and was well encapsulated. It had a yellow color and a diffuse, solid consistency. No macroscopic necroses or hemorrhages were visible.

Histologically, the tumor consisted of interweaving cords and nodules of the cortical adenoma on the background of the pheochromocytoma. In some areas cyanophilic stained pheochromocytoma component formed the majority of the tumor (like in the slide given to the AMR seminar), in other areas the pink-red staining cortical adenoma tissue formed the majority of the tumor mass. The cortical adenoma cells had a homogenous bright-pink color and the contours of the cell borders of the cortical adenoma cells were often accentuated so that it often acquired a mosaic pattern. In the slide the cortical adenoma tissue forms some 5% of the tumor and it forms thin cords and islands of the pink-eosinophilic tissue set in dark blue staining pheochromocytoma tissue. Cortical adenoma cells were without mitoses and atypias throughout of the tumor. The pheochromocytoma component revealed focal atypias and hyperchromatic nuclei but mitoses were rare. In two blocks of tissue there was a third tumorous component. It consisted of very cellular spindle cells with numerous mitoses (well seen in the submitted slides). The cellularity and the spindle cell quality of this component vaguely resembled an endometrial stromal sarcoma. Adjacent to rare foci of the spindle cell sarcoma we saw continuous transitions of the pheochromocytoma cells into the spindle cell sarcoma, which revealed a conspicuous cell spindling in these parts. Well differentiated cortical adenoma cells formed small isolated islands in the vicinity of the spindle cell sarcoma surrounded by the pheochromocytoma cells. Hypothetically I think that the spindle cell sarcoma arose in the pheochromocytoma component as several cases of spindle cell sarcoma arising in the pheochromocytomas were previously described. There are described some 11 cases of corticomedullary tumors in the literature (1-8). This case was previously published (2).

Diagnosis: Corticomedullary tumor of the adrenal glands.

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AMR SEMINAR #55
CASE 17

Contributed by: Michal Michal, M.D.

History: A 52-year-old man had a tumor of 2 cm in diameter of hypophysis. When I got for consultation and saw the tissue I thought that there was some error in sampling the material which was mistakenly exchanged with other patient. Than I was ascertained by the referring pathologist that he was sure that it was not possible, because no salivary gland tumor was that day accessed to grossing room.

Diagnosis: Salivary gland type adenoma of the hypophysis.

Comments: The tumor looks like an adenoma of salivary gland being composed of glandular structures having secretory and myoepithelial layer. All cells of myoepithelial layer reacted with myoepithelial markers (SM actin, calponin, p63....). The lesion focally looked like benign adenomyoepithelioma of the breast. There is just one paper which nicely documents occurrence of such tumors and I greatly recommend it (1).

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AMR SEMINAR #55
CASE 18

Contributed by: Markku Miettinen, M.D.

Clinical History: 31 year-old man noted hematuria end of September 2006. Diagnosis of ITP. CT of abdomen and pelvis revealed a 15x14x12 cm mass with multiple areas of necrosis. Elevated LDH. The mass was excised and found to be attached to small bowel.

Pathology: The slide contains two sections, one of which contains elements of hyaline vascular Castleman disease and spindle cell neoplasm, and the other contains purely tumor. The tumor is composed of mildly atypical, relatively uniform spindled to epithelioid cells with variably prominent nucleoli. Intermingling lymphocytes are present, often as perivascular clusters. Tumor necrosis is present, but mitotic activity is low. Immunohistochemical studies are positive for CD21, S100 protein, CD68, and vimentin and focally for desmin. The tumor is negative for CD34, CD35, CD117 (KIT), keratins (7,8,18, cocktail AE1/AE3), heavy caldesmon, and SMA. The overall findings are consistent with the above diagnosis.

Diagnosis: Dendritic reticulum cell tumor (sarcoma) arising in Castleman disease.

Comment: Dendritic reticulum cell tumor (sarcoma) is a rare nodal or sometimes apparently extranodal tumor. However, one can suspect that nodal nature can be easily missed if the tumor overgrows the lymph node. Occurrence in tonsils is also possible. In this case, origin from nodal Castleman disease is apparent, as reported in the literature in a small number of cases (especially by John Chan). The above immunophenotype seems to be in the spectrum of this disease, including S100-protein positivity. Desmin is somewhat odd, and in this case, features of other reticulum cells were considered although still the follicular dendritic one is the best fit. Given to atypical features, and tumor necrosis, malignant behavior cannot be ruled out, although this has been observed only in a minority of cases. Thrombocytopenia has been reported in Castleman disease is isolated cases.

AMR SEMINAR #55
CASE 19

Contributed by: James Strauchen, M.D.

Clinical History: 81 year old man presented with a right retroperitoneal mass on CT scan. At surgery a 6 cm x 4 cm x 3 cm apparently well circumscribed mass was resected.

Pathology: Sections show a fibromyxoid lesion with nodular lymphoid aggregates, numerous plasma cells, occasional eosinophils, and scattered bizarre giant cells. Some of the latter are vacuolated and appear to contain ingested inflammatory cells. Immunohistochemical stains demonstrate the giant cells to be positive only for vimentin. Histiocytic (S-100, CD68, CD163, lysozyme, alpha-1-antitrypsin), muscle (desmin, SMA), and dendritic/RS markers (CD21/35, CD30) were negative. The lymphocytes are predominantly CD20-positive B-cells and CD138-positive polyclonal plasma cells.

Diagnosis: Atypical lipomatous tumor/inflammatory well differentiated liposarcoma.

Comment: I received this case because of the impression on frozen section that this might be a hematopoietic neoplasm. The apparent phagocytosis and/or emperipolesis of inflammatory cells suggested the possibility of extranodal Rosai-Dorfman disease to the frozen section pathologist, however, the fibromyxoid stroma, inflammatory background, and bizarre stromal giant cells are rather characteristic of the inflammatory variant of atypical lipomatous tumor/well differentiated liposarcoma. This variant occurs mostly in the retroperitoneum and may be confused with an inflammatory process, Hodgkin or non-Hodgkin lymphoma, or Castleman disease. A curious finding in the case was that the giant cells were positive for nuclear Cyclin D1. Cyclin D1 overexpression has been reported in some soft tissue sarcomas (including synovial sarcoma and inflammatory myofibroblastic sarcoma) but not to my knowledge in atypical lipomatous tumors, which are instead characterized by supernumerary ring or giant chromosomes with 12q14-15 and MDM-2 amplification. Kim et al at Memorial Sloan-Kettering found overexpression of Cyclin D1 in 58% of retroperitoneal liposarcomas but did not specify the histologic type (1). Cyclin D1 overexpression in that study was found to be prognostically adverse. Atypical lipomatous tumor/well differentiated liposarcoma in the retroperitoneum, in contrast to the extremities, is often unresectable and has an eventual high mortality rate (up to 80% after 10-20 years) due to uncontrolled local tumor recurrence and/or dedifferentiation.

References:

1. Kim SH, et al. Prognostic role of Cyclin D1 in retroperitoneal sarcomas. Cancer 2001; 91:428-343.

AMR SEMINAR #55
CASE 20

Contributed by: Saul Suster, M.D.

Clinical History: A 57 year old lady was examined for a large palpable thyroid nodule of her right lobe. A total thyroidectomy was performed. The right lobe showed a well-circumscribed, encapsulated tumor measuring 10 cm. in greatest diameter showing focal cystic changes. The rest of the thyroid was unremarkable.

Pathologic Findings: Histologic examination showed a well-circumscribed, completely encapsulated follicular lesion. There was no evidence of either capsular or vascular invasion present. On higher magnification, the follicles were lined by cells with round to oval nuclei with finely dispersed chromatin pattern. Occasional longitudinal nuclear grooves could be identified, and a few cells showed thickening of the nuclear membrane with central clearing of nuclear chromatin. The overall low-power appearance, however, was evocative of the follicular variant of papillary thyroid carcinoma.

Diagnosis: Follicular neoplasm of undetermined malignant potential.

Comment: This case was submitted in consultation by a community pathologist who felt unsure whether the case warranted a diagnosis of FVPTC. I am still having trouble with cases like this and, although I am very aware that there are many expert consultants who would have not flinched at calling this the follicular variant of papillary thyroid carcinoma, I am still unable to bring myself around to doing that in cases such as this.

Although I also started my training in the pre-immunoperoxidase era and still believe that morphology should form the basis of our opinions, and although classical pathologists of old were trained to "declare" things either benign or malignant, we are finally coming to the point where we have to acknowledge some of our limitations. I think these thyroid tumors are a perfect example of this and, although we are still under the tyranny of criteria and opinions that were presented years ago by the leaders in this field, we are slowly (too slowly, perhaps) finally coming to the realization that it is no all so simple after all.

I agree with those who believe that the diagnosis of FVPTC has been greatly abused in the past, particularly for cases that are well-circumscribed and encapsulated. In this regard, I strongly support the paper that was published several years ago by the "Chernobyl Pathology Group" on this topic (Int J Surg Pathol, Vol.8: 181-183, 2000). Although my teachers would have (disapprovingly) said to me: "There are no borderline tumors…only borderline pathologists", I believe this is a valid concept that we ought to embrace until we find a better means for assessing the biologic potential of these tumors.

I would love to hear the opinions of the other members of the group, including our distinguished thyroidologists.

AMR SEMINAR #55
CASE 21

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

History: The patient is a 53-year-old man who presented with left distal tibia pain with no history of trauma. He noticed no masses in his leg. Plain radiographs demonstrated a mixed lucent sclerotic lesion with significant cortical disruption laterally within his distal tibia. MRI of his tibia demonstrated a lesion with significant heterogeneity demonstrating cortical disruption. Bone scan demonstrated increased uptake in his left tibia. Chest, abdomen, and pelvic CT scans showed no other lesions.

Diagnosis: Adamantinoma, squamous pattern, left tibia.

Comment: Since Janez had presented a beautiful case of adamantinoma at the Mexico City meeting this past June 2008, it prompted me to remember this case that I had over a year ago. The squamous pattern/variant of adamantinoma can be very frightening, and may even demonstrate keratin pearl formation. I had personally never observed squamous differentiation to this degree before in an adamantinoma, and thought club members would enjoy it. The patient is alive and well with no evidence of recurrent disease or a primary tumor elsewhere. His whole body bone scan demonstrates no evidence of distant disease 17 months later.

AMR SEMINAR #55
CASE 22

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

History: A 56-year-old woman presented with a 6-month history of increasing left leg pain. One year ago she fell in a bathtub. She had increased pain while she was at work, and now has pain at rest and night pain, and walks with a walker because of the pain. She has had no fevers, chills or night sweats, and no other trauma. Plain radiographs demonstrated a lucent lesion in the anterior tibial cortex in the mid shaft that appeared destructive without sharp borders. There appeared to be no surrounding soft tissue mass. CT scan of her chest demonstrated 1 small lung nodule which is relatively indeterminate. Her whole body bone scan demonstrated isolated left tibial uptake. MRI demonstrated a cortical based lesion which extended into the medullary cavity as well as having cortical breakthrough in the anterior tibial cortex.

Pathology: Immunohistology showed negative staining of histiocytic cells with cytokeratin AE1/3, CD1a, but positive staining with S-100 and CD68. GMS stain and AFB stain were negative for fungi and acid fast bacilli respectively. I asked Mike Klein to look at the case, and he was in agreement with my interpretation that this represents extranodal Rosai-Dorfman disease.

Diagnosis: Extranodal Rosai-Dorfman disease, left tibia.

Comment: She is no longer taking pain meds after her curettage, but still needs a walker. The case is only 6 months old, so I have no long-term follow-up. I realize that several club members have much greater experience with this entity than myself, and would appreciate their thoughts

AMR SEMINAR #55
CASE 23

Contributed by: Lawrence Weiss, M.D.

Short History: 47-year-old man with hepatosplenomegaly.

Long History: This 47 yo man had an abrupt presentation of headaches, fever, and malaise. He was found to have massive hepatosplenomegaly and pancytopenia. Splenectomy and bone marrow examination were performed.

Gross: Pathology received a 1500 gm. spleen. There was a focal infarct and the remainder of the spleen appeared congested without discrete masses.

Immunos:

CD20	Negative
CD2	Positive
CD3	Positive
CD5	Positive
CD4	Negative
CD8	Negative
CD30	Negative
TIA-1	Positive
Perforin	Positive
Granzyme A	Positive
CD56	Negative
BF-1	Negative

Comment: The spleen shows a pleomorphic lymphoid neoplasm, forming mini-nodules and infiltrating the splenic cords. It does not particularly involve the splenic sinusoids. In the accompanying marrow, the pattern was also not sinusoidal, but showed a focal nodule of tumor, encompassing about 10% of the specimen.

Diagnosis: Gamma-delta lymphoma, perhaps an aggressive variant of hepatosplenic T-cell lymphoma.

Follow-up: The patient did make it out of the hospital alive, succumbing to liver, kidney, and respiratory failures.

Discussion: Although the clinical presentation and many features are typical of hepatosplenic T-cell lymphoma (clinical; CD4/8 -; BF1 -, implying gamma-delta lineage; TIA-1 +), there are also numerous atypical features: the lack of sinusoidal involvement in the spleen and marrow, the pleomorphism of the cells, the lack of staining for CD56, and the presence of staining for CD5, granzyme A and perforin. Yet, the other gamma-delta neoplasms usually involve skin, gastrointestinal tract or the nasal region. I would like to think that this case may represent an aggressive variant of hepatosplenic T-cell lymphoma or perhaps transformation (although I really cannot see underlying typical hepatosplenic lymphoma).
Any thoughts from the group?

AMR SEMINAR #55
QUIZ CASE 1

Contributed by: Markku Miettinen, M.D., Case 7526

Clinical History: 8-year-old boy with mural tumor in the gastric wall.

AMR SEMINAR #55
QUIZ CASE 2

Contributed by: Joshua Sickel, M.D.

(Note: there are no slides – images only which are on the AMR website)

Clinical History: Elderly male from upstate New York was found to have a coin lesion on routine chest X-ray. Wedge resection of a 2 cm nodule was performed.

AMR SEMINAR #55
QUIZ CASE 3

Contributed by: Joshua Sickel, M.D.

(note: there are no slides – images only which are on the AMR website)

Clinical history: Middle-aged male with poor dentition, peri-apical abscess and maxillary osteomyelitis. Curettage of necrotic bony tissue is performed.

AMR SEMINAR #55
QUIZ CASE 4

Contributed by: Saul Suster, M.D.

Clinical History: A 63 year old woman with a history of invasive ductal carcinoma of the left breast, status post mastectomy and radiation therapy, is seen for the development of a soft tissue induration in the presternal area. An ill-defined soft tissue mass was noted in the left neck and chest wall. On surgical exploration, the soft tissue mass involved the thyroid gland, which was indurated and appeared to be completely replaced by the tumor, and infiltrated the surrounding structures including the pericardial fat, pleura and the skin of the chest wall. A total thyroidectomy was performed. The slide is representative of what was seen in all sections of the thyroid.