AMR Seminar #61 – Short Summary of Cases:

Case 1: F.64 with swelling of left labium thought to be a Bartholin's cyst.

Case 2: M.42 with 5.2 cm. posterior mediastinal mass.

Case 3: F.51 with numerous small subpleural and parenchymal nodules in right lung.

Case 4: M.58 with numerous small subpleural and parenchymal nodules in right lung.

Case 5: F.43 with muscle weakness; a muscle biopsy was done.

Case 6: F.50 with left breast mass.

Case 7: M.79 with painful mass in left submandibular gland.

Case 8: M.60 with intestinal obstruction and mesenteric mass.

Case 9: F.46 with tumor in transverse colon.

Case 10: F.56 with pedunculated large tumor attached to the pleura.

Case 11: F.56 with mass in right breast.

Case 12: M.24 with 9 cm. mass in the wall of the cecum.

Case 13: F.60 with firm mass in the neck, 2.5 cm., encasing the carotid artery.

Case 14: F.15 with ovarian mass with torsion of the ovary.

Case 15: M.69 with history of chondrosarcoma of femur; now with multiple osteolytic lesions of the spine.

Case 16: F.69 with recurrent skin lesions in left gluteal region.

Case 17: M.24 with right testicular mass.

Case 18: M.48 with adrenal mass.

Case 19: F.67 with history of infiltrating ductal carcinoma now presents with a mass in the breast implant.

Case 20: F.47 with polypoid intraluminal mass in proximal third of the esophagus.

Case 21: F.70 with large mass in her left proximal humerus.

Case 22: F.26 with parotid gland tumor.

Case 23: F.35 with left breast mass.

Case 24: F.68 with 7 cm. liver mass.

Case 25: F.32 with nodule in her labia initially interpreted as a Bartholin's cyst.

AMR SEMINAR #61
CASE 1

Contributed by: Philip Allen, M.D.

Case Identification: FMC 07/S06584 and 07/S04813
Contributor: Dr. Dimuth Gunawardane, Flinders Medical Centre, Adelaide, South Australia.

History: A 64-year-old female presented with a swelling, thought to be a Bartholin's cysts, in the left labium majus. At open biopsy, the tumor was solid, edematous was larger than apparent on external examination and was infiltrating deeper into the perineal muscles than the surgeon was willing to explore. The anterior abdominal wall was not involved. The tumor was biopsied (07/S04813, not distributed) and subsequently excised more widely (07/S06584, this seminar slide). The specimen measured 100 x 50 x 60 mm and involved the lateral and inferior surgical margins but had not recurred in early 2011, four years after the incomplete excision. The tumor cells stained positively for oestrogen, progesterone, vimentin and desmin.

Diagnosis: Aggressive angiomyxoma , left labium majus

Comments by Dr. Gunawardane: Aggressive angiomyxoma was first described by Steeper and Rosai in 1983 as a distinctive, rare, myxoid tumor with prominent vascularity and a high local recurrence rate[1]. Subsequently two instances of metastases have been reported.[2, 3] The tumor predominantly arises in the pelvic and perineal soft tissue of women[4, 5], with a peak incidence during the third decade.[6] Males may be affected.[6, 7] but the female/male ratio is more than 6:1[8]. In men, the tumor has arisen in the inguinal region, along the spermatic cord, in the scrotum and in the pelvic cavity.[7, 9-13] Although, aggressive angiomyxoma is nearly always encountered in the pelvi-perineal soft tissues, there are single reports of the tumor arising in the oral floor[14] and the iliacus muscle of a male.[15]

On MRI, the mass exhibits a high signal intensity on T2-weighted images with trans-levator extension and growth around perineal structures.[16] Macroscopically, aggressive angiomyxomas are soft, partly circumscribed and may be polypoid.[6] The cut surface is usually homogeneous and gelatinous and tumors range in size from a few centimetres to 60 cm.[1] Microscopically, there are fibroblasts in a myxoid background with variable sized vessels.[17]

The pathogenesis and cell of origin are controversial.[4] In the initial report, a myofibroblastic origin was postulated,[1] but other authors, on the basis of different ultrastructural details, proposed a fibroblastic origin.[10] Resemblance to the normal fibroblasts of pelvic soft parts has been found in both genders at both histological and ultrastructural level.[10] A recent publication proposed that these neoplastic cells differentiate towards smooth muscle.[18] Ultrastructural studies suggest an origin from undifferentiated mesenchymal cells that may differentiate into fibroblasts or myofibroblasts. These cells may be unique in being hormonally responsive to oestrogen and progesterone.[4]

Immunohistochemically, the neoplastic cells stain diffusely for oestrogen, progesterone, vimentin and desmin but are negative for S-100 protein and cytokeratins.[6, 17]

The main differential diagnosis is angiomyofibroblastoma, which also arises in the subcutaneous tissue of the vulva, vagina and rarely in the scrotum.[6, 19-21] Occasionally, aggressive angiomyxomas exhibit features overlapping those seen in angiomyofibroblastomas, including epithelioid cells arranged in cords around blood vessels and multinucleated cells, suggesting that these two lesions are possibly derived from the same primitive mesenchymal cell.[22, 23] However, angiomyofibroblastoma is usually a well circumscribed neoplasm not exceeding 3 cm in size

and features epithelioid neoplastic cells that are usually concentrated around the numerous thin-walled vessels. They rarely exhibit a myxoid appearance.[6]

Aggressive angiomyxoma can become extremely large and has a tendency to infiltrate the surrounding soft tissue, as in our case, raising the possibility of a myxoid sarcoma such as myxoid liposarcoma or myxofibrosarcoma.[6] However, a fine plexiform vasculature and lipoblasts should indicate a myxoid liposarcoma while more pronounced cytological atypia hyperchromasia and a curvilinear vascular pattern point to myxofibrosarcoma.[6]

The principal treatment for aggressive angiomyxoma is wide local excision. Local recurrence is seen in close to 40% of patients and may appear as long as 14 years after local excision.[1] Recently, aggressive angiomyxoma has been successfully treated with luteinising and gonadotrophin-releasing hormone agonists.[24-26]

I personally (PWA) have resolved never to make a diagnosis of aggressive angiomyxoma unless the tumor infiltrates deeply into the perineal muscles. I suspect that most superficial aggressive angiomyxomas behave like angiomyofibroblastomas and do not recur. Has any member of the club seen a superficial aggressive angiomyxoma that recurred or metastasized and has anyone had any experience with luteinising and gonadotrophin-releasing hormone agonists?

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AMR SEMINAR #61
CASE 2

Contributed by: Carlos Bacchi, M.D.

Case originally from Dr. Gabriela Acosta, Buenos Ayres, Argentina

Clinical History: This is a 42-year-old male with a posterior mediastinal tumor measuring 5.2 x 4.5 x 3 cm. The patient is otherwise in good health and has no other lesion.

Pathological Findings: This tumor is characterized by a nodular growth pattern. The tumor is involved by a striking lymphoid proliferation associated with abundant deposition of collagen. The neoplastic cells are epithelioid with vesicular nuclei but sometimes the nuclei are hyperchromatic with small nucleoli. In some areas the tumor shows pseudopapillary features as well arrangement of cells in cords or solid growth. There is no necrosis and the mitotic figures index is about 10/10hpf. Immunos showed **very strong** expression of S-100 protein with all the other markers (cytokeratin, HMB45, desmin, P63, synatophisin, chromogranin A, EMA, CD34) being negative. Saul Suster also stained for CD23, CD35 and GFAP with negative results.

Diagnostic Interpretation: I found this case difficult to interpret and I have no definitive diagnosis. One possibility that I considered was MPNST, epithelioid variant but low- grade. I also considered other diagnostic possibilities as myxopapillary ependymoma, thymoma (ectopic as it is located in the posterior mediastinum) but both the morphology and the immunohistochemistry results are not characteristics of these tumors.

I have shared this case with Saul who favored either benign lesion or at worst, low grade and suggested a provisional and descriptive diagnosis of low-grade mesenchymal tumor of undetermined malignant potential. Saul also suggested that I sent the case to the Club to see if someone can help us with a definitive diagnosis. What is the Club members' opinion in this case? Has anyone seen a tumor like this either in the mediastinum or in other anatomic location?

AMR SEMINAR #61
CASE 3

Contributed by: Michele Bisceglia, M.D.
(Slides labeled 134.960-7)

Clinical History: A 51-year-old female was advised to undergo resection of a 4 cm posterior mediastinal mass adherent to the oesophagus. During the operation, via a right intercostal thoracotomy, the surgeon palpated numerous small hard subpleural and parenchymal nodules all over the right lung, mainly in the lower lobe, a portion of which was resected and submitted to our anatomic pathology laboratory for intraoperative consultation. The specimen consisted of a 10 x 5 x 2 cm partial left lower lobectomy containing a collection of hard nodules scattered and aggregated to form a discrete cluster likened to a bunch of grapes. The cut surface of the specimen demonstrated apparently calcified nodules (up to 5 mm in diameter) protruding above the surrounding tissues, which could be even easily removed. Cryostat sections could not be performed and a gross impression report was issued.

The surgical intervention went on and the mediastinal mass was totally excised along together with adjacent lymph nodes, which were sent for routine pathological examination. The mediastinal mass was encapsulated 3.8 cm diameter and cystic, filled with white granular-mucoid material. The lung specimen was then decalcified and all the pathological material routinely processed. Histological examination of the lung specimen revealed numerous branching osseous structures, embedded in a fibrotic, expanded interstitial tissue in subpleural, interlobular and interalveolar locations. In places, the osseous trabeculae were extending into the alveolar spaces. Fatty marrow occupied the intertrabecular spaces, except for a small focus that contained hematopoietic elements. Non-specific inflammatory infiltrates were noted in the collapsed areas and in the alveolar septa. No necrosis, granulomas, cholesterol crystals, parasites, or hemosiderin were seen. The mediastinal cyst was lined by normal respiratory epithelium, and the lymph nodes showed mild reactive changes.

Pathological Diagnosis: Lung specimen - Diffuse dendriform pulmonary ossification in association with interstitial pulmonary fibrosis. Mediastinal cystic mass – foregut cyst (bronchogenic).

Follow-up: The patient's medical records were reviewed. Of note was that the patient manifested Raynaud phenomenon in the hands for 15 years and examination had been positive for antinuclear antibodies (ANA), thus she carried a diagnosis of rheumatoid disease, not otherwise specified. One year earlier, the patient had pneumonia (side not specified), and a follow up CT scan disclosed the posterior mediastinal mass, that prompted a recommendation for thoracotomy exploration. The CT scan also showed signs of interstitial lung disease and bronchiectasias. Calcifications or ossifications were not mentioned at the time of the imaging. Repeat rheumatologic evaluation led to a diagnosis of systemic sclerosis (scleroderma), based on positive ANA and some anti-extractable nuclear antigens (ENA) (anti-RNP, anti-Sm, and specifically anti-Scl-70 positivity). Additional tests for other autoimmune conditions were negative. There was no evidence of acquired heart disease or cardiac related symptoms.

Final Clinical-Pathologic Diagnosis: Systemic sclerosis with interstitial lung disease and diffuse pulmonary dendriform ossification.

AMR SEMINAR #61
CASE 4

Contributed by: Michele Bisceglia, M.D.
(Slides labeled 134.972-7)

Clinical History: *(Note: Received the same day as case #3, only 12 accession numbers separate the 2 cases of this presentation)*. A 58-year-old male underwent thoracoscopic partial right upper lobectomy because of bilateral, diffuse, multilobar small interstitial opacities. The surgeon felt numerous subpleural and intraparenchymal small hard nodules in all the 3 lobes of the right lung and noticed that some of them extruded from the cut surface when the lung tissue was incised. The specimen was sent to anatomic pathology for routine examination. Received in formalin was a 7 x 3 x 2 cm specimen with easily palpable small hard nodules (up to 0.5 cm in diameter). It was lightly decalcified prior to processing for histological examination. Histologically, the most prominent feature was the presence of numerous, small, variably-shaped, branching and angulated bone spicules buried within the alveolar septa which were focally broadened by connective tissue. The osseous trabeculae contained marrow, in complete fatty metaplasia. The alveolar septa away from the osseous spicules were normal. The alveolar spaces seemed normal. No significant interstitial inflammatory infiltrates, granulomas, hemosiderin or amyloid deposits, or any other pathologic process were seen, except for focal calcifications in transition to ossification. Some osseous trabeculae were surrounded by a sleeve of dense fibrous tissue, herein attesting for the metaplastic derivation of bone.

Pathological Diagnosis: Diffuse pulmonary dendriform ossification.

Follow-up: The medical history was reviewed. Ten years earlier, this patient manifested renovascular hypertension, which was only partially controlled by renal angioplasty. Hypertension persisted, but of a lesser degree. Six years before the thoracoscopy, the patient suffered an ischemic stroke. A routine chest-X-ray done one year before thoracoscopic surgery revealed focal opacities and thickening of interstitial septa along with bronchiectasias that led to the procedure. There was no evidence of mitral valve stenosis, pulmonary arterial hypertension, previous chemotherapy, or autoimmune disease.

Final Clinical-Pathologic Diagnosis: Idiopathic diffuse pulmonary dendriform ossification.

Discussion: Pulmonary ossification may be idiopathic or result from a variety of underlying pulmonary, cardiac, extracardiopulmonary disorders, or even in absence of any known cause (*see Table 2 in ref. by Chan ED et al*). The pathogenetic mechanisms have not been fully elucidated. However, tissue injury seems to be an important initial factor. An alkaline environment fosters precipitation of calcium salts, enables alkaline phosphatase activity, and activates pro-fibrogenic cytokines. Other influences, such as angiogenesis, chronic venous congestion, and abnormal mineral metabolism may play a role as well. There are two types of ossification, the localized and the diffuse. The localized type refers to focal deposition of bone within or in adjacent injured lung tissue by any kind of disease. The diffuse type refers to the disseminated formation of bone spicules or nodules of bone in the interalveolar, interlobular and subpleural connective tissue of the entire lung as well in the alveolar spaces. Furthermore, two types of diffuse pulmonary ossification are recognized: the dendriform (branching or racemose) type, usually seen in association with chronic lung disease (including idiopathic pulmonary fibrosis), and the nodular (or circumscribed) type, which instead is usually seen in association with heart diseases (especially mitral valve stenosis and other conditions leading to venous pulmonary hypertension). The dendriform type is usually intraparenchymal, with branching osseous structures of mature lamellar bone containing marrow (either fatty or hematopoietic), whilst the nodular type is characterized by rounded intra-alveolar bone fragments, often made of woven bone adherent to the alveolar walls. When any underlying known cause is carefully excluded, a diagnosis of idiopathic diffuse pulmonary ossification is warranted.

Diffuse pulmonary ossification is very rare. In two large adult autopsy studies, diffuse pulmonary ossification was histologically found in 17 cases out of 10,426 postmortem (incidence of 1.63 cases/1000 autopsies), and in 8 cases out of 1,393 (prevalence of 0.5%; incidence of 0.28 cases per year), respectively. In these two studies, no case was diagnosed antemortem. There was a predilection for males (>80%) and underlying pulmonary disease (>80%). The overwhelming majority of individual were over 60. The condition is often asymptomatic, despite diffuse

pulmonary lesions as attested by the fact that the diagnosis is usually made as an incidental finding at autopsy and, when the diagnosis is made in life, the discovery is usually also incidental. On a computerized search of the literature, less than 20 cases of diffuse pulmonary ossification diagnosed by lung biopsy (open surgery or thoracoscopic lung biopsy in all cases, except for 1 case that was diagnosed by needle biopsy) have been found on record. Two of these cases were diagnosed in the same family. Radiologically, diffuse pulmonary ossifications are easily misdiagnosed as other interstitial lung diseases and bronchiectasias.

Our case of the 51 year-old female was diagnosed as diffuse dendriform pulmonary ossification associated (or due to) systemic sclerosis, which is a multisystem disorder characterized by vascular damage and fibrosis, commonly associated with Raynaud's phenomenon, and of which more than half of patients have interstitial lung disease. Although interstitial lung disease associated with systemic sclerosis in isolation evolves to end-stage respiratory insufficiency in only a few patients, it may be associated with precapillary pulmonary hypertension, which an important cause of death for these patients. Interstitial lung disease associated with scleroderma, unlike its idiopathic counterpart, corresponds to non-specific interstitial pneumonia in most cases, whereas usual interstitial pneumonia is less frequently encountered. Although interstitial lung disease and/or idiopathic pulmonary fibrosis are listed in tables and textbooks as known conditions associated with lung ossification, in our literature search we did not find systemic sclerosis as specifically mentioned in any case of diffuse pulmonary ossification, and we could verify the extreme rarity of ossification in systemic sclerosis in general, since only 5 cases have been found on record involving soft tissue and skin. Thus, this case may possibly be the first associated with pulmonary ossification. The 58 year-old man in our second case of this presentation, according to our investigation, was considered idiopathic.

References ***(for cases 3 & 4)***

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AMR SEMINAR #61
CASE 5

Contributed by: Michele Bisceglia, M.D.
(Slides labeled: 101910-5 (A&B)

Clinical History: A 43-year-old female complaining of progressive palpebral ptosis for 3 years, followed by mild dysphonia, dysphagia, episodes of cramps, arthralgias and proximal muscular asthenia, was admitted in our hospital. Two years previously this patient had been diagnosed elsewhere with polymyositis, due to moderate elevation of serum levels of CPK (range: 325 to 735 U/l; normal value <170) and LDH (range: 546 to 1820 U/l; normal value <460) and electromyographic signs of myogenic disturbances. Accordingly she was given corticosteroid therapy. After 1 year, the clinical biochemistry normalized and corticosteroid therapy was interrupted; however, the clinical symptomatology continued to progressively deteriorate, mainly the palpebral ptosis with the patient occasionally needing to lift manually her eyelids. On admission, neurologic examination documented myopathic facies with bilateral non-fluctuant palpebral ptosis, inability to look downward, reactive contraction of the frontal muscle, and bilateral atrophy of the temporal muscles, with no loss of strength of the orbicularis oculi muscle. Additionally, slight columnar scoliosis, bilateral winged scapula, and slight loss of strength of the neck muscles, left pectoralis muscle and the right medium gluteal muscle were discovered. Walking was unaffected, while movement from a sitting to supine position was impaired. Osteo-tendinous reflexes were reduced.

Laboratory and Clinical Investigations: Routine blood chemistry tests as well as CPK and LDH values were in the normal range; free T3 and T4 tests for thyroid function were normal; anti-acetylcholine receptor antibodies to exclude myasthenia gravis were absent; HBsAg and anti-HCV antibodies were absent. Thoracic X-ray was normal; electrocardiogram and electroencephalogram were essentially normal; echo color doppler of the supra aortic trunks was normal; brain MRI did not reveal any significant pathologic findings; otorhynolaryngologic examination as well as audiometric test and ophthalmoscopic examination all were normal.

Muscle Biopsy and Tissue Preparation: With the clinical suspicion of mitochondrial myopathy the patient underwent open biopsy of the deltoid muscle. Tiny fragments of fresh muscle tissue were selected for ultrastructural examination and molecular investigation. The main part of the muscle tissue was appropriately oriented (both longitudinally and transversely) and mounted on thin cork discs, using Tissue-Tek® as adhesive, and snap-frozen in isopentane cooled in a metal container suspended in the mouth of a vacuum flask half-filled with liquid nitrogen. The cork disc with the mounted fragment of muscle tissue was then fixed to a metal chuck and the snap-frozen tissue serially sectioned in a cryostat at a temperature of minus 20°C. A double series of 20 five-micron thick transverse sections were obtained for histochemical and enzymohistochemical stainings.

Histochemical and Histoenzymatic Stains – Methods and Indications: The following histochemical stains were performed: haematoxylin and eosin (H&E) for a general view, modified Gomori trichrome for mitochondria (which stain red due to their DNA content), Veroheff van Gieson for interstitial fibrous tissue, PAS and D-PAS for glycogen, oil red O and Sudan-black for neutral lipids. Specific histochemical stains were performed for the following enzymes: myosin adenosine triphosphatase for myofibrils (myosin ATPase - preincubated at pH 10.0, pH 4.5, pH 4.28); myophosphorylase, phosphofructokinase, and myoadenylate deaminase for cytosol intermyofibrillary enzymatic reactivity; and nicotine adenine dinucleotide dehydrogenase tetrazolium reductase (NADH), cytochrome oxydase (COX), and succinate dehydrogenase (SDH) for mitochondrial activity of the muscle fibres. Since COX reflects the activity of complex IV of the mitochondrial respiratory chain and is mainly encoded by mitochondrial DNA [mtDNA], COX-deficient fibres are considered as the histologic marker of the mitochondrial disorders: for this reason and to easily detect COX-deficient fibres, sequential staining for COX followed by SDH was done (SDH represents the activity of complex II and is encoded exclusively by nuclear DNA [nDNA]). With this serial staining method COX-deficient fibres are highlighted as dark-blue on the background of the rest of the normal fibres which stain grey-brownish (a balanced color imparted by the dark-blue of the SDH stain and the light brown of COX, if employed in isolation on normally reacting fibres). Non-specific esterase for any possible denervated fibre and acid phosphatase for any autophagic intrafibrillary vacuoles were also performed.

Note regarding the glass slides circulated: *each AMR member will receive 1 slide which is labeled either as 101910-05/**A** corresponding to Gomori stain or as 101910-05/**B** corresponding to COX stain (assessing complex IV activity of the mitochondrial respiratory chain) followed by SDH (assessing complex II) .* I apologize for not providing all members with both types of sections.

Histopathological Features: On H & E the striated muscle tissue exhibited a normal fascicular architecture. The muscle fibres were uniformly normal in size with normal polygonal contours and normal peripherally placed nuclei. No necrotic fibres or inflammatory infiltrates were seen. Veroheff van Gieson staining did not document any increase of interstitial collagen, and PAS and D-PAS did not disclose any increase of intrafibrillary glycogen content. Gomori trichrome highlighted numerous (10% of the total) patchily distributed ragged-red fibres, i.e. fibres with an irregular subsarcolemmal rim of reddish material, indicating subsarcolemmal accumulation of mitochondria (*slide labeled 101910-05/**A***). The sequential COX-SDH stained sections showed numerous scattered hyperreactive dark-blue fibres (20% of the total), corresponding to those fibres with hyperplasia of the mitochondria and COX activity deficiency, on a background of grey-brownish fibres (*slide labeled 101910-05/**B***). NADH stain also documented some hyperreactive dark fibres (10% of the total). Myosin ATPase reactions showed both normal type I and type II fibres, predominately slow-twitch type I fibres, in accordance with the biopsy site (deltoid muscle). All the rest of the enzymatic stains highlighted normal activity of the intermyofibrillary network. Oil red O and Sudan black stainings revealed a slight increase of intrafibral neutral lipid droplets.

Ultrastructural Features: The most prominent finding were the subsarcolemmal and intermyofibrillar aggregates of numerous abnormal mitochondria seen in several muscle fibres. Mitochondria were usually larger than normal and polymorphic, often exhibiting paracrystalline inclusions, replacing the cristae and situated between the inner and outer membranes of the mitochondrial walls. These paracrystalline inclusions were frequently multiple and arranged in parallel rows ("parking-lot inclusions") and consisted of rectangular arrays of mitochondrial membranes in a linear or grid-like pattern. Mitochondrial cristae with anomalous annular or undulated configurations as well as intramitochondrial osmiophilic dense bodies in the matrix were also seen. Other pathologic findings were focal and moderate lysis of the sarcolemmal myofibrils as well as focal and moderate increase of the cytoplasmic lipid and glycogen content.

Clinical-Pathologic Diagnosis: based on both clinical, histological, histoenzymatic and ultrastructural findings the diagnosis of mitochondrial myopathy presenting with progressive external ophthalmoplegia (PEO) was made.

Discussion: Mitochondria are the main source of energy production in mammalian cells and accordingly primary mitochondrial disorders clinically involve tissues with the highest energy requirements, such as nervous, muscular, cardiac, and endocrine systems. Mitochondrial myopathies (MM) are mitochondrial disorders, which feature myopathy, and should be suspected when myopathy is accompanied by clinical disturbances affecting multiple organ systems. Extraocular muscles have fundamentally distinct properties that make them selectively vulnerable to certain neuromuscular disorders, including MM and myasthenia, although the latter is a completely different disease that impairs neuromuscular transmission due to autoantibodies to receptors and ion channels at neuromuscular junctions. Involvement of these muscles ("ocular myopathy"), manifesting as bilateral palpebral ptosis and ophthalmoparesis, is an important feature in various MM, and is the dominant symptom in chronic progressive external ophthalmoplegia (CPEO) syndrome, which may present in childhood up to late adulthood. PEO can also be part of other more complex syndromes with severe multi-organ dysfunction, such as Kearns-Sayre syndrome [occurring in childhood or adolescence in association with pigmentary retinopathy, cardiac conduction abnormality, ataxia, sensorineural deafness, and diabetes mellitus], various forms of ataxia neuropathy syndromes [ANS], and myopathy with neurogastrointestinal encephalopathy [MNGIE]. As in our case, proximal myopathy may be often present in PEO syndrome, while other symptoms deriving from multisystem involvement may be absent or variably present and of mild degree. However there are also several other types of MM with multi-organ involvement, which do not manifest ocular myopathy, such as MELAS [myopathy, encephalopathy, lactic acidosis, stroke-like episodes] and MERFF [myoclonus, epilepsy, and ragged-red fibres], just to mention the best known, both of which may also be associated with ataxia and cardiomyopathy, and as to the former even with deafness and endocrinopathy.

The prevalence of mitochondrial disorders is approximately 1 in 10,000 people. They have a poor genotype-phenotype correlation, and an extremely variable pattern of inheritance, ranging from maternally inherited (but randomly transmitted due to genetic heteroplasmy) to autosomal dominant or recessive (in case of nuclear DNA mutation). MM can occur at any age and have a broad variety of phenotypes. Regarding the clinical approach there are a few considerations to be taken in account: *i.* all patients with suspected MM should undergo cardiac, endocrine, auditory, and visual investigations; *ii.* in some patients with MM the myopathy can well be overshadowed by other clinical manifestations; *iii.* all patients with ocular myopathy should be suspected to harbour MM, after excluding

other diseases, mainly myasthenia, the latter being clinically characterized by fluctuant ophthalmoplegia and weakness of the orbicularis oculi muscle and mainly diagnosed on the presence of anti-acetylcholine receptors autoantibodies (it should be noted that unnecessary thymectomies, recorded in the literature, have been performed due to primary ocular myopathy misunderstood as myasthenic syndromes). *iv.* muscle biopsy is the main diagnostic tool to correctly ascertain MM (note: clinically two relatives in our patient's family, who were likely affected by MM, had previously been diagnosed with muscular dystrophy-NOS). In our patient the MM involved exclusively the muscular system and manifested with chronic progressively deteriorating ocular myopathy (i.e. PEO) in association with moderate proximal myopathy. Diverse genetic etiologies can be responsible for the mitochondrial dysfunction, since mitochondrial proteins are both encoded by mtDNA and nDNA, with lots of interplay between the two genomes (most of the mitochondrial proteins are encoded by nDNA). Point mutations and single large-scale deletions involving mtDNA derive from a direct involvement of mtDNA, while depletions and multiple deletions of the same mtDNA are a secondary effect of mutation involving the nuclear genome encoding mitochondrial protein. There are two main patterns of morphological changes suggesting to the pathologist which one of the two molecular events is involved: as a general rule, when COX-deficient fibres are scattered in a mosaic-pattern, mtDNA mutation is suggested, while when COX is uniformly decreased a nDNA mutation is likely. The major diagnostic features of mitochondrial myopath are: the presence of a substantial number (over 5%) of COX-negative fibres as seen by histoenzymologic (and their equivalent ragged-red fibres as seen with Gomori stain) and the ultrastructural detection of hyperplastic and abnormal mitochondria. However, there's a caveat: rarely, the biochemical defect does not involve complex IV/COX, in which case histoenzymologic analysis is normal.

Follow up: Molecular analysis was then performed for MERFF, MELAS, NARP, Kearns-Sayre syndromes, including direct sequencing of $tRNA^{leuc}$ and $tRNA^{lys}$ genes, but no mtDNA single deletion or point mutation were discovered. However, since negative findings from molecular analysis of the mitochondrial genome may not exclude MM, the previously established diagnosis remained unchanged.

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AMR SEMINAR #61
CASE 6

Contributed by: Ira Bleiweiss, M.D.

Brief Clinical History: Excision of a left breast mass in a 50-year-old woman

Clinical History: Routine mammographic screening revealed a well circumscribed density in a 50 year old woman's left breast. Sonography (see attached image) reveals an oddly irregular marginated partially solid lesion with peripheral duct dilatation. This was core biopsied and then removed after sonographic localization. As you all may know, I am a big believer in being aware of imaging findings whilst reading core biopsies and correlating; however, this one breaks all the rules. My most trusted breast imaging colleagues have told me that the sonographic image is like none they have ever seen – it reminds me of a bird – perhaps a stork. Maybe this is some sort of pathology Rorschach test.

The excision shows (much like the core did) a cellular benign spindle cell proliferation with no mitoses and no atypia. While it seems well circumscribed, the spindle cells infiltrate fat and breast tissue. There is no subepithelial stromal condensation as in phyllodes , and there are no big keloid-like areas as in myofibroblastoma, and the cells don't look right for that anyway. The cells are negative for beta-catenin (arguing against fibromatosis) and positive for CD-34. I think the ductal dilatation is probably secondary to the tumor growing into a duct and blocking it.

So I'm pretty sure what this tumor is not-not a phyllodes, not fibromatosis, not myofibroblastoma. Since I thought the pattern looked most like solitary fibrous tumor, along with the positivity for CD34, I finally called it that, although I was by no means convinced.

I notice that Falco and Janez have reported once case in the breast, so I'll be particularly interested in their thoughts.

Diagnosis: Solitary Fibrous Tumor of breast (I think)

AMR SEMINAR #61
CASE 7

Contributed by: Kum Cooper, M.D.

Clinical History: This 79-year-old man presented with left neck pain and submandibular gland enlargement. The surgeon resected the gland with a clinical impression of adenoid cystic carcinoma.

Diagnosis: Chronic sclerosing sialadenitis (Kuttner's tumor).

Discussion: Importantly, the lobular architecture of the gland is preserved, with chronic inflammation, periductal fibrosis, ductal ectasia and acinar atrophy. The degree of fibrosis and inflammation varies from lobule to lobule, within the gland. The inflammation is predominantly lymphocytic and plasmacytic, which has led recent investigation to include this entity in the spectrum of IgG4 lymphoplasmacytic sclerosing disease. Both IgG and IgG4 failed to show sufficient diagnostic immunoreactive plasma cells in this case. The clinical presentation in this patient is also typical, with recurrent pain and swelling (often associated with food ingestion).

AMR SEMINAR #61
CASE 8

Contributed by: Ivan Damjanov, M.D., Kansas City, Kansas

Clinical History: A 60-year-old man presented with clinical signs suggestive of bowel obstruction. Explorative laparotomy did not reveal any obstruction. Nevertheless a suspicious loop of the small intestine was resected and was found to be normal on pathologic examination. A month later he was readmitted and underwent extensive work-up with the presumptive diagnosis of intraabdominal adhesions. Radiologic studies revealed multiple fistulas and adhesions which made us suspect Crohn disease. His condition deteriorated and the signs of intestinal obstruction became critical, necessitating another laparotomy. A portion of the small intestine measuring 160 cm, attached to a thick and foreshortened mesentery was resected together with a portion of the corresponding mesentery. The surgeon noticed that the mesentery is very firm and rigid. The patient tolerated surgery very well and six months after surgery he is in good health and without significant abdominal or GI symptoms.

Pathological findings: The resected loop of the small intestine was attached to a fibrotic and thickened mesentery which contained nodular firm areas. On sectioning the mesentery appeared gritty. Microscopically the small intestine was congested but otherwise unremarkable. The mesentery showed extensive fat necrosis and broad areas of fibrosis, myofibroblastic proliferation, and prominent trabeculae of osteoid and calcified bone lined by osteoblasts. No nuclear atypia was noticed.

Diagnosis: Heterotopic mesenteric ossification (HMO), also known as mesenteritis ossificans.

Comments: The rapid onset of bone formation in the mesentery, which occurred in this patient in less than 6 weeks seems to be typical of this condition. Zonal osteogenesis and a lack of cytologic atypia and other signs of malignancy are important for the histologic diagnosis.

HMO, a term suggested by Wilson et al. (1) is a relatively rare condition usually related to trauma or previous abdominal surgery. The condition can involve the mesentery or the omentum, in which case it should be called obviously HOO (2). There are probably less than 50 published cases on record, but some cases were most likely not recognized as such or were labeled otherwise. Some of the cases reviewed by Patel et al.(3) were hiding in their files under other names such as "ossifying pseudotumor," "reactive myofibroblastic proliferation with ossification". Xiaohui Shi et al (2) like the term "pseudomalignant osseous tumor of the extraskeletal soft tissue". Intraabdominal myositis ossificans (IMO) is yet another name for the same lesion (1,4).

Zamolyi et al. (4) emphasize that HMO or IMO (as they call it) should be distinguished from extraosseous osteosarcoma, which could theoretically occur in the mesentery or the omentum. According to these authors there are published cases of mesenteric osteosarcoma, but "most of the existing reports are poorly documented" (4).There is no reason to doubt that one day a true extraosseous osteosarcoma of the mesentery will be reported, nevertheless.

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AMR SEMINAR #61
CASE 9

Contributed by: Otto Dietze, M.D.

Clinical History: 46 –year -old lady with a tumor in the transverse colon.

Diagnosis: Endometriosis of the colon.

Comments: (Nothing exciting.) Endometriosis of the colon is most frequent in the sigma and rectum and stenosis occurs most frequent due to growth within the muscular wall. I have not seen this polypoid growth pattern before.

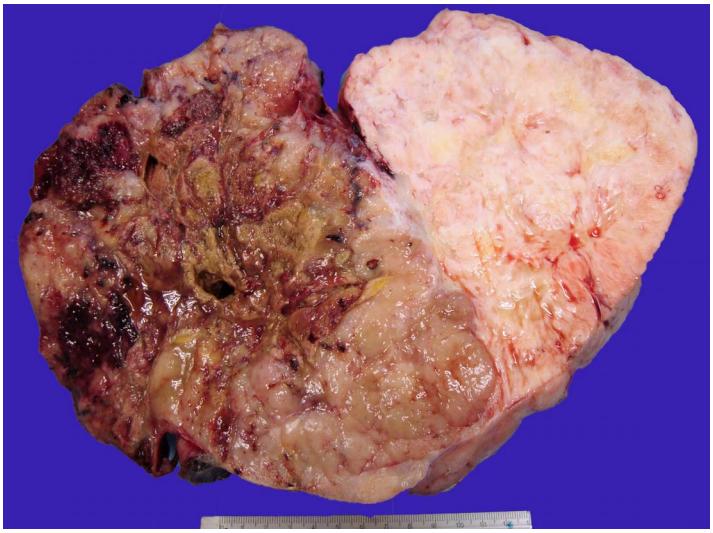
AMR SEMINAR #61
CASE 10

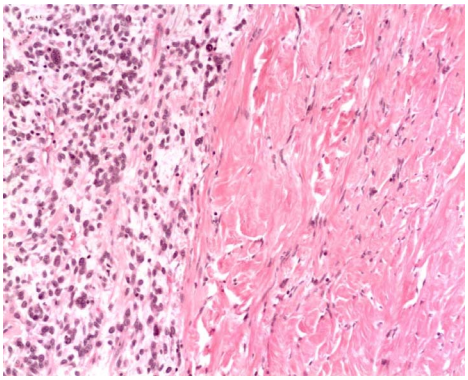
Contributed by: Hugo Dominguez Malagon, M.D.

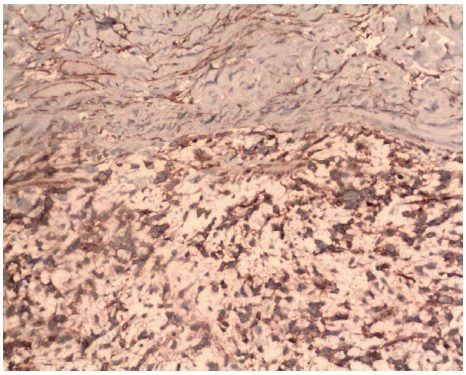
Clinical History: A 52-year-old female, 6 months before admission complained of productive cough, thoracic pain and weight loss of 10 kg, two months later appeared progressive dispnea and cough with dispnea. A CT scan revealed a large tumor (18 cm) occupying almost totally the right hemithorax with lung atelectasis and mediastinal shift and enlargement of subcarinal lymph nodes. A trucut biopsy was obtained interpreted as a solitary fibrous tumor. A thoracotomy revealed a pediculated tumor depending of the pleura.

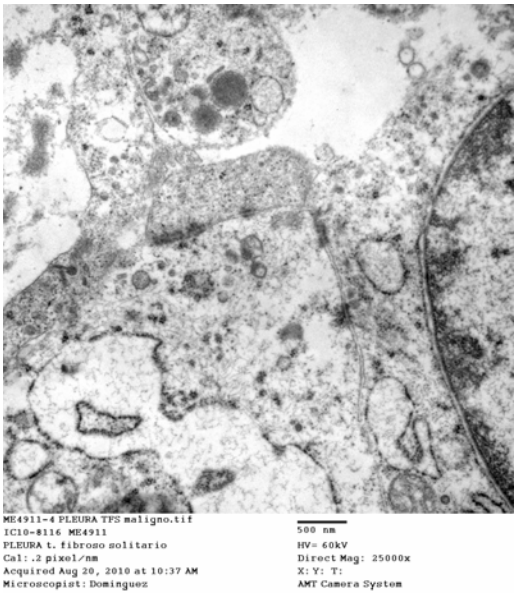
Pathologic findings: The tumor measured 28 x 18.8 x 12.5 cm, on cut section two components clearly separated were seen, a bland zone with myxoid and necrotic areas, and other with a solid dense appearance.
Histologically the dense zone had the typical morphology of a SFT with dense collagen, whereas the dedifferentiated zone has the appearance of a pleomorphic sarcoma with necrosis and many mitosis.
It was positive for vimentin, bcl-2, CD34 (in both components), and P16 (in the sarcomatous area). Negative for S100, EMA, CD99, and CK AE1-AE3. Proliferation index (Ki67) 15% in the sarcomatous area.
Electron microscopy demonstrated mesenchymal cells with long processes joined by primitive junctions or well formed desmosomes

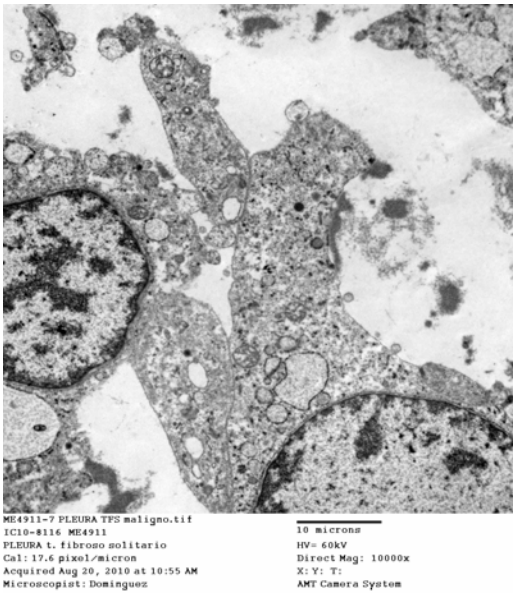
Diagnosis: Dedifferentiated solitary fibrous tumor.











Discussion. This case nicely illustrates grossly and histologically the differentiation phenomenon of solitary fibrous tumor (nicely described by Mosquera and Fletcher, AJSP 2009;33:1314) with expression of CD34 in both components. The cases that I have seen in the EM all show these finger-like processes delicately joined by macula adherens, most authors consider the cells of SFT simply as "fibroblastic", however I believe SFT belongs to the group of CD34+ dendritic cell tumors.

AMR SEMINAR #61
CASE 11

Contributed by: Vincenzo Eusebi, M.D.
(Case 11-10235)

Clinical History: A 56-year-old lady presented with a palpable lump in the upper outer quadrant of right breast. A core biopsy revealed an invasive poorly differentiated carcinoma which was scored B5.
This diagnosis led to quadrantectomy together with axillary sentinel node excision.
A 3 cm white-grey mass with invasive margins was present. Margins of the quadrant were free from tumour.

Histologically at low power the lesion has irregular margins, is multinodular and no plexiform growth pattern is evident . Undifferentiated malignant epithelial cells are immersed in lymphoid stroma. Epithelial cells are arranged in small clumps, show large irregular nuclei with prominent nucleoli, cytoplasms are amphophilic. Epithelial cells are surrounded and infiltrated by lymphocytes and plasma cells. Mitoses are numerous.

Diagnosis: lymphoepithelioma-like carcinoma, Rigaud type similar to those neoplasms seen in nasopharynx.

Immunohistochemistry revealed positivity for keratin 7. Ki 67 decorated 20% about of epithelial cells. Keratin 14, P63, ER,PR, AR, HER-2 were all negative. In situ hybridization for EBV was negative in epithelial cells. BRCA-1 test was not done.

The sentinel node revealed one macrometastasis.
Lymph node axillary dissection followed and all 22 lymphnodes found were reactive.

Lymphoepithelial-like carcinoma of the breast has been described in 2001 as an independent entity, and a few cases have been reported since. It is distinguished from medullary carcinoma as it shows invasive borders , no plexiform architecture is seen and so far no cases showing high weight keratins have been reported or seen.

Prognosis has been stated to be not very aggressive, although cases reported are very limited and FU is short in most of the cases.

The present carcinoma is a recent one.

AMR SEMINAR #61
CASE 12

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

Clinical History: A 24 year old male had abdominal pain. A 9 x 7 x 5 cm solid mass, with foci of necrosis, was found infiltrating the cecum.

Pathology: This shows ulcerated intestinal wall infiltrated by a lesion composed of mitotically active atypical epithelioid cells in a chronically inflamed focally myxoid stroma with scattered spindle cells. Immunohistochemistry was positive for desmin, SMA, and ALK in a nuclear membrane pattern (image provided). FISH confirmed *ALK* gene rearrangement.

Diagnosis: Epithelioid inflammatory myofibroblastic sarcoma.

Comment: This is an intra-abdominal variant of inflammatory myofibroblastic tumor, recently termed epithelioid inflammatory myofibroblastic sarcoma,[1] that is aggressive with rapid local recurrence and sometimes liver metastases. The 11 reported cases[1] occurred in childhood and adults (mean age 39 years) in mesentery or omentum and showed plump atypical epithelioid cells with vesicular nuclei and prominent nucleoli, with a minor spindle component, in a predominantly acutely inflamed myxoid stroma including focal necrosis in some. This case is unusual in apparently arising in the cecal wall. A distinctive feature on immunostaining for ALK is the ring-like pattern of nuclear membrane positivity as seen here, related to *ALK* gene rearrangement with fusion (in 3/3 cases) of *ALK* with *RANBP2* at 2q13, the latter encoding for a protein in filaments of the nuclear pore complex. A smaller number of cases showed a cytoplasmic pattern with perinuclear accentuation. Desmin, CD30 and SMA (in 50%) are also positive, with the myoid markers and ALK staining pattern excluding ALCL, and the absence of h-caldesmon, ALK pattern and genetic findings helping to exclude leiomyosarcoma.

Reference

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AMR SEMINAR #61
CASE 13

Contributed by: Christopher Fletcher, M.D.

Clinical History: A 60-year-old woman presented with a firm mass in the neck, apparently with no associated vascular symptoms. At surgery, a 2.5cm mass, which firmly encased the carotid artery, was excised.

Diagnosis: Sclerosing fibroinflammatory lesion ? type

Comments: At least to me, this is a very unusual perivascular fibroinflammatory lesion, in which one can also appreciate a focally prominent lymphoplasmacytic infiltrate extending into the vessel wall. Naturally I considered the possibility of a IgG4 sclerosing lesion but our immunostains show that only a very small number of the plasma cells were IgG4 positive. I could not identify anything to suggest an infective etiology. No doubt this lesion belongs somewhere in the spectrum of processes such as retroperitoneal fibrosis and sclerosing mediastinitis but I have not personally encountered a strikingly vasculocentric case such as this in the past and I will welcome any comments or suggestions from other members of the club as to how better to classify this lesion.

AMR SEMINAR #61
CASE 14

Contributed by : Andrew Folpe, M.D.

Clinical History: A 15-year-old girl presented with abdominal pain and was found to have an ovarian mass, which had undergone torsion. Following resection, the patient is currently disease free, without evidence of involvement of any other organ.

Pathological Findings: A hemorrhagic, partially infarcted, cystic 11 cm mass was received. On sectioning, a thin rim of viable-appearing tissue was present in the cyst wall.

Microscopic examination of the viable areas of the mass showed a distinctly nested neoplasm composed of epithelioid cells with voluminous clear to lightly eosinophilic cytoplasm and round to ovoid nuclei, with small nucleoli. Many of the neoplastic cells contained finely granular melanin pigment. Mitotic activity was absent. Stromal calcifications were frequently present adjacent to nests of tumor cells.

By immunohistochemistry performed at the referring institution, the tumor was negative for various cytokeratins, inhibin, Melan A, smooth muscle actins, PLAP, S100 protein, chromogranin, synaptophysin, desmin, caldesmon, calretinin, CD117 and AFP. HMB45 and tyrosinase were positive.

Molecular cytogenetic studies performed at the referring institution showed the tumor to be negative for EWSR1 rearrangement by FISH.

Immunohistochemistry performed at Mayo Clinic was negative for wide spectrum cytokeratins (OSCAR and AE1/AE3), EMA and CD10.

By FISH performed at Mayo Clinic, the tumor was positive for TFE3 gene rearrangement.

Diagnosis: Melanotic translocation Xp11-related neoplasm of renal type, primary to the ovary.

Comment: This tumor was sent to me in consultation with a suggested diagnosis of a PEComa of the ovary, with a request that I comment on its malignant potential. The outside institution had regarded it as histologically benign (as a PEComa), whereas a central pediatric pathology review had regarded it as high-grade malignant, mistaking the torsion-related changes for spontaneous tumor cell necrosis.

Although a PEComa is a very reasonable consideration for this tumor, especially in the absence of cytokeratin expression, I believe this neoplasm to be morphologically and immunophenotypically identical to those tumors previously reported in the kidney by Pedram Argani and colleagues as "melanotic Xp11 translocation renal carcinomas" (American Journal of Surgical Pathology 2009;33:609). In particular, the distinctly epithelioid appearance of the tumor cells, the abundant intracytoplasmic melanin pigment, and the stromal calcifications are all highly characteristic of these extraordinarily rare renal tumors, and not features I associate with PEComas. Our finding of TFE3 gene rearrangement would also seem to support classification of this tumor as a melanotic Xp11 translocation neoplasm of renal type, rather than a PEComa. Although a subset of PEComas shows TFE3 protein expression, TFE3 gene rearrangement has not been shown in PEComas, to the best of my knowledge.

Why use the term "neoplasm" rather than "carcinoma"? As is very nicely discussed by Argani et al, the epithelial nature of these Xp11-related tumors is tenuous at best, and they may in fact be much more closely related to PEComas. Turning it around, I very much wonder if some tumors previously reported as PEComas might instead be more closely related to these Xp11 tumors. I also chose to use the term "neoplasm" because of the unique clinical

issues surrounding this particular case, hoping that I could spare the patient potential over treatment, from over-aggressive gynecologic oncologists.

I'll be very curious in the opinions of the AMR members about this case. To the best of my knowledge, this is the first Xp11 melanotic neoplasm to be identified outside of the kidney. Does anyone else have a similar case in their files?

AMR SEMINAR #61
CASE 15

Contributed by: Jerónimo Forteza Vila, M.D.

Clinical Data: 69-year-old male, with a history of grade II chondrosarcoma of the femur diagnosed in 2002. The patient went to a doctor consultation with pain in the dorsal spine, poorly controlled since 2009 with analgesic treatment. CT scan identified soft tissue mass in the 4th thoracic vertebra and osteolytic lesions in 5th and 9th thoracic vertebrae, also found wedging of several vertebral bodies, these findings are confirmed in PET and bone Gammagraphy.

A biopsy was performed, suspecting a clinical diagnosis of metastasis.

Complementary tests do not show any primary tumor or other signs that may suggest metastatic disease.

Microscopic Description: Diffuse proliferation of large cells with histiocytic and pleomorphic appearance, accompanied by small lymphocytes. The Immunohistochemical study showed positivity for vimentin, fascin, and in focal form for CD68, lysozyme, and LCA. S100 shows positivity in isolated cells. CD23, CD21, CD35, CD1a, CD20, CD3 and CD30 were negative. Also negative were epithelial markers (CK AE1-AE3, CK 5 / 6 and CK 18), muscle markers such as smooth muscle actin and desmin, and other markers such as CD34 and HMB45.

Diagnosis: Histiocytic Sarcoma / Dendritic cell tumor.

AMR SEMINAR #61
CASE 16

Contributor: Janez Lamovec, M.D., Institute of Oncology, Ljubljana, Slovenia

Clinical History: A 69-year-old woman was admitted because of recurrent extensive skin lesion in the left gluteal region. Five year previously she had had a similar lesion on her left vulvar labia that extended toward left gluteal region; the lesion was excised, the excision margins were not free of the lesion. She was irradiated to the region, including lower abdominal wall where similar changes were seen.

The patient had a 30 year long history of recurrent bilateral chylothorax and chylous ascites that was drained on numerous occasions without identifying a real cause; obstruction or malformation of ductus thoracicus was suspected but never proven; lymphangiography results were inconclusive. She had an explorative laparotomy performed 25 years ago and several lymphangiomata, some of them cystic, of the adipose tissue of mesentery were identified; she also had a pleural biopsy performed with no conclusive results – histologically only fibrous and inflammatory reactive changes were seen.

The patient has more or less constant lymphedema of lower abdomen and lower extremities with occasional vesicular/papular lesions of the skin in these regions that sometimes rupture and leak sero-sanguinous fluid.

Pathologic Findings: Grossly, the excised specimen was represented by elipse of skin and subcutaneous tissue that measured 18 x 5 cm. Practically the whole surface was studded by innumerable projections, knob-like or button-like, of grayish, pink or blue color that were soft on palpation, some leaked sero-sanguinous fluid (see photograph). Histologically, there is a multitude of lymphatic channels predominantly in subcutis but also in dermis, some anastomosing and dissecting collagen fibres and adipose tissue. The spaces are lined by flattened endothelium, one-cell thick, and surrounded by nests and strands of smooth muscle cells. Some spaces are cystic, particularly the most superficial ones, subepidermally, forming grossly evident projections. Lumens are mostly empty, some filled with blood. Aggregates of lymphoid tissue are focally seen. Immunohistochemically, endothelial cells showed positive reaction for CD31, CD34 and podoplanin.

Diagnosis: Superficial (dermal/subcutaneous) lymphangiomatosis (with visceral – pleural/peritoneal involvement with chylothorax and chylous ascites).

Comment: I have problem with this lesion and am eagerly awaiting your comments. I reexamined the small biopsy from the mesentery and indeed it appears as lymphangioma, exactly as this one in the submitted slide. The lesion from vulva is also identical with it. Computerized tomography did not reveal any parenchymal organ, deep soft tissue and bone involvement. We have no information whether the patient had any lesion of this type in her childhood. Such lesions are unusual in adults but definitely possible. The association of soft tissue and bone lymphangiomatosis with chylothorax has been observed before although rarely.
The submitted lesion is not morphologically very exciting but in the clinical setting quite rare and unusual. I would be happy to hear your comments, suggestions, etc.

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2. Gomez Singh C et al. Lymphangiomatosis of the limbs. Clinicopathologic analysis of a series with a good prognosis. Am J Surg Pathol 1995; 19: 125-133.

AMR SEMINAR #61
CASE 17

Contributed by: Michal Michal, M.D., Czech Republic
(Case # M31793/08)

Clinical History: A 24-year-old man presented with a right testicular mass that was noted because of enlargement of the testis. The serum level of β-hCG was elevated whereas that of alpha-fetoprotein was normal. An inguinal orchiectomy was performed. In the testis, there was a 2,5 cm large, well demarcated, non encapsulated tumor. The cut surface was heterogeneous, with solid and cystic areas. No areas of hemorrhage or necrosis were seen. A laparoscopic retroperitoneal lymph node dissection was performed which yielded 15 tumor-free lymph nodes. No additional treatment was given. The patient is alive and well three years after the orchiectomy.

Histopathological examination of the tumor revealed two types of intermingled neoplastic tissues, the majority (65%) of which showed classical features of a teratoma consisting of hyaline cartilage and cystic structures lined by keratinizing squamous or enteric type epithelium with goblet and cylindrical cells. In small areas there was a granulomatous tissue response around keratinous debris. The other component (35%) displayed sheets, nests and single dispersed polygonal variously sized epithelioid cells in a loose myxoid stroma. These cells mostly showed abundant focally vacuolated oxyphilic cytoplasm and the nuclei were moderately pleomorphic. Some nuclei had moderately large nucleoli. The majority of these cells had one nucleus but some cells with three and up to four nuclei were seen. Some areas revealed a clear cell change in the neoplastic intermediate trophoblasts and extracellular fibrin deposits. The morphology of these cells was consistent with intermediate type trophoblasts- placental site trophoblastic cells (PSTT cells). Mitotic figures including atypical ones were easily discerned. In some areas we found condensation of intermediate trophoblastic cells around blood vessels with frank invasion to the muscular vessel walls undermining the endothelium so that in places the mononuclear neoplastic cell replaced the whole thickness of small veins. No syncytiotrophoblastic cells were seen. Testicular tubules contained intra tubular germ cell neoplasia-ITGCN. No neoplastic cells were seen in sections from the rete testis or the spermatic cord. Beside the neoplastic trophoblastic cell there were found small groups of nonneoplastic eosinophilic Leydig cells in between the testicular tubules, which were easily discerned from neoplastic cells by having small nuclei devoid of atypism and mitoses.

The proliferation index as estimated with Ki67 in the Immunohistochemical study was on average 50% in the PSTT cells, however, in some areas up to 70% of these cells showed proliferative activity. Human chorionic gonadotropin (hCG) and human placental lactogen were expressed in 10% and 30% of PSTT cells respectively of the cells with a highly variable intensity. None of the teratomatous or trophoblastic components displayed any immunoreactivity with PLAP, OCT3/4 or Nanog , all three of which were distinctively positive in the ITGCN-U. Inhibin stained most of the PSTT cells and normal Leydig cells while PSTT cells were calretinin negative. All testicular structures were alpha-fetoprotein negative. Minority of PSTT cells stained with EMA antibody. All these neoplastic cells were cytokeratin 7, cytokeratin 18 and pan-cytokeratins positive and cytokeratin 20, S-100 protein and p63 negative.
In the molecular genetic study (FISH), performed as described previously, we found that all neoplastic cells showed a 12p : CEP 12 ratio of 2.04, i.e. amplification.

Diagnosis: Placental site trophoblastic tumor of the testis arising as a component of germ cell tumor.

Comment: Testicular tumors with intermediate trophoblastic differentiation are extremely rare occurrences. I am only aware of one such case which occurred in a 16 month old boy **(1)** where PSTT occurred as a pure tumor and a case, where intermediate trophoblastic tumor component that was labeled as PSTT was part of a testicular mixed non-seminomatous germ cell tumor with a late retroperitoneal recurrence **(2)**. We have recently published this case in the Human Pathology **(3)**.

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AMR SEMINAR #61
CASE 18

Contributed by: Markku Miettinen, M.D.

Description: 48-year-old male. Adrenal mass. No known radiation history.

Diagnosis: Epithelioid angiosarcoma involving adrenal

This angiosarcoma has predominantly epithelioid cytology and contains both vasoformative and solid areas. I believe it was reported in the article: "Epithelioid angiosarcoma of the adrenal glands. A clinicopathologic study of nine cases with a discussion of the implications of finding "epithelial-specific" markers. Wenig BM, Abbondanzo SL, Heffess CS: Am J Surg Pathol 1994;18:62-73.

This tumor is positive for endothelial markers CD31, ERG, and claudin-5. The first two are fairly specific endothelial markers among mesenchymal tumors. However, ERG is also present in some Ewing sarcomas and claudin-5 is widely present in various carcinomas. Keratin-positivity is fairly common in angiosarcomas with epithelioid features.

AMR SEMINAR #61
CASE 19

Contributed by: James Strauchen, M.D.

Clinical History: This 67-year-old woman underwent right mastectomy for infiltrating mixed lobular and duct carcinoma in 1994 and left mastectomy for infiltrating duct carcinoma in 1998 followed by bilateral reconstruction with McGhan silicone implants. She also underwent right hemicolectomy for moderately differentiated adenocarcinoma of the transverse colon in 2005. In 2011 she presented with complaints of increasing discomfort around the right implant and biopsy of the right implant capsule was performed. She subsequently underwent removal of both the right and left implants and capsules.

Pathologic Findings: The specimen was a surgical biopsy of the right implant capsule and consisted of a portion of firm, fibro-membranous tissue measuring 2.5 x 1.5 x 0.3 cm. Microscopic examination revealed a dense infiltrate of histiocytes and numerous eosinophils. Scattered among these and partially obscured by them are large atypical cells. These are readily appreciated on the CD30 stains (Fig 1&2). Immunohistochemical stains showed the atypical cells to be positive for CD30, CD3, and CD5 (focal); negative for EMA, ALK, cytokeratin, CD34, S100, CD1a, and CD163. Subsequent complete excision showed focal residual lymphoma within the capsule.

Diagnosis: Anaplastic large cell lymphoma, ALK negative, breast implant-related.

Comments: In January 2011 the FDA issued an advisory regarding the possible association of breast implants (both silicone and saline) with the development of anaplastic large cell lymphoma around the implant. 34 cases have been reported in the literature worldwide and the FDA is aware of 60 cases in total. The median time to development of lymphoma is 8 years with cases as early as 1 year and as late as 23 years. The lymphomas typically involve an effusion around the implant and the implant capsule without invasion of the surrounding breast. The vast majority of lymphomas have been ALK negative. The prognosis is generally favorable following surgical removal of the implant and capsule, however, rare fatal cases have occurred. Adjuvant radiation and chemotherapy is generally not recommended if there is no spread beyond the implant capsule. Aspiration cytology of persistent peri-implant effusions has been recommended for early diagnosis.

AMR SEMINAR #61
CASE 20

Contributed by: Saul Suster, M.D.
(Case contributed by Dr. Luis Antonio Diaz, Mexico City, Mexico).

Clinical History:
A 47 year old woman with no pertinent past history was seen for dysphagia. An upper endoscopy revealed a polypoid, luminal tumor mass in the proximal third of the esophagus. The lesion was removed piecemeal, and consisted of several tissue fragments that measured in aggregate 3.7 x 3.0 cm.

Pathologic Findings:
This is a polypoid, submucosal spindle cell proliferation composed of fascicles of atypical spindle cells admixed with a heavy lymphoplasmacytic cell infiltrate. The atypical cells scattered in the stroma have large, vesicular nuclei with very prominent eosinophilic nucleoli. Reed-Sternberg-like forms can be appreciated, as well as cells with cytoplasmic vacuoles resembling lipoblasts. Many of the cells display intranuclear vacuoles or inclusions. Despite the marked nuclear pleomorphism and atypia, however, mitoses were very scarce.

Immunohistochemical staining showed focal, weak positivity for calponin in the stromal spindle cells, but the spindle cells were negative for SMA, CD34, CD117, DOG-1, ALK-1, desmin, S-100 protein, cytokeratin AE1/AE3, CD21 and CD35. Ki-67 was negative in the nuclei of the atypical cells.

Diagnosis: Not sure - ?myofibroblastic tumor ?inflammatory pseudotumor ?myxoinflammatory fibroblastic sarcoma.

Discussion:
The case was submitted in consultation from Mexico City with a diagnosis of inflammatory myofibroblastic sarcoma of the esophagus. Although this may well be the case, I felt that the cytologic atypia was "too much" for an inflammatory pseudotumor. The prominent eosinophilic nucleoli and pseudolipoblastic cells reminded me of myxoinflammatory myofibroblastic sarcoma of soft tissues. Although these tumors are supposed to be restricted to the extremities, we have seen cases with identical features in more central locations; under those circumstances the tumors are most often declared to be "inflammatory MFH".

In the present case, I'm disturbed by the striking nuclear pleomorphism and prominent eosinophilic nucleoli, although the good circumscription, polypoid configuration, and absence of necrosis or mitotic activity speak against a malignant neoplastic process.

Any suggestions for further work-up? Has anyone come across a similar case in the esophagus before?

AMR SEMINAR #61
CASE 21

Contributed by: Lawrence Weiss, M.D., City of Hope, Duarte, CA

Long History: 70-year-old female with a 3 weeks history of pain, who was found to have a 16.5 cm. destructive mass in her proximal humerus with invasion into the glenoid and surrounding shoulder tissue. A forequarter amputation was performed.

Gross: There was a 16.5 x 14.0 x 12.0 cm. fleshy tumor obliterating the upper part of the humerus.

Immunos: None.

Diagnosis: Dedifferentiated chondrosarcoma with giant cell tumor-like areas.

Discussion: I tried to get both areas on one slide, and I hope I was successful. This was not a diagnostic challenge, but hopefully a pretty case. Most of the tumor was chondrosarcoma. These areas transitioned to a pleomorphic sarcoma, often with giant cells, which transitioned to areas histologically acceptable for giant cell tumor of bone. Such cases, while rare, have been reported, and should not be mistaken for a benign lesion on misguided biopsy.

Reference: Estrada, Ayala, Valerie, and Czerniak: Dedifferentiated chondrosarcoma with a noncartilaginous component mimicking a conventional giant cell tumor of bone. Ann Diagn Pathol 6:159, 2002.

AMR SEMINAR #61
CASE 22

Contributed by: Bruce M. Wenig, M.D.

Clinical History: 26-year-old female presented with an enlarging painful left parotid mass of a few months duration. The patient denied a history of a long-standing parotid mass. Clinically and radiographically the mass involved the facial nerve. A left radical parotidectomy with sacrifice of the facial nerve was performed.

Histology: The resected mass was described as tan-brown, firm and well-circumscribed measuring 2.4cm in greatest dimension. Histologically, the neoplasm was multinodular and entirely comprised of oncocytic cells lacking significant nuclear pleomorphism, increased mitotic activity or necrosis. However, there was infiltrative growth including perineural invasion (present in the submitted slides) and lymph-vascular invasion (not present in the submitted slides).

Special stains: Histochemical stains for epithelial mucin including mucicarmine and periodic acid Schiff with diastase were negative. Immunohistochemical staining for S100 protein confirmed the presence of perineural invasion.

Diagnosis: Oncocytic carcinoma**.**

Discussion: Oncocytic carcinoma is a malignant salivary gland epithelial tumor predominantly or exclusively composed of oncocytic cells with cytomorphologic features of malignancy and/or invasive growth. It is a rare tumor type representing less than 1% of all salivary gland tumors. Oncocytic carcinoma most frequently occurs in the 5th-8th decades of life. Approximately 80% of oncocytic carcinomas occur in the parotid gland (80%); other sites of occurrence may include submandibular gland and much less often in association with minor salivary glands. Typically, the clinical presentation is that of a mass or swelling with or without associated pain and/or facial nerve paralysis; cervical lymphadenopathy at presentation is fairly common. Oncocytic carcinoma may arise from a long-standing benign oncocytoma or occur de novo; those cases occurring in association with an oncocytoma may present with rapid enlargement of a preexisting mass lesion.

The histology of oncocytic carcinomas include a partially encapsulated or unencapsulated lesion showing varied growth patterns, including sheets and nests of neoplastic cells infiltrating surrounding tissues with loss of normal lobular architecture. The neoplastic cells are characterized by the presence of large, round to oval cells with abundant granular eosinophilic cytoplasm due to the absolute increase in the number of cytoplasmic mitochondria; nuclei tend to be enlarged, centrally located, round to oval with vesicular chromatin and often with prominent nucleoli. Ductal differentiation may be present; oncocytic cells may form pseudoluminal spaces. Nuclear pleomorphism varies from case to case and even within the same case. Any n tumor may demonstrate foci with absent nuclear pleomorphism near to or admixed with cells showing moderate to marked nuclear pleomorphism; these features raise the possible occurrence of an oncocytic carcinoma arising in association with an oncocytoma. Increased mitotic activity and necrosis may be present. Invasion is present and includes infiltration of nonneoplastic salivary gland parenchyma, surrounding connective tissues, neurotropism and/or angioinvasion. Special stains (histochemistry and immunohistochemistry) are not usually required in the diagnosis of oncocytic carcinoma.

The differential diagnosis includes oncocytoma and oncocytic variants of more common types of malignant salivary gland tumors (e.g., mucoepidermoid carcinoma, acinic cell adenocarcinoma). The presence of infiltrative growth differentiates this patient's neoplasm from an oncocytoma. While it is possible that this carcinoma developed from an oncocytoma, given the absence of a long-standing parotid mass and short duration of symptoms it would appear this carcinoma occurred de novo rather than from a preexisting oncocytoma. The absence of foci diagnostic for mucoepidermoid carcinoma and acinic cell adenocarcinoma excludes such diagnostic considerations.

Treatment and Prognosis: **T**he usual treatment for oncocytic carcinoma is complete surgical excision that often necessitates total parotidectomy; nodal dissection is advocated given the increased incidence of regional (nodal) metastasis. The biologic behavior is that of a high-grade malignancy with a tendency to recur; tendency to metastasize including regional lymph nodes and distant metastases (e.g., to lungs, kidney, mediastinum, liver, bone and thyroid gland). Distant metastasis is associated with poor prognosis resulting in tumor-related death within 4 year.

This case: From the above discussion, the majority of parotid gland oncocytic carcinomas occur in older aged patients, show high-grade histomorphology and tend to disseminate early in the disease course. The unusual features of this patient's case are the young age of the patient and the presence of a morphologically bland (i.e., benign) appearing oncocytic neoplasm but with clinical aggressive behavior and histologic evidence of invasive growth. It is conceivable that she may have a favorable prognosis given the young age of occurrence and absence of metastatic disease.

AMR SEMINAR #61
CASE 23

Contributed by: Ady Yosepovich, M.D., Tel-Aviv, Israel.

Clinical History: A 35 year-old female addressed for medical help because of left breast pain that continued for over a year. She did not have any significant medical history or any family history of breast cancer. Breast mammography and U.S. was normal, breast MRI revealed an ill defined 2.5 CM mass with irregular contour.
A core needle biopsy was performed and the pathological report was indicative of a "well to moderately differentiated infiltrating ductal carcinoma" – the immonostatus of ER, PR and HER 2 were negative (triple negative case).
Lumpectomy and SLN biopsy was performed.

Pathology: The lumpectomy specimen showed a 2.4 CM irregular firm mass. Sections taken from the tumor showed carcinoma with invasive growth pattern, shrinkage artifacts are evident. At areas there is a mixture of proliferating glands and basement membrane components (cylindromatous component). Some areas consist of glandular structures creating a close resemblance to cribriform carcinoma. Some areas show solid growth pattern with increased mitotic activity.

P63 immunostain was positive in part of the tumor cells
c-KIT immunostain was also positive.
ER, PR, HER 2 immunostains were all negative.
The margins were free of tumor. The sentinel node was negative.

Diagnosis: Adenoid cystic carcinoma of the breast with solid high grade areas.

Comments: ACC of the breast is a rare histological subtype of invasive breast cancer, usually showing a triple negative phenotype. Although there is limited data, it is regarded as a low grade tumor with favorable prognosis. In the era of neoadjuvant therapy, in which treatment decisions are made according the limited tissue from core needle biopsies, it is important to consider this subtype when assessing low grade tumors with triple negative phenotype in order to avoid aggressive systemic treatment.
According to recent literature, unless the tumor is very large there is no need for systemic therapy, the tumors only rarely metastasize to axillary lymph nodes and the need for SLN biopsy in small tumors is questioned.
This case posed a difficult decision to for the oncologists – a young patient, pretty large tumor, favorable histological triple negative subtype, high grade solid area. The decision was not to give systemic treatment but to proceed only with adjuvant irradiation therapy.

Although the presenting symptom was pain, perineural invasion was not identified in this case. Unlike the head and neck counterpart, only rarely is it identified in the breast. It remains to be elucidated if tumor microenvironment factors contribute to pain pathogenesis in these cases.

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AMR SEMINAR #61
CASE 24

Contributed by: Abbas Agaimy, M.D.

Clinical history: This 68-year-old woman with a history of diabetes mellitus type 2 and chronic alcohol abuse presented with unexplained weight loss. Her liver function test and tumor markers (AFP, CEA) were normal. Imaging showed a 7-cm mass in the left liver lobe (segment III). The liver tumor was completely resected. Intra-operatively, there was no evidence of peritoneal tumor spread or a pancreatic mass. The patient has no recurrence or metastasis 38 months after surgery.

Macroscopic features: A 7-cm well circumscribed lobulated mass with grey-whitish cut-surface. The resection margin was free. There were no foci of necrosis.

Histological findings: The tumors formed large lobules separated by fibrous septa containing bile ductules. The tumor cells were large and polyhedral with basally located nuclei and distinct cell borders. They were predominantly arranged in small well organized acini that occasionally blended with solid foci. The impression at low power magnification was that of "ectopic pancreatic tissue". Some lobules were composed predominantly of cystically dilated acinar glands containing detached epithelial cells, a few histiocytes and eosinophilic material. Bile secretion was not detected. The apical cytoplasm contained numerous amorphous hyaline bodies that were PAS-positive and diastase-resistant. PAS stain also revealed apical cytoplasmic positivity. Mitoses were uncommon (<4 mitoses/10 high power fields). Despite extensive sectioning, no additional component of hepatocellular carcinoma, cholangiocarcinoma or ectopic pancreas was detected. The surrounding liver parenchyma showed no signs of chronic liver disease, steatosis or fibrosis.

Immunohistochemical findings: The tumor cells stained variably (>50%) with pankeratin (KL-1) and CK 18, focally with EMA and amylase and lipase (the latter two showed luminal and occasionally apical cytoplasmic reactivity). They were negative for trypsin, AFP, HepPar-1, CK7, CK19, CK20, CD56, and CDX2. CD10 showed weak luminal staining in one case. No canalicular staining for CD10 or polyclonal CEA was detected. The proliferation fraction (MiB1) varied within the tumor from 2%-10%. P53 stained 10-15 of tumor cell nuclei.

Diagnosis: Pancreatic-type acinar cell carcinoma of the liver

Comment: In our opinion, this unusual liver neoplasm fulfilled both histological and immunohistochemical features to be diagnosed as pancreatic-type acinar cell carcinoma of the liver. It clearly deviates from tubular or acinar-like cholangiocellular carcinoma by: 1) arising in a non-cirrhotic liver, 2) lacking prominent stromal desmoplasia, 3) absence of biliary-type cytokeratins and other facultative biliary markers, 4) displaying a peculiar acinar differentiation and lobular pattern that is very reminiscent of ectopic pancreatic tissue and 5) following a less aggressive clinical course compared to common liver cancer. The clear-cut atypical cellular features, the infiltrative microscopic pattern and the large tumor size are consistent with a malignant neoplasm. We could exclude liver metastasis from an occult pancreatic acinar cell carcinoma by absence of metastasis in other organs, solitary nature and large size of the lesion and unremarkable pancreas intra-operatively and on follow-up (38 months). The tumor histology also clearly separates it from pseudoacinar hepatocellular carcinoma.

Previous reports of extra-pancreatic acinar cell carcinomas suggested an origin from heterotopic or metaplastic pancreatic tissue, and this could be demonstrated in some cases. It is known that both pancreatic and biliary tract epithelia develop from the same progenitor cells making an origin from non-committed biliary stem cells possible. In a recent study, metaplastic pancreatic acinar tissue has been detected in 4.2% of liver explants and showed close spatial relationship with reactive bile ductules with immunophenotypic transition from bile ductules to pancreatic acinar tissue. On the other hand, acinar cell carcinoma of the pancreas occasionally produces AFP similar to

hepatocellular carcinoma and a rare example of pancreatic neoplasm with hepatocellular differentiation has also been reported. These observations make it likely that a mechanism of "transdifferentiation" might explain the origin of primary acinar cell carcinoma in the liver without the need for ectopic pancreatic tissue as a precursor.

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AMR SEMINAR #61
CASE 25

Case submitted by: Saul Suster, M.D.
(Case contributed by Dr. Irene Aguilera-Barrantes, Costa Rica, Central America).

Clinical History: A 32 year old woman was seen for a nodule in her vulva that was thought to represent clinically a Bartholin's cyst. The nodule was excised.

Pathologic findings: the nodule is well circumscribed and composed of a proliferation of spindle cells embedded in a myxoid matrix. The lesion has a striking lobular architecture on scanning magnification. On higher power, many of the cells display an epithelioid appearance with some nuclear atypia and pleomorphism. Very few mitoses (none atypical) could be identified. Inflammatory cells with numerous eosinophils are present scattered in the background. Some of the cells displayed intranuclear inclusions, others has a vacuolated, pseudolipoblastic appearance. I was not able to find any good virocyte-like nucleoli or Reed-Sternberg-like cells.

Special stains: Immunoperoxidase stains showed cytoplasmic positivity only for pan-actin (HHF-35). All other markers tested, including CD34, cytokeratin AE1/AE3, desmin, SMA, S-100 protein and EMA were negative.

Diagnosis: Don't know! (?pseudotumoral reactive fibro/myofibroblastic proliferation; ?inflammatory myxoinflammatory fibroblastic sarcoma)

Comment: I don't know what this tumor is. The growth pattern is not good for nodular fasciitis, inflammatory myofibroblastic tumor, or any of the other reactive/pseudotumoral entities that I know. Neural or lipomatous conditions were considered but are not supported by the special stains. A myxoinflammatory fibroblastic sarcoma could fit well for the combination of spindle+atypical cells, myxoid stroma, and inflammatory infiltrate, but the location would be atypical and there are no convincing Reed-Sternberg-type nucleoli. I would appreciate any ideas for workup of if any of our soft tissue gurus can come up with a name and/or confidently recognize what this is.