

# AMR Seminar #70

## Case – 1

**Contributed by: Volkan Adsay, M.D.**

**Clinical History:** 44-year-old male with history of glioblastoma, ALS (amyotrophic lateral sclerosis), status post stem cell transplant, and hypertension who presented with fever, tachycardia, and severe ascites. He was treated for presumed bacteremia, underwent paracentesis to manage ascites, and had new onset seizures. Due to increased deterioration and complications, he was discharged home with hospice and expired at home. At the request of the clinical team, an autopsy was performed.

**Gross Findings:** Severe clear-yellow fluid in abdominal cavity with omental caking was striking.

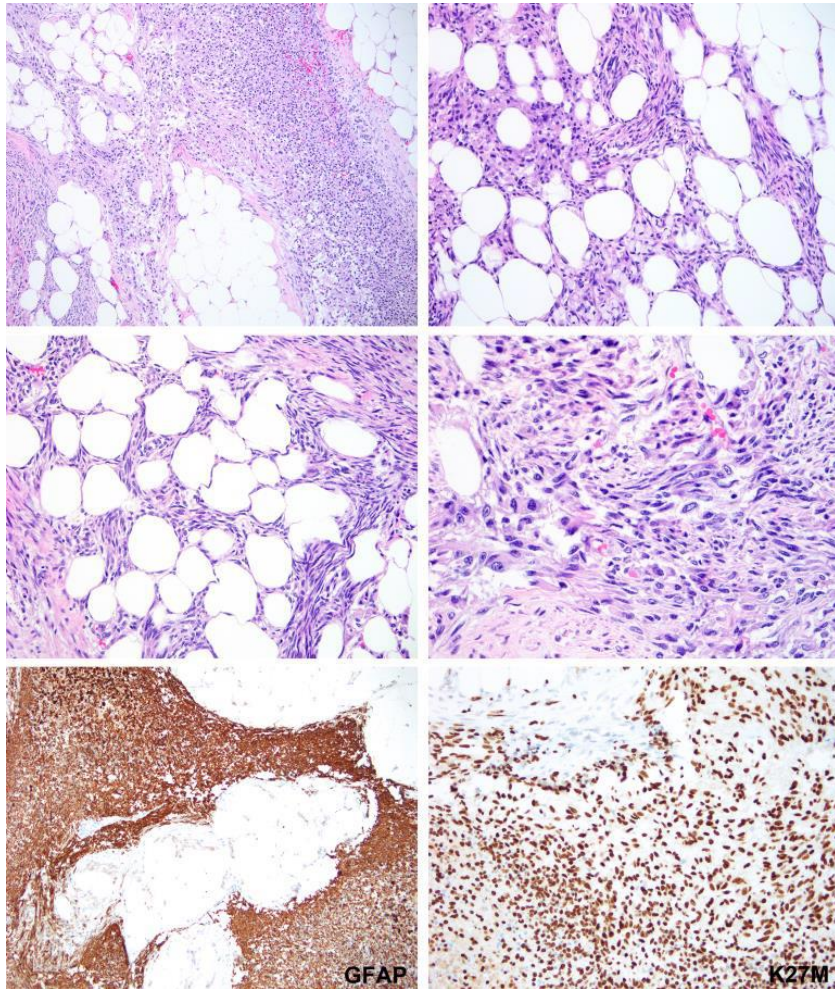
**Histopathological and Immunohistochemical Findings:** Autopsy revealed that the surfaces of the pleura, small intestine, large intestine, stomach, gallbladder, pancreas, liver, and spleen have attached atypical spindled and epithelioid cells arranged in sheets and covering the surfaces of the organs. In many sections, the tumor cells appeared to be preferentially distributed on the peritoneal surfaces. The omentum is involved by sheets of these atypical cells also in fibrous bands. Neoplastic cells showed positivity for GFAP, K27M and OLIG2.

**Diagnosis:** Hard to believe-oma, but seems to be real: Metastatic Glioblastoma of Diffuse Midline Glioma (H3K27M mutant) type.

**Discussion:** I have to tell you from the get-go that I have no idea what I am talking about here. The discussion below is coming from our neuropathology gurus. In fact, I have to tell you all that I had a very hard time believing this, first, but it seems to be real. The patient had a glial neoplasm that was located in the midline and was high grade with necrosis and all other attributes of glioblastoma multiforme. Apparently (I am just learning this), the midline location and specific mutation (H3 K27M), which was confirmed both by immunohistochemistry and molecular analysis, makes this a distinctive entity. This entity apparently occurs in children, but recently, it was observed that mutations arising in the histone variant H3.3 (encoded by the genes H3F3A and H3F3B), or H3.1 genes have been identified as a genetic signature of pediatric high grade gliomas also occurs in a smaller subset in adults (1). Two specific histone mutations in H3-mutant GBMs that are mutually exclusive with IDH mutations have been identified; one is present at amino acid 27 resulting a substitution of lysine for methionine (K27M) and the second at position 34 resulting in a substitution of glycine for either arginine or valine (G34R/V) (2,3). H3 K27M mutation was found to strongly correlate with midline high-grade gliomas of younger children, with the classic presentation in the pons (ex. DIPG) or thalamus, though they have been identified in adults to a lower extent. The G34R/V variant is more often seen in supratentorial high-grade astrocytomas.

The revised 4th edition of the WHO Classification recognizes the entity of diffuse midline glioma, H3 K27M-mutant, with a corresponding WHO grade IV designation (4). The presence of an H3 K27M mutation correlates with malignant behavior and shorter survival regardless of its histologic features. H3 K27M mutations have been described in high-grade astrocytomas of the spinal cord in the pediatric and young adult population, further supporting the associations with younger age, aggressiveness and midline location. This new entity highlights the tight coupling of this mutation to a specific form of high-grade glioma. H3 K27M mutations can be detected by nuclear staining using H3K27M immunohistochemistry with a sensitivity and specificity of 100%.

In this patient, this very rare and distinct entity, also did something very rare (although well recognized in the literature) and spread to the peritoneal surfaces through the shunt. When this case was first shown to me, I went through the differential of a peculiar mesothelioma, melanoma, GIST, sarcoma(toid) malignancies of all kinds along with other weirdomas. But the positivity of the peritoneal tumor sent to you for GFAP, K27M and OLIG2, along with the striking similarity of the tumor cells to those in the midline brain tumor makes this bizarre diagnosis pretty convincing. [Acknowledgement: The discussion and diagnosis of this case came from our superb neuropathology fellow, Dr. Jose Velazquez].



**References:**

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# AMR Seminar #70

## Case – 2

**Contributed by: Phil Allen, M.D.**

(Case Identification: FMC 15/S02161)

**Clinical History:** A 37-year-old female patient presented in October 2015 at 24 weeks of pregnancy with right sided abdominal pain. Organ imaging showed a left ovarian cyst measuring 7.2 x 9.6 x 7 cm. At 28 weeks, the cyst had enlarged and the serum CEA was rising so a laparotomy was performed. There was no free blood in the peritoneal cavity but black pigmentation was seen on the omentum and on the serosa of the uterus. The ovaries were not visualized because of the pregnancy and the enlarged uterus, but no ovarian cyst was palpable in the pouch of Douglas. The excised omentum measured 110 x 30 x 10 mm and was studded with dark brown/black areas, hemorrhagic foci, whitish nodules and intervening normal yellow fat, as in the photograph below.

Post-operatively, the CA 125 returned to normal and organ imaging showed that the cyst had collapsed. The patient had a normal delivery in February 2016. An ultrasound of the pelvis done in May 2016, three months post-partum, showed that the cyst had persisted but was smaller (5.8 x 6.4 x 7.1 cm) than during the pregnancy. A further ultrasound performed in November 2016 showed persistence of the left adnexal mass with irregular peripheral echogenic regions and hypoechoic areas, most likely fluid, consistent with organizing collections secondary to a ruptured endometrioma.



Gross photograph of the omentum showing dark brown/black areas, red foci of hemorrhage, small, inconspicuous pale white areas which are the foci of decidual change and normal intervening yellow omental fat.

**Diagnosis:** Peritoneal lipofuscinosis and deciduosis in pregnancy.

**Comment:**

The omental pigmentation, which was initially thought to be melanin, is associated with a florid, multinodular decidual reaction in keeping with the patient's pregnancy. The pigment is granular and light brown, has been ingested by macrophages and is associated with small aggregations of degenerating red cells as well as scattered areas of necrosis. No formalin induced acid hematin pigment is present. The pigment is Perl's negative and is very weakly PAS-diastase positive. Some of the granules stain faintly with the Masson-Fontana stain for melanin as well as with a "cocktail" stain for Melan-A, HMB-45 and tyrosinase but the staining was weak and was not diagnostic of melanin. Electron microscopy performed on tissue retrieved from a paraffin block revealed swollen rough endoplasmic reticulum containing material interpreted as the remnants of lipofuscin remaining after the lipid extraction sustained during the paraffin embedding processing. No melanin was seen. This established a diagnosis of peritoneal lipofuscinosis. X-ray micro-analysis of the specimen showed plenty of carbon but no iron.

Peritoneal lipofuscinosis was apparently first described by Peter Russell and Patricia Bannatyne in 1989 in their book "Surgical Pathology of the Ovaries."<sup>(1)</sup> Their description was based on a single case. The second case was reported by White and Chan in 1994.<sup>(2)</sup> Bannatyne confirmed her original observations on her case in 1994<sup>(3)</sup> but I have been unable to find any other published reports on this condition in the 22 years since 1994. Both published patients were pregnant and there was marked peritoneal decidualosis, as in this case.

Peritoneal lipofuscinosis should be distinguished from the rare peritoneal melanosis, which is usually associated with a benign cystic ovarian teratoma<sup>(4)</sup>, and from melanosis due to widespread metastatic malignant melanoma.

Based on the clinical features of this case, I think the lipofuscinosis resulted from intraperitoneal haemorrhage from ruptured ovarian endometriosis. The iron from the breakdown of the intraperitoneal haemoglobin was quickly resorbed because of the increased iron demand of pregnancy, leaving only the iron free red cell breakdown products to be ingested and degraded into lipofuscin by omental macrophages. As there has been a pronounced peritoneal decidual reaction in all three cases, the decidual cells could well play a part in the pathogenesis of this condition.

Dr Gunawardane and I would be interested in the Club Members' opinions on this apparently very rare condition. Has anyone seen another case?

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# AMR Seminar #70

## Case – 3

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

**Case History:** An 83 year old man with a previous medical history of chronic lymphocytic leukemia consulted the plastic surgery clinic for a mass on the lateral aspect of the first right toe which had been present for a year. A biopsy was taken and sent with a suspicion of squamous cell carcinoma.

Biopsy pathology: the submitted biopsy sample showed a neoplastic proliferation of rather homogeneous small to medium sized rounded, polygonal, or spindle shaped cells showing numerous mitoses and arranged in groups separated by eosinophilic fibrillary material staining positive for Masson trichrome (assumed to be collagen). The workup focused on a differential diagnosis of sarcomatoid carcinoma or an epithelioid sarcoma and a number of immunohistochemical stains were ordered. There was staining with low molecular weight keratin and pankeratin (MNF 116); otherwise actin, CD 34, CD 31, S100, neuroendocrine markers, were negative. Based on these findings the diagnosis of sarcomatoid carcinoma was submitted. Excision of the first ray was performed.

Excision specimen: a 3.5 cm tumor mass was documented which was present on the cutaneous surface and involved the deeper soft tissues. Histology showed essentially the same findings as in the biopsy along with some staining for pankeratin. Histological sections of the underlying bone showed tumor infiltrating into the marrow fat between the native bone trabeculae. However in this iteration the diagnosis of carcinoma seemed less convincing so the case was sent to Prof. Christopher Fletcher for his expert opinion.

Prof Fletcher's opinion: the histology shows "irregularly infiltrative sheets of cytologically malignant epithelioid cells with palely amphophilic cytoplasm and vesicular nuclei showing very numerous mitoses. *However more deeply one can appreciate that similar cells are clearly associated with multifocal deposition of osteoid which is undergoing mineralization.* There is indeed multifocal positivity for keratin CAM 5.2 and EMA ... *but most importantly there is multifocal positivity for SATB2, an osteoblastic transcription factor... I think that there is no doubt that this is an osteoblastic osteosarcoma*" (all italics mine).

Discussion: I think this case is unusual enough to warrant presentation in this forum, from the point of view of age and location. According to the chart on page 137 of the latest AFIP fascicle on bone tumors, approximately 5% or less of osteogenic sarcomas appear in the ninth decade, and 1.2% arise in the foot (0.9% in the proximal foot and 0.3% in the distal portion; a report by Anninga et al revealed that in their experience 0.64% of osteosarcomas involve the foot, and of these 56% arose in the tarsal bones, 33% in the metatarsal, and 11% in the phalanges). This case was associated with the distal metatarsal, so the probability of an osteogenic sarcoma arising in a toe bone in this age group would seem to be statistically very low. However given that as indicated the tumor involved the bone I can't summarily rule this out, though this occurrence can of course be explained by tumor invading the bone from the outside. I am including a copy of the flat X-0ray which shows the mass on the side of the metatarsal seeming to overly the bone which itself does not seem to be deformed. On the histological section of the bone (see attached photos) the trabeculae seem to me to be too regular to be neoplastic and in my opinion represent the native anatomy with tumor cells infiltrating the fatty marrow between them. On high power there are delicate eosinophilic deposits between the cells in proximity to the bone trabeculae but not necessarily merging with them. However, in all due modesty I do not feel qualified to make a final judgment on this.

If the lesion is not primary in bone then it invariably becomes extraskelatal osteosarcoma. These are usually considered within the context of soft tissue tumors and by definition, they should not involve bone (though one can argue about secondary invasion of bone as may be the case here: the toe being a relatively small compartment the tumor doesn't have much room to grow without invading other compartments adjacent to where it originated).

These are rare tumors which comprise 1-2% of all soft tissue sarcomas and approximately 4-5% of all osteosarcomas (AFIP soft tissue tumor fascicle). In a survey by Lee et al based on 40 cases from the Mayo Clinic, the mean age was 50 yrs. (with one 81 yr old patient), and 68% arose in the lower limb, usually the thigh or buttock (but none in the foot!), mostly in the deep soft tissues. The histological typing corresponds to that in the bone- osteoblastic, chondroblastic, fibroblastic, and telangiectatic. Roughly homologous findings were reported by Jensen et al. from Denmark (25 cases), who also point out that many intramuscular lesions of the fibroblastic subtype showed sparse amounts of osteoid. Radiation may be an etiologic factor in some cases. Though the location may be a bit off the age of the patient would be more tenable for this tumor.

This brings me to the third possibility- cutaneous osteosarcoma, which is a specific subtype of extraskeletal osteosarcoma. If the above possibilities are rare then this is a true zebra. Most recently two cases were published by a club member, Giovanni Falconieri. Another recent report (Llamas-Velasco et al) of two more cases was coauthored by another group member, Thomas Mentzel. Both these articles include literature review and all told there is a total of 15 reported cases in the literature (including their own cases). The patients in both these reports were elderly- in their 70's and 80's- and three tumors appeared on the head and one on the hand. Histologically the tumor cells in both reports were described as being pleomorphic, spindle, rhabdoid, and/or polygonal, and osteoid was apparent to abundant. The diagnosis in the Falconieri case was facilitated by positive nuclear staining with the SATB2 immunostain. In their analysis encompassing the previously reported cases Falconieri points out that aside from elderly patients such as the ones he personally reported in whom the tumors tended to appear on sun damaged skin of the head, there is a younger group (between 50-65 yrs) in whom the tumors arose in varying locations- the limbs, buttocks, and girdle, and behaved more aggressively.

The SATB2 immunostain which confirmed the diagnosis of osteosarcoma in this case is a relatively recent new actor on the immunohistochemistry scene (reviewed by Ordonez, and by Conner and Hornick). SATB2 itself is a DNA binding protein that reacts with transcription factors regulating craniofacial development and cortical neuron differentiation. Deficiency of this factor results in craniofacial deformities. In a survey of normal tissues (reported by Magnusson et al) SATB2 can be detected in epithelial cells of the lower GI tract, neurons of the hippocampus and cerebral cortex, and to a certain extent in the seminiferous ducts of the testis and glandular cells of the epididymis (interestingly bone was not included in this survey). As expected from these observations the stain is positive in colorectal tumors (Magnusson et al), but besides these Conner and Hornick showed that it is also positive in 100% of osteosarcomas of the bone (89% of extraskeletal osteosarcomas), osteoblastomas, osteoid osteoma, and in areas of heterologous bone in dedifferentiated liposarcoma. Antibodies to the bone related proteins osteocalcin and osteonectin stain matrix and osteoblasts in bone tumors and have been shown to have potential for diagnostic use (as shown by Fanburg et al). However, use of these has not caught on for reasons concerning sensitivity, specificity, and optimization (Conner and Hornick).

By definition osteogenic sarcomas are tumors that produce osteoid. On my initial examinations I was not aware that there was any in the biopsy or excision and I certainly accept and respect Prof Fletcher's confirmation of its presence. There is abundant eosinophilic fibrillary material separating groups of cells which I assumed was collagen and which stains blue with Masson trichrome. I tried to find information about the staining properties of osteoid with this stain and to the best of my understanding, initially it stains red and as it turns into bone it becomes blue. On review of the slides I did find in one block from the resection (not the submitted one) a focus showing mineralized extracellular lace-like material (see photograph). As other authors have mentioned, and in my own personal experience, osteoid may be difficult to separate from hyalinized collagen (Conner) and especially in some subtypes may often be unapparent.

Another point to be taken up is the confusion with squamous cell carcinoma on the biopsy. This misidentification is promoted by bias- the clinical suspicion of the surgeon and my own expectation (curiously I looked up in google references to tumors of the toes to see how prevalent squamous cell carcinoma really is in this location and most of those that came up referred to dogs). It would be very convenient to call this an "epithelioid" osteogenic sarcoma but in the literature this is not accepted nomenclature (as mentioned above, the official histological subtypes are osteoblastic, chondroblastic, fibroblastic, and telangiectatic). However there are osteogenic sarcomas that are

considered to show epithelial differentiation to varying degrees and this dovetails with cytokeratin expression. Okada et al reported on six osteosarcomas (out of 131 cases) which showed 2+ reactivity for cytokeratin. Three of those cases were osteoblastic and the keratin positive cells were described as having "epithelioid cytologic features- eccentric vesicular nuclei with prominent nucleoli and abundant pale eosinophilic cytoplasm". However, the other three keratin positive cases were fibroblastic or chondroblastic and the positive cells were pleomorphic or spindle shaped without any particular "epithelioid" features. Likewise, Kramer et al. reported on a case of osteogenic sarcoma showing "pleomorphic cells with prominent nucleoli arranged in cohesive clusters and nests and forming trabecular and acinar (glandular) structures suggesting epithelial differentiation". These areas were cytokeratin positive. So the use of the modifier "epithelioid" in this context requires more than a tumor having rounded cells with ample cytoplasm - there has to be some obvious organizational changes suggestive of epithelial differentiation.

In this vein Layfield et al discussed a case of osteogenic sarcoma which had focal well developed squamous differentiation showing keratin pearls and intercellular bridges. They paraphrase the argument of Folpe and Gown that other than synovial and epithelioid sarcomas, which show true epithelial differentiation and stain positively with high molecular weight keratins, other sarcomas may show "anomalous" reactivity with low molecular weight cytokeratins (8/18) in which a subset of cells show staining of only a portion of the cytoplasm which in their opinion does not indicate true epithelial differentiation. Layfield et al go on to say that while the "epithelioid" differentiation may take the form of "nests or clusters of polygonal epithelial cells lacking definitive glandular or squamous differentiation" some cases may be biphenotypic and show legitimate epithelial features such as true glands, rosettes, and squamous differentiation. In reviewing the case I'm presenting I think I overdid the significance of the cytokeratin stain. The 8/18 did show some moderate cytoplasmic staining in places, and also foci of dot like staining. The MNF pankeratin looked stringy and seemed to stain either cell processes or fragments of cell membranes. EMA was focally positive and AE1/AE3 performed on the excision was mostly negative. In retrospect this doesn't add up to much and I would have to consider it anomalous and not diagnostic. I don't know to what extent others will agree about the extent to which the cells of the tumor can be considered "epithelioid" but there is certainly no evidence of glandular or squamous differentiation.

To finish this discussion: this isn't the first occasion in which I was confronted by a tumor deemed to be epithelial at first and which was eventually diagnosed correctly as bone related. The previous case (included in photos below) concerned a young woman with a palate mass. Biopsy showed a proliferation of rounded cells which considering the location was evaluated for the possibility of myoepithelial tumor. EMA was positive but keratins, S100, and smooth muscle stains were negative. This case made the rounds and here also Prof Fletcher bailed me out and made the diagnosis of aggressive epithelioid osteoblastoma confirmed by SATB2 positivity. Osteoid was extensive. As testified by the nomenclature this entity commonly seen in the head and neck is officially deemed to be epithelioid. Interestingly two relevant publications I have at my disposal- (Filippi et al; and Harrington et al) don't discuss the role of immunohistochemistry in making the diagnosis. In looking at this case from a distance of a few years the presence of bone now seems obvious!

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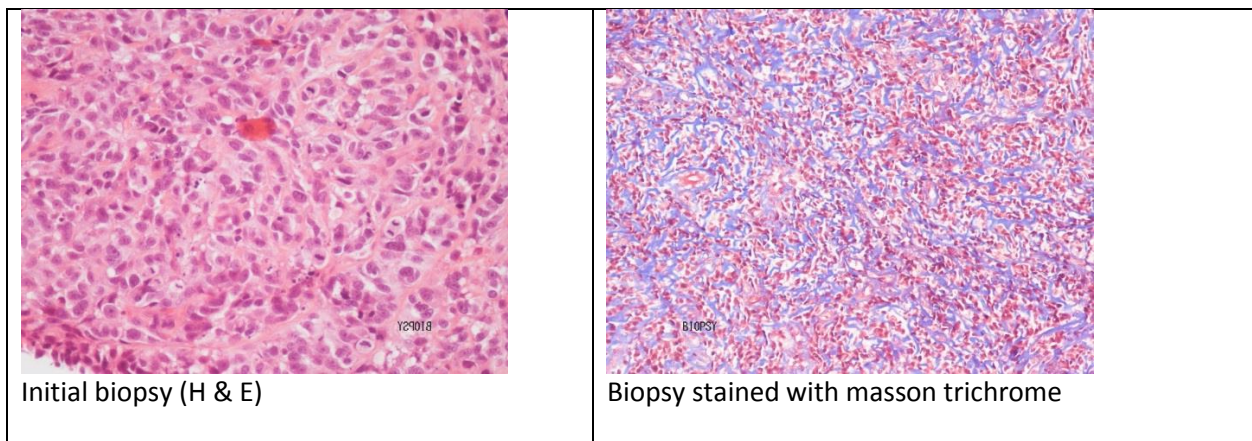
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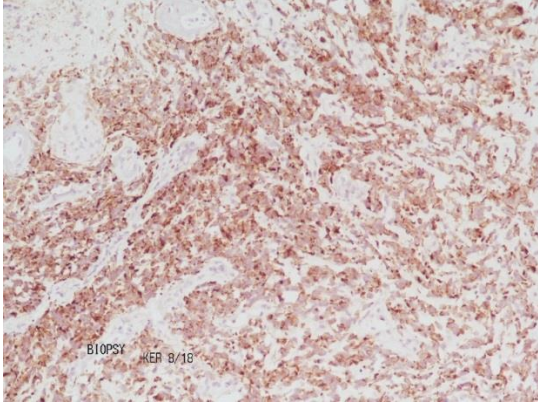
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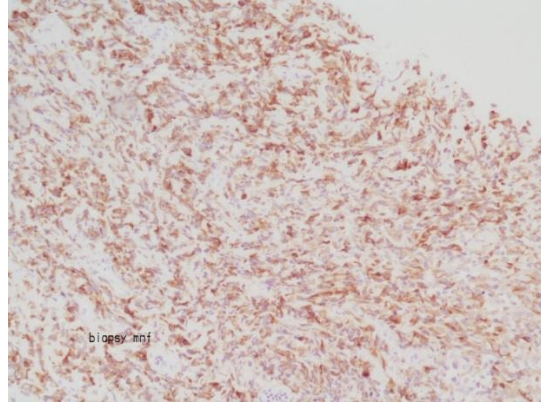
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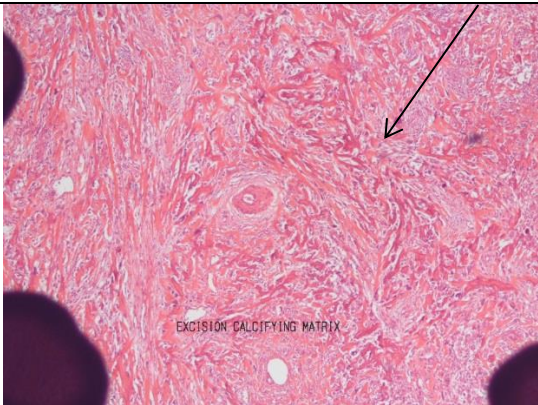




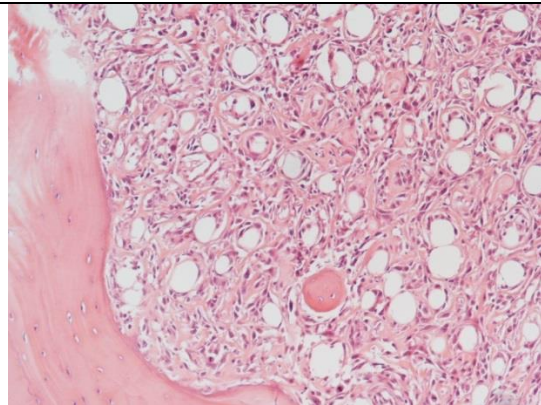
Biopsy stained with keratin 8/18 (CAM 5.2)



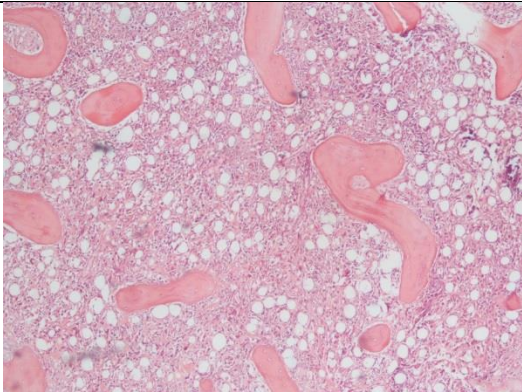
Biopsy stained with MNF pankeratin



Focus of calcifying matrix in excision



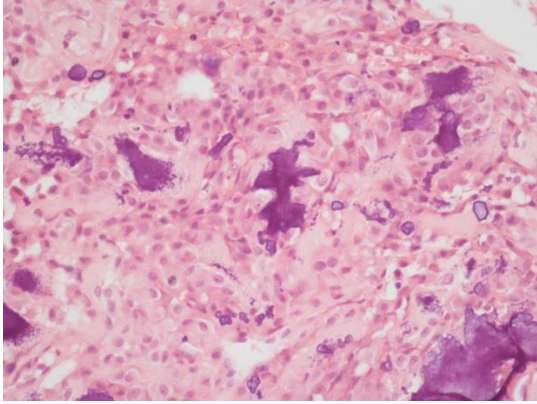
Tumor infiltrating amidst bone trabecules in toe in excision specimen



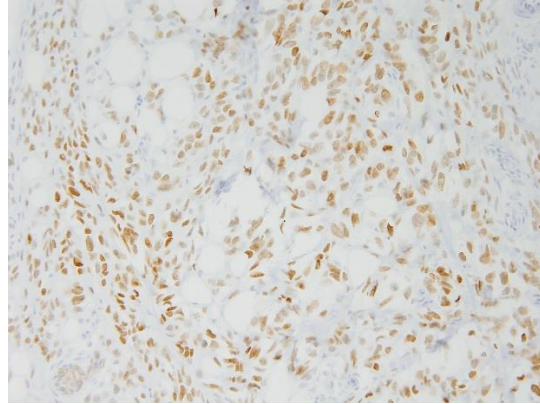
Tumor in bone- excision specimen



x ray of foot



Biopsy of palate tumor showing epithelioid cells amidst bone spicules



SATB2 positivity in toe osteosarcoma (courtesy of Prof. C. Fletcher)

# AMR Seminar #70

## Case – 4

**Contributed by:** Ira Bleiweiss, M.D.

**Clinical History:** A 22 year old female with a palpable left breast mass. The lesion was core biopsied first and came only with clinical information stating “rule out sebaceous cyst.” The correct diagnosis was made on the core biopsies, and the lesion was surgically excised. The slides are from the excision. Gross description was non-contributory. Microscopically there is a diffuse population of cells with granular pink cytoplasm and bland, uniform nuclei without mitosis. The lesion appears well circumscribed and is just below skin.

**Diagnosis:** Granular cell tumor of skin of breast (not of breast)

**Comment:** I send this not because of any diagnostic difficulty but because I learned something from the case. First of all, this is a classic appearance of granular cell tumor and I thought the members would appreciate an easy one for a change and one they could use for teaching purposes. The wrinkle in the case, however, is that granular cell tumor of the breast is radiologically and clinically indistinguishable from invasive breast carcinoma in that it forms an ill-defined, stellate, solid mass when seen on mammography and ultrasound. When palpable it is a hard mass, equally suspicious for carcinoma. In every single core biopsy of this lesion I have received (and there have been many), I have had a post-diagnosis phone call from a radiologist asking me if I’m sure of the diagnosis. By the way the differential diagnosis for granular cell tumor of breast is invasive apocrine carcinoma, which can be ruled out in difficult cases by simply staining for keratin, granular cell tumor being negative of course.

So, imagine my surprise when I read the clinical history and then saw the biopsy. The fact that the radiologist stated “rule out sebaceous cyst” meant that the lesion was superficial and well circumscribed, both factors confirmed by the excision specimen. I showed the slides to one of my dermatopathology colleagues who confirmed the diagnosis and said “I see these all the time, and they are well circumscribed”. I wasn’t aware that granular cell tumor occurred in the skin at all, certainly not in the skin overlying the breast.

Moral of the story- Granular cell tumor looks like breast cancer when it’s a primary breast lesion, but not in the skin. I find that rather odd, that the same tumor can have such a different local growth pattern. Can anyone think of any similar examples?

# AMR Seminar #70

## Case – 5

**Contributed by: Alberto Cavazza, M.D.**

**Clinical history:** The patient was a 55 year-old male, with an unremarkable past clinical history other than some episodes of rhinitis, presenting with dysuria, fever and acute urine retention. Laboratory exams showed an increase of erythrocyte sedimentation rate and a mild anemia. CT scan of the pelvis showed uniform enlargement of the prostate, and the clinico-radiologic findings were considered suspicious for prostatitis. Multiple prostate biopsies were performed.

**Pathologic Findings:** The histologic features may vary a little bit depending on the slide you received, but in general they consist of an inflammatory process with necrotic suppurative foci. In some slides the necrotic foci are tiny, in others are large, and somewhere an irregular/serpiginous configuration of the necrosis can be appreciated as well as a few scattered giant cells. Well-formed granulomas are absent, and special stains for microorganisms are negative. At that time a descriptive diagnosis of necrotizing prostatitis was rendered by an experienced urologic pathologist.

A couple of weeks later the patient presented with tinnitus (with a clinical diagnosis of otitis), hemoglobinuria, cough and progressive dyspnea. MR showed an opacification of the maxillary sinus, whereas a CT scan of the chest showed bilateral pulmonary consolidation with ground-glass opacities. The search for infective agents was negative. At this point ANCA were tested, and c-ANCA were positive with high titre. A review of the prostate biopsies was requested, and in retrospect the histology was considered consistent with **granulomatosis with polyangiitis** (GPA, Wegener's granulomatosis). A treatment with steroids and cyclophosphamide was instituted, but unfortunately the pulmonary disease worsened and the patient died of diffuse alveolar hemorrhage a few days after the therapy was started (probably before cyclophosphamide could be effective). No autopsy was requested.

**Comments.** I thought this case was of some interest because it reminds some critical points about GPA:

- It remains a potentially fatal disease if the treatment is not instituted promptly, so an early diagnosis is essential.
- Its clinical features are proteiform: any organ can be involved (GPA can present anywhere), and in atypical presentations the diagnosis is frequently delayed by clinicians and pathologists alike. The pathologist may have the opportunity to be the first to suggest the correct diagnosis, but particularly if the biopsy does not come from the classical sites (nose/nasal sinuses, lung, kidney), he/she may simply not consider the possibility.
- In any organ the clue is to pay attention to the character of the parenchymal necrosis, as shown in this case and beautifully described in the following papers (not very recent, but evergreen!).

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# AMR Seminar #70

## Case – 6

**Contributed by:** Kumarasen Cooper, M.D

**Case History:** This is an 11 year old child from Haiti who presented with a right cervical neck mass. The surgeon from our hospital (Vermont, 2007) was a volunteer in Haiti and resected the tumor. He assured me that this was entirely soft tissue with no bone involvement. He brought back samples for histological examination. There is no follow-up. I apologize in advance for the poor fixation and poor morphology.

**Microscopic Features:** The tumor has a lobulated architecture with sheets of round cells (mostly large likely due to the poor fixation). There is an abrupt transition to areas of mineralization (which I think is largely hyaline cartilage that has been mineralized; in other areas/slides there are islands of well differentiated cartilage). In some areas these abrupt eosinophilic areas resemble osteoid. Between tumor cells there is a fine matrix formation. The vasculature although not open is quite rich in number. Areas of necrosis are noted as well. Focal osteoclast giant cells are present.

**Immunohistochemistry:** The tumor cells were positive for CD 99 and negative for muscle and lymphoid markers.

**Diagnosis:** Mesenchymal chondrosarcoma (arising in soft tissue)

**Discussion:** The only update on these rare tumors is that SOX-9 is positive and they harbor a recurrent *HEY1-NCOA2* fusion. This fusion is detected in well characterized mesenchymal chondrosarcoma and negative in other subtypes of chondrosarcoma. Notably IDH1 and IDH2 point mutations are absent in mesenchymal chondrosarcoma.

# AMR Seminar #70

## Case – 7

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

**Case History:** An 80-year-old gentleman of Thai origin was referred to Örebro University Swedish Centre for penile diseases with a clinically clear penile carcinoma. Initial biopsies did not prove malignancy but clinicians undertook a total penile amputation and sentinel node biopsy.

**Pathological Findings:** A total penis resection was performed and penis was finally totally embedded for histological examination. No signs of malignancy detected. Microscopy revealed a dense keloidal hypocellular fibrotic reaction with perivascular lympho-plasmacytic inflammation. On closer inspection a pattern of oval to round holes, which are only partly filled with silicone, recognizable as small round to irregular translucent droplets of amorphous refractile non-polarizing material was seen. Throughout the pseudotumor fibrosis foam cells were present. There was basically no granulomatous inflammatory component and no foreign body-type giant cells present. Epidermis was slightly hyperpigmented and focally showed hyperkeratosis, spongiosis and a pseudoepitheliomatous hyperplastic reaction probably as a reactive response to silicone injections.

**Diagnosis:** Penile silicone reaction after autoinjection clinically simulating penile carcinoma.

**Follow-up:** Alive without evidence of malignancy. On closer history patient admitted autoinjection of free silicone in penis with enlargement and increased potency as goal.

**Discussion:** Sad case and actually second penile amputation specimen I saw at Örebro national centre for penile tumors within two years without evidence of cancer on final examination. On scrutinizing the literature one can notice descriptions of silicon reactions simulating cancer grossly in many organs mostly breast but also on histology as mimicker of low-grade liposarcoma. The literature on silicone in penis is surprisingly large with more than 360 articles but to my knowledge silicone pseudotumor of the penis has not previously been described.

One of the first papers on side effects of silicone injections was on the use to cure potency problem with penile implants (Pearman 1967) and the following year silicone mastitis was reported in a series from topless waitresses (Symmers 1968). Silicone has however found wide applications in most organ systems and a high index of suspicion for pseudotumor reaction and a good familiarity with this simple type of tissue reaction pattern is important.

**Conclusions:** Confirmatory histology before surgery still important!

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# AMR Seminar #70

## Case – 8

**Contributed by: Giovanni Falconieri, M.D.**

Case made generously available by Alessandro De Pellegrin (Pathology Staff , Udine General Hospital, Italy).

**Clinical history:** A 10 y/o girl underwent enucleation of a radiolucent maxillary mass of the superior incise area associated with an unerupted tooth within (21) area. The lesion measured 3 x 2 cm, was partly cystic and containing a dental element.

Microscopically, tumor sections featured cuboidal to columnar cells arranged in nests, rosettes or solid whorled areas. The ground substance was loose to fibrous or focally calcified.

**Diagnosis:** adenomatoid odontogenic tumor.

**Comments:** I think that this may represent an example of **adenomatoid odontogenic tumor (AOT)**, a benign, rare lesion parentally related to the dental lamina. Though described under various headings such as adenoameloblastoma, ameloblastic adenomatoid tumor, adamantinoma, epithelioma adamantinum or teratomatous odontoma, it was Philipsen and Birn who first introduced the term "AOT" in 1969. AOT is relatively more frequent in females in their second decade of life, and occurs more frequently in Black Africans than in Caucasians (9% vs 1.2%). In 2/3 of cases AOT is associated with an unerupted tooth and arise within the maxillary bone area of the canine teeth.

More than 20 microscopic patterns have been described in AOT, hence the appellation of "master of disguise". Occasional presence of necrosis, hyalinization, melanin pigmentation, and dysplastic dentinoid compounds further the microscopic interpretation. Furthermore, mitotic figures and nuclear atypia have been reported in some instances. Treatment usually involves removal of the tumor in toto. Recurrence is unusual but not exceptional.

It is still debated whether AOT is a true neoplasm or a hamartoma. The latter view is supported by the relatively small size of the tumor and lack of recurrences in most cases, yet the increased variation in size and aggressive behavior, though rarely reported, may indicate that AOT is of neoplastic origin.

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# AMR Seminar #70

## Case – 9

**Contributed by: Franco Fedeli, M.D.**

**Clinical History:** A 41-year-old Chinese man was subjected to our observation for the presence of diffuse lymphadenopathy. A cervical lymph node was taken out and sent to the path lab with the clinical diagnosis of lymphoma.

**Macroscopic Findings:** At gross examination nodal parenchyma was pinkish and nodular in appearance.

**Microscopic Findings:** Histologically nodal architecture was largely preserved and follicular hyperplasia with germinal centers vascularization was evident. In addition, eosinophils were present, especially in interfollicular zone, and occasionally they made up eosinophilic micro-abscesses.

Immunohistochemical findings and flow cytometry did not show any monoclonal component.

**Diagnosis:** Kimura disease.

**Comments:** Kimura disease was originally described as “eosinophilic hyperplastic granuloma” in 1937, however, the eponym derives from a later description by Kimura from Japan in 1948. Such condition is more common in Asian men, although it may be seen in all races, with a median age of 32 years; the M:F ratio is 3.5–6:1. Clinical findings include peripheral blood eosinophilia, increased tumor necrosis factor (TNF) alpha, increased interleukin (IL)-4, -5, and -13, and elevated serum IgE as well. Systemic symptoms such as fever or weight loss are rare. Cases commonly present as masses in the head and neck region, especially in salivary glands. Regional lymph nodes are often involved (30–100%). Patients occasionally may concurrently have or may develop nephrotic syndrome. At present, no clear association with a known viral or other etiologic agent has been found. Histologically, Kimura disease in extra nodal and nodal tissue is characterized by follicular lymphoid hyperplasia with prominent germinal centers and expanded interfollicular areas containing an increased number of eosinophils. Tight clusters of eosinophils or eosinophilic micro-abscesses may be present. Sometimes the eosinophilic infiltrate may partially disrupt reactive follicles to give a moth-eaten appearance (“folliculolysis”). Other common morphological features include vascular hyperplasia with flattened or low cuboidal endothelial cells, presence of vessels and proteinaceous deposits within germinal centers, concentric perivascular and periductal sclerosis and dense stromal fibrosis associated with plasma cells and eosinophils as well. Immunohistochemical studies show preservation of the overall lymph node architecture with prevalence of B-cells in follicles and T-cell predominant interfollicular areas. Special stains for microorganisms are negative. Historically, Kimura disease has been confused with angiolymphoid hyperplasia with eosinophilia (ALHE); however, it is now well established that these two entities are unrelated with distinct clinical and pathological features. In addition, it is critical to exclude other diseases with eosinophilia, including infections, especially parasitic, Hodgkin lymphoma, and T cell lymphomas.

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# AMR Seminar #70

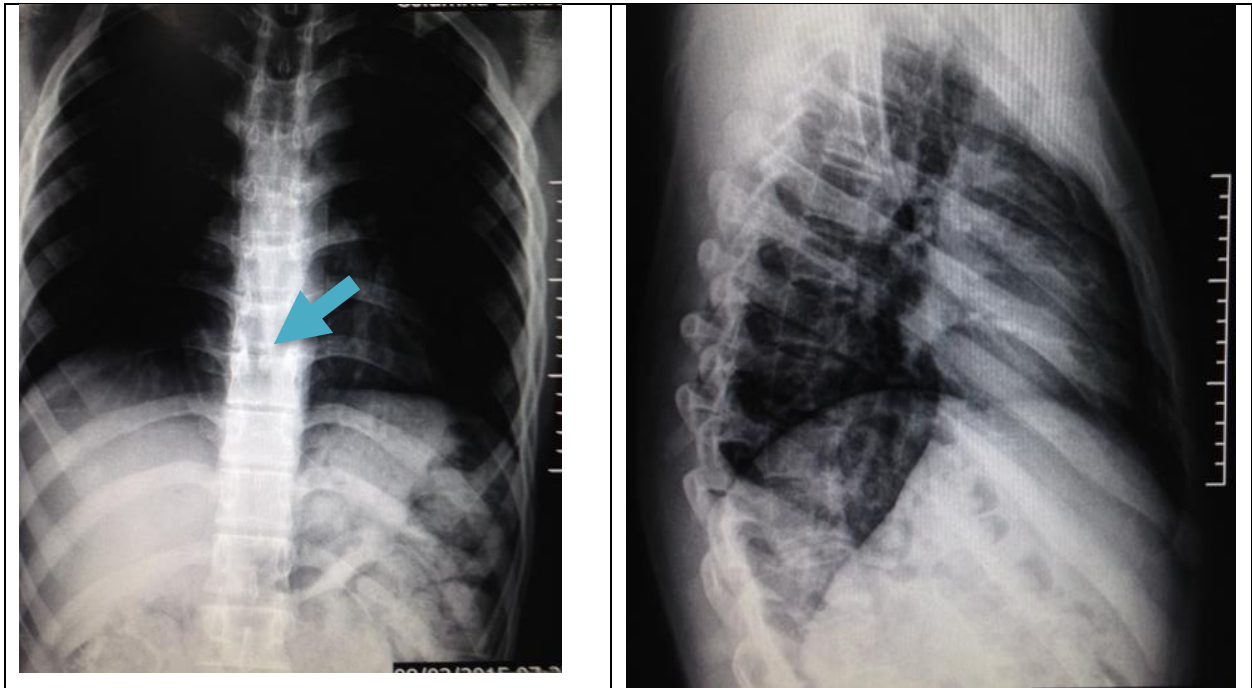
## Case – 10

**Contributed by:** Jeronimo Forteza Vila

**Clinical History:** A 18-years-old man without pre-existing conditions. Starting with a progressive strength loss in his lower body, he ended paraplegic in bed after 10 days. After column surgery he successfully recovered, being able to walk afterwards. A MRI was performed which showed loss of posterior T9 right arch. He shows a cyst with sclerotic walls full of blood. Other areas have solid fibroblastic proliferation and osteoclastic-like multinucleated giant cells.

**Diagnosis:** Aneurismatic bone cyst (ABC), solid variant.

**Comment:** ABC is a young patient lesion, more frequent in women. Vertebrae are a typical location. They frequently have a hemorrhagic component. Occasionally the lesions have a solid component with variable histological appearance, but osteoblastic giant cell proliferation is a constant feature.





- X-ray images of the patient: the lesion can hardly be seen. Only *a posteriori*, and having knowledge of the lesion by MRI, could be mentioned the loss of posterior T9 right arch.



# AMR Seminar #70

## Case – 11

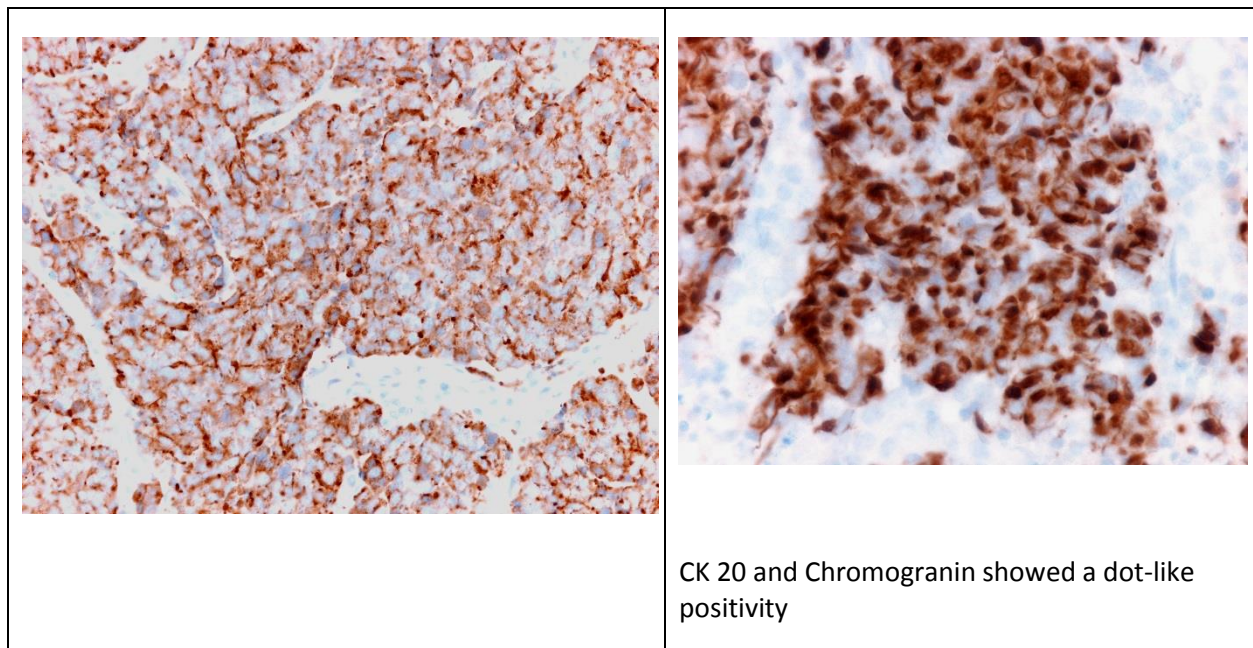
**Contributed by: Maria Pia Foschini**

**Clinical History:** A 67 year-old man presented with acute ataxia, vertigo, and nausea. Subsequently, he developed dysarthria, diplopia, xerostomia, fatigability and progressive anorexia. During diagnostic workup, a high titre of voltage-gated calcium channel antibodies, in serum and cerebrospinal fluid, was demonstrated leading to the diagnosis of Lambert-Eaton myasthenia and neurological signs compatible with cerebellar degeneration.

Extensive radiological imaging studies revealed a 9-cm mass located in the axilla. The lesion was surgically removed.

**Pathologic findings:** The tumour was composed of small cells, with central, clear nucleus, inconspicuous nucleolus and scanty cytoplasm. Atypical mitotic figures were numerous, wide areas of necrosis were present.

The neoplastic cells were immunoreactive for low-molecular weight cytokeratin (CK), CK 7 and CK20. In addition, neuroendocrine markers were expressed, such as chromogranin, synaptophysin and NSE. CK20 and chromogranin showed a dot-like positivity. At the periphery of the neoplastic lesion, remnants of a lymph-node were seen.



**Diagnosis:** Merkel cell carcinoma, primary in a lymph node.

The remnants of lymph nodal tissue indicated that the neoplastic cells were located within a lymph node. No primary was found in any other body site despite careful investigations. Therefore, the case was considered as Merkel cell carcinoma primary in a lymph-node showing Lambert – Eaton myasthenia.

**Comment:** Merkel cell carcinoma (MCC) is a rare type of cutaneous tumour, showing neuro-endocrine differentiation (1,2). In addition to the classical morphological patterns, MCC can show squamous, glandular, melanocytic, striated muscle, and lymphoepithelioma-like features (2). MCC usually affects the skin, but rare cases arising primarily in lymph-nodes have been described. Eusebi et al. (3) described 8 cases of MCC arising in inguinal, axillary and submandibular lymph-nodes. Despite extensive search no cutaneous primary MCC were detected, therefore the authors suggested that MCC can develop from epithelial inclusions or derive from anomalous carcinomatous differentiation of lympho-reticular cells. MCC arising in lymph-nodes are similar to the skin counterpart, as they share chromosome 6 trisomy (4) and polyomavirus DNA (Merkel cell Polyomavirus – MCPyV) (5).

The present case showed symptoms related to paraneoplastic syndrome (PNS) Lambert-Eaton type. Lambert Eaton syndrome is a myasthenic syndrome usually associated with neuroendocrine carcinoma of the lung. The association between MCC of the skin and PNS has been reported (6-13). The present case has been regarded and hence reported as MCC primary in a lymph-node associated with Lambert Eaton syndrome (Pavolucci et al. (13)).

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# AMR Seminar #70

## Case – 12

**Contributed by: Masaharu Fukunaga, M.D.**

**Clinical History:** A 67-year-old, gravida 0, para 0, female presented with abdominal discomfort. CT, MRI and physical examination indicated a left ovarian tumor. Mucinous borderline tumor was the clinical diagnosis. She had no hormonal signs or symptoms. The patient underwent a left salpingo-oophorectomy and omentectomy. The patient is alive with no evidence of disease at five months after surgery.

**Macroscopic features:** An ovarian tumor measuring 14x12x10cm was multi-cystic containing serous liquid. Cut surface looked like a mucinous cystic tumor, but no mucin was noted. Numerous yellowish small nodules were seen. No necrosis, hemorrhage and hemosiderin deposits were observed.

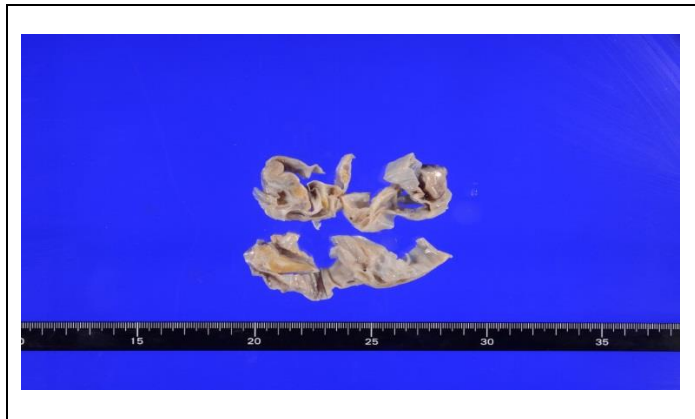
**Diagnosis:** Gynandroblastoma.

**Comments:** This type of tumor usually occurs in young adults but may be encountered at any age. They may be associated with androgenic or estrogenic manifestations. They are almost always stage I and clinically benign. To my knowledge, there is one reported case with retroperitoneal recurrence 10 years after surgery. Malignant transformation has not been reported.

Histologically, this lesion is composed of two components, granulosa cell tumor (juvenile type) and well-differentiated Sertoli cell tumor. The former is characterized by a mixed solid-cystic appearance; multiple cystic changes, follicle-, sheet- like and cord-like arrangements of round cells with uniform small to medium-sized round nuclei and moderate amount of cytoplasm. The latter shows open or closed tubules composed of columnar cells with elongated nuclei and eosinophilic cytoplasm. Cluster of luteinized cells are observed in the fibrous stroma. The granulosa cell tumor occupies 70% of the lesion and well-differentiated Sertoli cell tumor occupied the remaining 30% in this case. It is defined that smaller component accounts for more than 10% of the tumor. There may be very limited areas of Sertoli cell tumor component in some distributed slides.

Immunohistochemically both components are positive for vimentin, CK8/18, CAM5.2, ER, PR, androgen receptor, inhibin, WT1 and CD99. CD10 is positive in the well-differentiated Sertoli cell tumor component but negative in granulosa cell tumor component. Calretinin is positive only in the luteinized stromal cells. Adult type granulosa cell tumor and Sertoli-Leydig cell tumor are characterized by somatic mutations in *FOXI2* and *DICER1*, respectively.

Gynandroblastoma is very rare and is a characteristic tumor; however, its category disappeared in the new WHO classification.



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# AMR Seminar #70

## Case – 13

**Contributed by:** Thomas Krausz, M.D.

**Clinical History:** A 13-year-old previously healthy female presented to her pediatrician for a routine sports physical. She was found to have a 19 x 15 x 10 cm right ovarian mass with pelvic lymphadenopathy and small, bilateral lung nodules concerning for metastatic disease. A right salpingo-oophorectomy was performed and a representative section of the ovarian mass is provided for this seminar. A biopsy of the grossly normal left ovary showed no diagnostic abnormality.

**Pathologic findings:**

*Gross findings:* The 19 cm ovarian mass had a mostly smooth, nodular outer surface, but there were also features consistent with adhesions. The cut surface of the mass had both solid and cystic components. The solid areas were yellow-tan and firm, with foci of hemorrhage and necrosis. The cystic spaces had a smooth lining. No calcifications, hair, or sebum were identified. A narrow rim of normal appearing ovarian parenchyma was also seen. The fallopian tube was normal.

*Histology:* This relatively large (19 cm) right ovarian mass consists entirely of thyroid tissue (struma ovarii). Struma ovarii is regarded as a monodermal teratoma. Some cases are associated with other components of mature cystic teratoma. In this particular case no other teratomatous components are identified on extensive sampling. The tumor (struma ovarii) mostly consists of microfollicular thyroid tissue, but focal cystic alteration and variably sized solid nodules without follicular formation are also identified. The micro-follicles are lined by monotonous follicular epithelial cells with small round nuclei. The solid nodules are composed of follicular-type cells with either clear or pale eosinophilic cytoplasm. In places there is some nuclear enlargement with nuclear membrane irregularity, but no diagnostic features of papillary thyroid carcinoma are observed. There is variable mitotic activity, up to 3 mitoses per 10 high power fields, in the solid regions. There are foci of tumor necrosis. Some of the peripheral blood vessels appear to be invaded by tumor. The intravascular tumor islands are covered by endothelium and are not associated with thrombus formation. The tumor cells, as expected, are immunoreactive for thyroglobulin. Immunostains for synaptophysin, chromogranin and calcitonin did not reveal neuroendocrine differentiation (strumal carcinoid).

*Molecular study* is in progress.

**Original diagnosis:** Struma ovarii with atypical histologic features, follicular carcinoma cannot be excluded.

**Follow-up diagnosis:** Follicular thyroid carcinoma arising in struma ovarii.

**Discussion:** The main reason for submitting this case is that I had diagnostic difficulty determining whether this ovarian mass just an atypical struma ovarii or a follicular carcinoma, and if it is the latter, then which part is benign and which part is malignant (our molecular study has not been completed yet). Of course the large size, focally solid component, mitotic activity, focal necrosis and intravascular bulging of tumor are worrying features, but are they sufficient for a definitive malignant diagnosis in this young patient? Historically endothelial covering of intravascular tumor in thyroid capsule was accepted as vascular invasion, however recently the criteria are tightened. Of course, if the lesions in the lungs are confirmed metastatic nodules (follicular thyroid carcinoma) and there is no tumor in the thyroid gland proper, then the problem is solved. However, the clinicians were not prepared to biopsy the pulmonary lesions and radioactive iodine scan had to be delayed until post-thyroidectomy. The subsequent thyroidectomy did not reveal tumor in the thyroid gland.

I would like to know how confidently club members would have diagnosed this ovarian mass as malignant struma ovarii without the knowledge of pulmonary metastases of follicular thyroid carcinoma.

Struma ovarii is a monodermal teratoma consisting of thyroid tissue. It is more often seen in conjunction with a mature cystic teratoma, containing various other tissue elements. In the case submitted for this seminar no other teratomatous elements were identified. The vast majority of struma ovarii consists of benign thyroid tissue with variably-sized follicles containing colloid. In most instances microfollicular, solid, and trabecular pattern (literature data) is not associated with aggressive clinical course. Some cases of struma ovarii show additional neuroendocrine differentiation (strumal carcinoid).

Rarely, malignant transformation may occur in struma ovarii, which may be either papillary thyroid carcinoma or, less commonly, follicular carcinoma. The diagnosis of papillary thyroid carcinoma arising in struma ovarii can be made by accepted morphologic criteria. The diagnosis of follicular thyroid carcinoma, arising in struma ovarii is more difficult. The large size (19 cm), solid architecture, microfollicular pattern, increased mitoses, and some nuclear atypia are worrying. However, as in the thyroid gland proper, differentiation between benign follicular lesions and well-differentiated follicular thyroid carcinoma is largely based on vascular invasion. Invasion into the surrounding benign ovarian tissue (not present in the submitted case) can also be a clue. Presence of distant metastasis (proven subsequently in the submitted case, see below) may be the only definitive evidence of malignant behavior in some cases.

Several studies of malignant thyroid-type carcinomas arising from struma ovarii have shown that tumors with larger size (>12 cm) and with predominant solid growth pattern tend to behave more aggressively, with increased risk of recurrence and/or metastasis. Patients with struma ovarii often do not present with hyperthyroidism. However, serum thyroglobulin levels can be used clinically as a marker of disease.

**Follow-up:** 6 weeks later the patient underwent total thyroidectomy and pathology showed normal thyroid gland and one reactive lymph node. Following resection of the abdominal mass and thyroidectomy, thyroglobulin levels continued to rise, suggesting that her lung nodules may represent metastatic tumor from the malignant struma ovarii.

5 months later, she had radioactive iodine scan showing marked abnormal uptake in the thorax, which correlated with suspected pulmonary metastatic disease when compared to a prior chest CT. This result confirmed metastases from malignant struma ovarii. No suspicious activity was identified within the abdomen or pelvis. Subsequently she was treated with 83.8 mCi I-131. A post-therapy scan showed multiple pulmonary metastases, appearing similar to the pre-therapy study. She is expected to return for follow-up scan in six months. She is taking levothyroxine for post-thyroidectomy for hypothyroidism.

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# AMR Seminar #70

## Case – 14

**Contributed by: Anais Malpica, M.D.**

**Clinical History:** A 35 year-old woman presented with a one-month history of vaginal bleeding. Physical examination showed a cervical tumor. A biopsy was obtained. Subsequently, the patient underwent a radical hysterectomy with pelvic and periaortic lymphadenectomy. A 4.5 cm exophytic tumor was located in the transformation zone and invaded 1.3 cm of a 2.6 cm thick cervical wall. Multiple foci of vascular/lymphatic invasion were seen. The margins were free of tumor. Metastatic tumor was found in one lymph node designated as left external iliac sentinel node and in one of four lymph nodes designated as left pelvic lymph nodes. The patient received extensive field chemo-radiation, autologous peripheral stem cell transplant and high dose chemotherapy. She died of disease 17 months after the initial diagnosis.

**Diagnosis:** Large cell neuroendocrine carcinoma with focal glandular differentiation. (Note: The tumor was diffusely positive for synaptophysin and CD56 and patchy positive for chromogranin).

**Discussion:** Neuroendocrine carcinoma of the uterine cervix still represents a diagnostic challenge. This diagnosis has to be considered not only when facing a neoplasm with readily recognizable neuroendocrine features, but also when dealing with a cervical carcinoma showing an aggressive course or metastasis to unusual sites such as the liver or brain. Neuroendocrine carcinoma of the uterine cervix can be small or large cell type. Large cell neuroendocrine carcinoma shows nests, sheets and trabeculae of cells with a moderate amount of cytoplasm and nuclei with an irregular distribution of the chromatin, prominent nucleoli, numerous mitoses and apoptotic bodies. Geographic necrosis and hemorrhage are common. Areas with glandular formation can be seen and this finding tends to represent a confounding factor. In contrast, small cell neuroendocrine carcinoma is composed of cells with scanty cytoplasm and nuclei with a "salt and pepper chromatin pattern". Molding is usually seen. Some tumors show a combination of both cells types. Neuroendocrine carcinoma of the uterine cervix is typically associated with a HRHPV infection (either HPV 18 or 16). Small cell neuroendocrine carcinoma is seen in patients with a wide age range from 22 to 86 years (median 43 or 46 years) while large cell neuroendocrine carcinoma is detected in young patients, average age: 34 years (range, 21 to 75 years). Immunohistochemical studies show that the tumor cells are usually positive for keratin AE1/AE3, but not in all cases, and keratin 7 (50% of cases). Keratin 20 is positive in 9% of cases. Pax-8 is usually negative; however, the experience with this immunomarker is still limited. CD56 and synaptophysin are positive in 90% of cases while chromogranin is positive in 50% of cases. A recent report shows that INSM1 (insulinoma-associated protein 1) is a robust marker for neuroendocrine carcinoma of the uterine cervix. TTF-1 is positive in 70% of cases. Her 2-neu is positive in 50% of cases (small cell neuroendocrine carcinoma). In addition, CD99 and neurofilament can be positive. The role of other immunomarkers of neuroendocrine differentiation (i.e., ASH1 and NKX2.2) has not been explored. Regarding the expression of markers of squamous differentiation in neuroendocrine carcinoma: p63 can be positive in 43% of the cases, p40 is usually negative (limited experience in cervix, but in lung <5% cases are positive) and keratin 5/6 is usually negative (limited experience in cervix, but rare cases are positive in the lung).

Neuroendocrine carcinoma of the uterine cervix is an aggressive neoplasm which is usually associated with lymphovascular invasion and lymph node metastasis.

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Nonaka D. A study of  $\Delta$ Np63 expression in lung non-small cell carcinomas. *Am J Surg Pathol.* 2012;36:895-899.

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# AMR Seminar #70

## Case – 15

**Contributed by: Alberto Marchevsky, M.D.**

**Clinical History:** The patient is a 25 y.o. man with a history of cough and recurrent fevers for 6 months that were attributed to asthma and recurrent upper respiratory infections. He underwent bronchoscopy that showed an endobronchial mass that was biopsied. The submitted slide is from the tumor present in a subsequent left pneumonectomy specimen.



# AMR Seminar #70

## Case – 16

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

**Clinical History:** A 85-year-old male patient developed a soft tissue tumor on his chest wall, that was marginally excised.

**Pathological Findings:** Histologically, a nodular neoplasm of varying cellularity is seen, that is composed of relatively uniform epithelioid and plump spindled tumor cells containing a limited amount of pale eosinophilic cytoplasm and almost uniform nuclei. Scattered mitoses are noted. In addition numerous narrow blood vessels are present. Immunohistochemically, tumor cells did not stain for S-100 protein, ASMA, CD34, STAT6, pancytokeratin, EMA, and claudin-1, and NKIC3 staining revealed scattered mast cells only. The Ki-67 proliferative index was only slightly increased.

**Diagnosis:** "I don't knowoma"

**Comments:** I received this enigmatic case in consultation and had the impression on H&E that the lesion looks quite distinct, but the line of differentiation seems to be problematic to establish. Also after the use of multiple immunohistochemical stains, I had no definitive idea. I've started to send the material to many colleagues but also Chris Fletcher wrote "Personally, I could do no better than to label this as an atypical epithelioid and spindle cell neoplasm". Has anyone of you seen a similar case, has anyone an idea about the line of differentiation or of additional antibodies that should be applied? Many thanks for any help and suggestion!

# AMR Seminar #70

## Case – 17

**Contributed by: Delia Perez-Montiel, M.D.**

**Clinical History:** An 18 year old female with abnormal vaginal bleeding for 3 months. An Abdominal US shows a mass occupying all uterine cavity. PET-CT Showed a large uterine neoplasm with retroperitoneal and pulmonary metastasis. A D&C was performed as diagnostic approach.

**Pathology findings:** Sections showed a biphasic neoplasm with dilated endometrial glands without atypia surrounded by cellular stroma composed by fusiform low grade cells with scarce cytoplasm, monotonous, and with increased number of mitosis. Next to these areas, there was a mantle of small and short-fusiform cells with scarce cytoplasm and dense chromatin, without glands, alternating with areas of mature striated muscle-like.

**Immunohistochemistry stains** were positive for CD10 and estrogen receptors, negative for desmin and myogenin. The areas with small cells showed a mirror staining, mainly, negative for CD-10 and estrogen and positive for myogenin and desmin. The glandular component was positive for broad spectrum keratin and negative for BLC-2.

**Diagnosis:** Adenosarcoma with sarcomatous overgrowth and rhabdomyoblastic differentiation.

**Comment:** Müllerian adenosarcoma is an uncommon neoplasm composed of malignant stroma and benign glands. Age of presentation ranges from 14 to 89 years and some cases are associated to prolonged hyperestrogenism. Tumor sizes ranges from to 1 to 17 cm and usually presents as a polypoid mass. Typically, at low magnification the biphasic nature of the neoplasm is apparent. The glands are surrounded by moderated to markedly atypical, hypercellular endometrial or fibroblastic stroma showing periglandular condensation. Nearly 10% of adenosarcomas may present with sarcomatous overgrowth.

Sarcomatous overgrowth is defined as tumor composed only of neoplastic stroma, without epithelial component in more than 25% of the surface of the tumor. Frequently this sarcomatous overgrowth is a high grade sarcoma (low grade have also been described) with rhabdomyoblastic, fibroblastic, or NOS sarcoma.

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Wu RI, Schorge JO, Dal Cin P, Young RH, Oliva E. Müllerian adenosarcoma of the uterus with low-grade sarcomatous overgrowth characterized by prominent hydropic change resulting in mimicry of a smooth muscle tumor. Int J Gynecol Pathol. 2014;33:573-80.

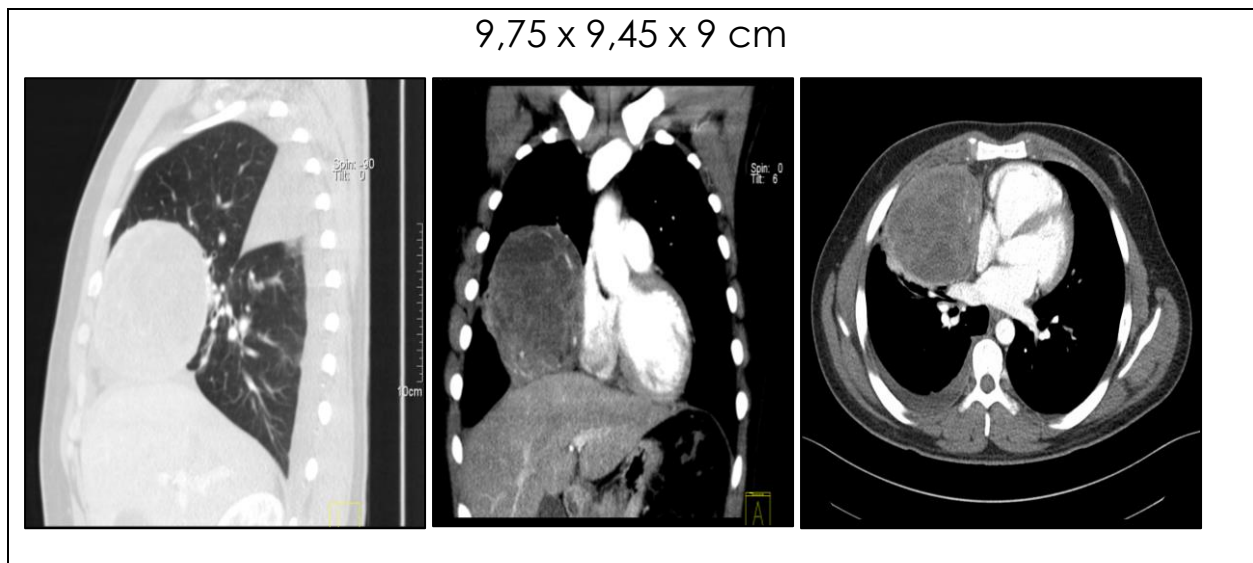
# AMR Seminar #70

## Case – 18

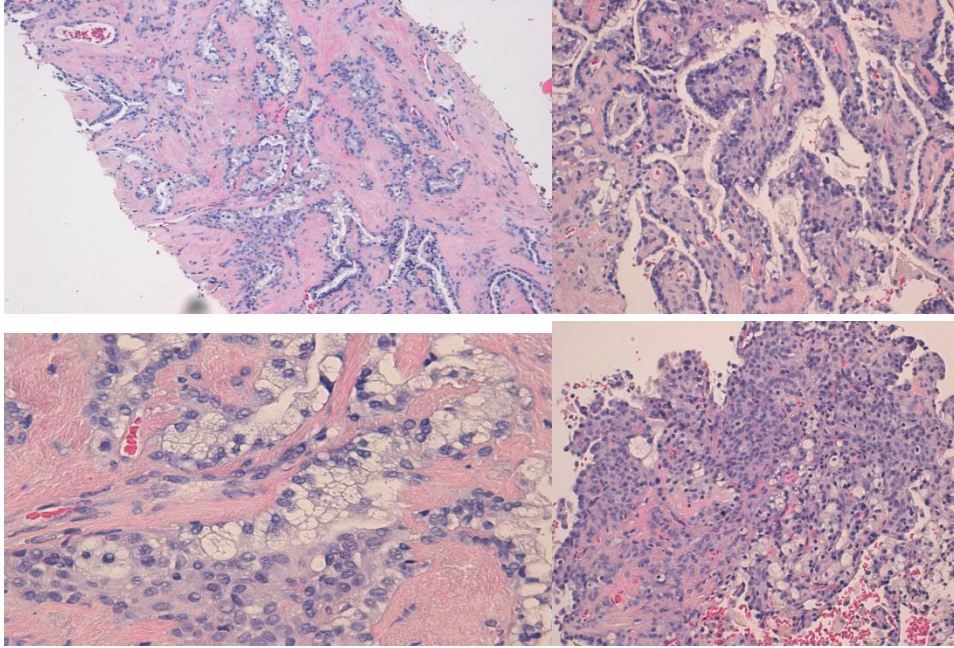
**Contributed by: Santiago Ramón y Cajal, M.D.**

**Clinical History:** A 21 yo man was seen for a medical history of rhino-conjunctivitis and intermittent extrinsic asthma. In 2013, after an accident, a Chest x-ray showed a rounded image with well delimited borders (>7 cm) in the anterior right mediastinum. The patient did not allow any clinical procedure until November 2014. The patient came to the hospital with thoracic pain at rest. No associated symptoms (no dyspnea, no fever) The x-ray and the CT scan showed a round to oval mass with smooth margins, at the right cardiophrenic angle, measuring 9x 9,75 x9,45cm. Calcification was observed on computed tomography. By PET a slight increase in the heterogeneous metabolism was informed, which could be related to low-grade tumor (low affinity for FGD).

The clinical differential diagnosis included a germ cell tumor or lymphoma.



Initially a small biopsy was performed and the diagnosis of adenocarcinoma was made (see pictures). With this diagnosis, the patient was referred to our institution where he underwent surgical excision



**Diagnosis:** Sclerosing pneumocytoma (positive for CK7, TTF1, AE1-AE3. EGFR: no mutated and ALK, not translocated).

Pneumocytoma can present with four different histological patterns: papillary, solid, sclerotic and hemorrhagic. It is quite characteristic in SP to see a dual population of polygonal type II pneumocytes, cohesive papillae, clusters or flat sheets lined by medium/large-sized cells. These cells show abundant pale eosinophilic cytoplasm and bland, round nuclei with inconspicuous nucleoli. Patent intranuclear inclusions are a helpful sign that must be investigated and appreciated. The neoplastic population is intermingled with thin-walled vascular spaces placed in a hemorrhagic background and accompanied by foamy, sometimes hemosiderin-laden, macrophages.

Identifying 3 of the 4 major architectural patterns within the tumor can be extremely helpful in suggesting sclerosing hemangioma during intraoperative consultation. Additionally, sclerosing hemangiomas rarely have significant cytologic atypia.

Both the surface cells and the round cells exhibit nuclear expression of thyroid transcription factor 1 (TTF-1) and membranous/cytoplasmic expression of epithelial membrane antigen (EMA) in most cases. The surface cells also exhibit strong cytoplasmic positivity for both pancytokeratin (AE1/AE3) and surfactant proteins A and B. However, the round cells frequently lack surfactant expression and have a more variable keratin profile. Round cells are often negative with pancytokeratin antibodies (AE1/AE3) but can have variable, focal expression of cytokeratin 7 and low molecular weight cytokeratin (CAM 5.2). Neuroendocrine markers, chromogranin and synaptophysin, may stain scattered cells, especially among the surface cells.

Calretinin is uniformly negative. Few cases exhibited progesterone receptor expression, and only rare examples were estrogen receptor-positive.

**Comments:** This tumor was described by Liebow and Hubbell in 1956 and called “Sclerosing hemangioma”, because the prominent vascularization and fibrosis of the tissue.

It is a very rare benign neoplasm, more frequent in Asian population, middle-aged adults from 11-80 years and 80% women

The epithelial differentiation to type II pneumocytes was demonstrated later (Tanaka et al. in 1986). The tumor displays very low cytological atypia, and the positivity for keratins are more prominent in the peripheral layers of the tumor nests. The differential diagnosis may include carcinoid tumors, adenocarcinoma, papillary adenoma and metastasis from papillary thyroid carcinoma.

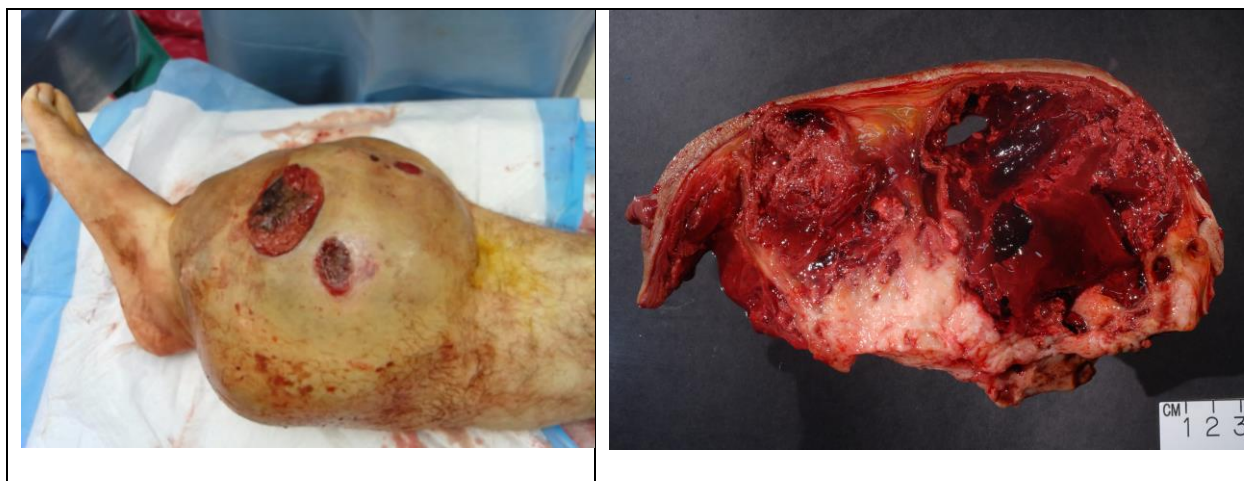
# AMR Seminar #70

## Case – 19

**Contributed by: Brian Rubin, M.D.**

**Clinical History:** The patient is a 37 year old man who presented recently with a large mass involving the right leg. CT scan revealed a 30 cm in greatest dimension mass obliterating the mid-tibia and fibula as well as the surrounding soft tissues. Chest x-ray revealed several lung nodules bilaterally, suspicious for metastatic lesions. The patient has a long history of osteofibrous dysplasia of the right tibia dating back more than 20 years. I was able to review a biopsy of the patient's osteofibrous dysplasia from 22 years ago and the findings were typical of osteofibrous dysplasia. Three years before the current presentation, he developed a large mass involving the lower right leg. After biopsy, he refused further therapy and was lost to follow-up until his current presentation.

**Gross Pathology:** The specimen from which your section was taken was a right above-the-knee amputation. There was a large mass with several areas where the skin was ulcerated (see image below on left). On cross section the mass measured 30cm in greatest dimension and was fleshy with large areas of necrosis and hemorrhage (see image below on right). The tumor involved the tibia, fibula and soft tissue.



**Histology:** Histologically, the lesion is densely cellular and composed of a monomorphic population of spindle shaped cells arranged in intersecting fascicles and set in a variably fibrous/desmoplastic stroma with scattered atrophic skeletal muscle cells. The lesional cells have ovoid nuclei, nuclear hyperchromasia, indistinct nucleoli and scant amounts of pale eosinophilic cytoplasm. The lesional cells plump up and are a bit more epithelioid in some areas. Scattered mitotic figures in the realm of about 10/10 hpf are identified but atypical mitotic figures are not noted.

**Immunohistochemistry and Molecular Pathology:** Immunohistochemical studies revealed the lesional cells to be strongly and extensively positive for cytokeratin AE1/AE3 with patchy immunoreactivity for EMA. S-100, HMB45, and Melan-A were negative. FISH for *SYT* gene region rearrangement was negative.

**Diagnosis:** Classic adamantinoma of long bone, predominantly spindle cell type arising in the setting of osteofibrous dysplasia.

**Discussion:** This case is not morphologically difficult. However, adamantinomas are very rare and I don't think one has been submitted to this slide club before, at least not recently.



The association between osteofibrous dysplasia and adamantinoma of long bones is well-documented and has been known since 1942, possibly longer. Osteofibrous dysplasia is a rare neoplasm that typically occurs in the 1<sup>st</sup> two decades of life with an equal sex predilection. The fibula or tibia can be involved and many cases involve both bones. Radiologically, there is a multiloculated radiolucent expansion of the anterolateral cortex of the tibia. Bowing of the tibia and fibula can also occur. Rarely osteofibrous dysplasia can be bilateral. Histologically, osteofibrous dysplasia is characterized by an admixture of benign-appearing fibroblastic stroma, typically arranged in a storiform growth pattern, admixed with bony spicules with prominent osteoblastic rimming. Recently, *MET* germline and somatic mutations have been found in osteofibrous dysplasia (1). The *MET* mutations found in osteofibrous dysplasia result in aberrant regulation and stabilization of the mature MET protein. *MET* encodes a receptor tyrosine kinase that is important in normal and neoplastic growth.

Classic adamantinoma typically arises in patients older than 20 years of age. Lesions arise exclusively in the tibia and fibula, usually both bones. Patients present with pain or bowing deformity of the tibia and may have a palpable mass. Bowing may be present for decades before diagnosis. Radiologically, the lesions usually have a mixed lytic and sclerotic appearance with a destructive growth pattern and cortical disruption. Grossly, the lesions are described as fleshy. Histologically, there can be several patterns and most cases exhibit multiple patterns. The different patterns are: basaloid pattern, spindle cell pattern, tubular pattern, squamous pattern and osteofibrous-dysplasia pattern. The case submitted in this seminar is predominantly the spindle cell pattern. All of these patterns are characterized by at least nests of keratin positive tumor cells. Typically, the lesions are positive for keratins 5, 14, 9, 1, 13, and 17. Keratins 8 and 18 (Cam 5.2) are not expressed. Cytogenetic studies show numerous numerical chromosomal aberrations. Taken together with the finding of *MET* mutations in osteofibrous dysplasia, this suggests that adamantinoma is propelled by progressive genetic mutations that are layered on top of *MET* mutations but this has yet to be demonstrated conclusively.

Differentiated (osteofibrous dysplasia-like) adamantinoma is an exclusively intracortical variant along the spectrum of osteofibrous dysplasia and adamantinoma. I think of it as exclusively intracortical osteofibrous dysplasia with scattered keratin positive epithelioid cells. I don't particularly like this diagnosis because some surgeons and oncologists don't distinguish between differentiated adamantinoma and classical adamantinoma and there is potential for massive over treatment. Cases that some would call differentiated adamantinoma, I classify as osteofibrous dysplasia.

Classic adamantinomas are truly malignant neoplasms. 25% exhibit metastasis, mostly to regional lymph nodes and lungs. Differentiated adamantinomas do not exhibit metastatic behavior.

**Differential Diagnosis:** If a history of osteofibrous dysplasia has been established then there isn't really a differential diagnosis. However, on morphological grounds, the major differential diagnosis of spindle cell predominant classic adamantinoma of long bone is synovial sarcoma, malignant peripheral nerve sheath tumor, fibrosarcomatous dermatofibrosarcoma protuberans (DFSP) and possibly an unusually spindly desmoplastic small round cell tumor. Synovial sarcomas tend to be more focally positive for keratin/EMA, are also positive for TLE1 (nuclear) and exhibit rearrangements of *SYT* gene region by FISH or have *SYT-SSX* gene fusions by RT-PCR or next generation sequencing. Malignant peripheral nerve sheath tumors tend to lack cytokeratin expression. Fibrosarcomatous DFSPs are typically superficial (above the fascia) and lack cytokeratin expression. Desmoplastic small round cell tumors typically have rounder cells, have desmoplastic stroma and are positive for cytokeratins but they are also positive for desmin and have *EWSR1* gene region rearrangements or *EWSR1-WT1* gene fusions by RT-PCR or next generation sequencing.

**Summary and follow-up:** This is a typical case of a very rare entity, classic adamantinoma of long bone, arising in the setting of long-standing osteofibrous dysplasia. The patient is alive with lung metastasis, four months after above the knee amputation.

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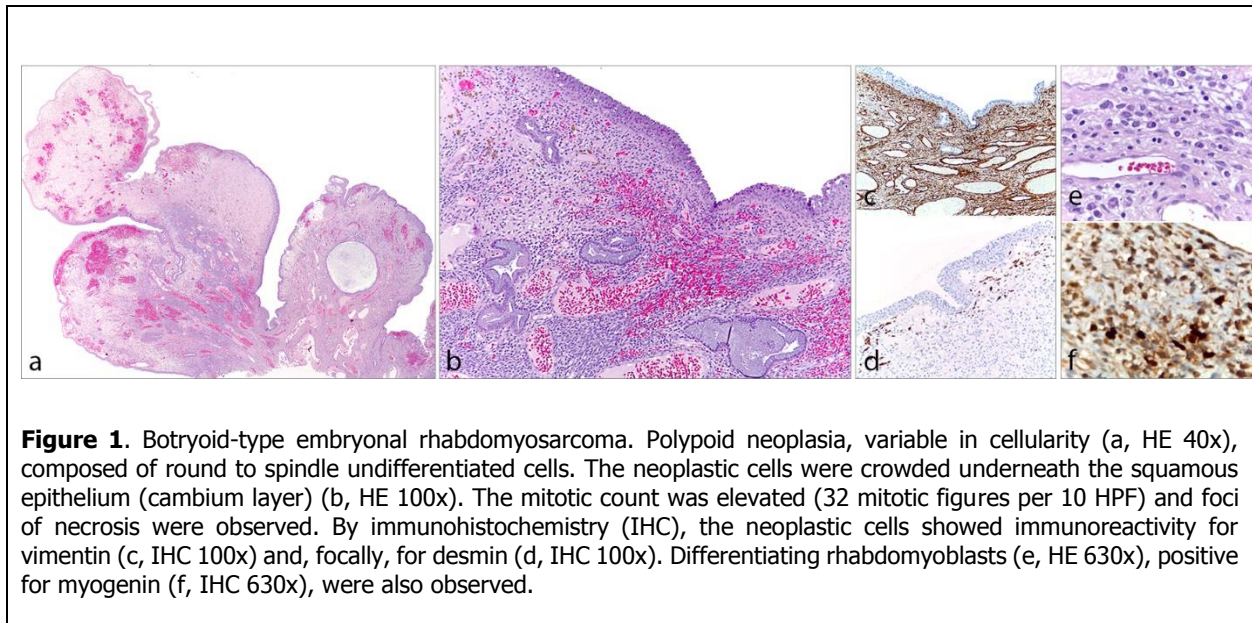
# AMR Seminar #70

## Case – 20

**Contributed by: Manual Sobrinho Simoes, M.D.**

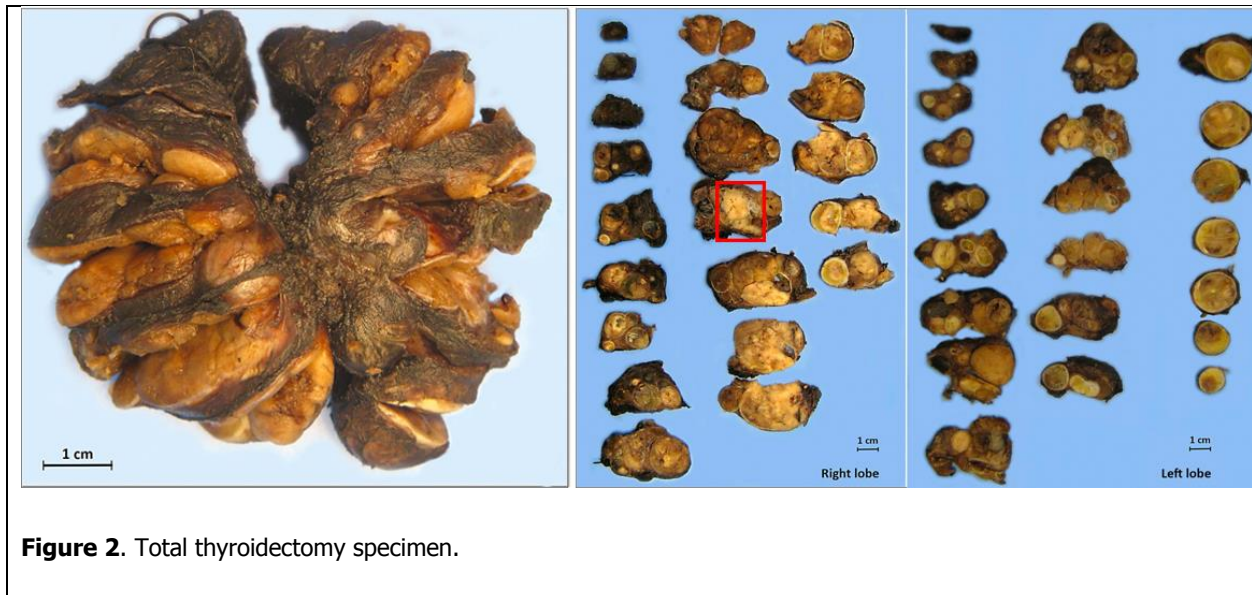
(This case was studied by Dr. Irene Gullo, a Resident in our Department)

**Clinical History:** Multinodular thyroid lesion in a 12 year-old girl, who had had a botryoid-type embryonal rhabdomyosarcoma (**BERMS**) of the cervix (Fig. 1) at the age of 7. Surgery and adjuvant chemotherapy (nine courses of the IVA regimen - ifosfamide, vincristine and dactinomycin) were performed. Five years later, at a follow-up examination, the clinician palpated an enlarged thyroid gland. Ultrasonography revealed multiple nodules in both thyroid lobes, the largest measuring 2.1cm (left lobe). Fine-needle aspiration biopsy was performed in the two largest nodules: the right nodule was interpreted as a follicular neoplasm (Category IV of the Bethesda system) and the left nodule as a benign colloid nodule (Category II of the Bethesda system). Total thyroidectomy was performed.

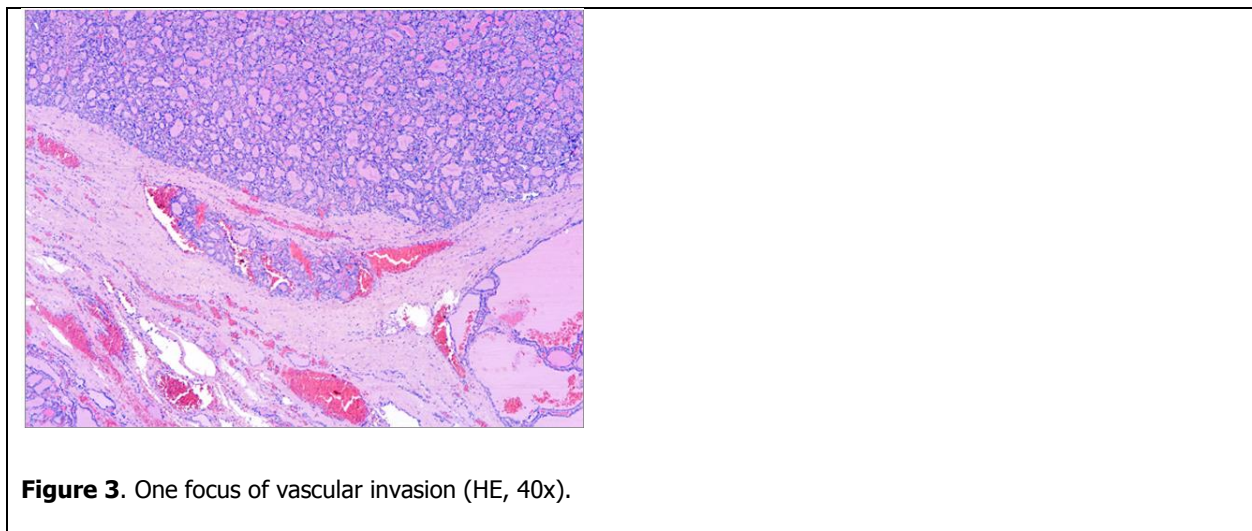


**Macroscopy:** the total thyroidectomy specimen weighted 61g. On cut surface, multiple and heterogeneous nodules were identified. The nodules were mostly well demarcated and, occasionally, encapsulated. The slide is representative of the nodule enclosed by a red rectangle (Fig. 2).

**Diagnosis:** multinodular adenomatous goiter with a well circumscribed, partly encapsulated 1.4 cm well differentiated thyroid carcinoma, not otherwise specified (NOS), with angioinvasion (Fig. 3), in the context of a DICER1 syndrome.



**Figure 2.** Total thyroidectomy specimen.



**Figure 3.** One focus of vascular invasion (HE, 40x).

**Comments:** Well differentiated thyroid carcinoma in DICER1 syndrome, an emerging phenotype.

We considered the association of bERMS and multinodular goiter/well-differentiated thyroid cancer highly suggestive of DICER1 syndrome (Foulkes *et al*, 2014). The genetic testing, performed in this case, confirmed the presence of a germline pathogenic (nonsense) DICER1 mutation (p.Arg1060Ilefs\*7). Familial multinodular goiter is the most frequent manifestation of germline DICER1 mutation in the thyroid gland. Despite being usually considered as “rare”, the occurrence of well differentiated thyroid carcinoma is emerging as a not so rare phenotype.

### **Papillary or follicular thyroid carcinoma?**

Ten cases of thyroid malignant neoplasms have been reported previously in the context of germline DICER1 mutations: three cases of follicular thyroid carcinoma (FTC) and seven of papillary thyroid carcinoma (PTC). Curiously, Shin *et al* described a case of FTC that, when revisited by Kock *et al*, was re-classified as PTC, underlying the difficulty of diagnosing these tumours using the classic dual classification. Our specimen showed morphological features that did

not match follicular carcinoma nor papillary carcinoma. Hence, we preferred the term of well differentiated thyroid carcinoma, NOS.

The "intermediate" morphologic appearance of the nuclei of the neoplastic cells of these tumours fits with a peculiar molecular profile. As reported by other authors (Lumbreras C *et al*, 2016, Rutter MM *et al*, 2016, Shin SH *et al*, 2012) we did not find any of the molecular alterations that are characteristically associated to FCT or PTC (*BRAF*599/600, *NRAS*61, *HRAS*12/61, *TERT* promoter mutations and *PAX8/PPAR $\gamma$* , *RET/PTC1* and *RET/PTC* rearrangements). Furthermore, in the three-tiered molecular classification, recently proposed by Yoo SK *et al* (including *BRAF*-like, *RAS*-like and Non-*BRAF*-Non-*RAS* tumours), *DICER1* is one of the driver genes defining the novel Non-*BRAF*-Non-*RAS* molecular subgroup. It looks like that thyroid carcinomas arising in the background of *DICER1* syndrome may reflect a carcinogenic process different from the classical pathways towards PTC or FTC.

#### **Post scriptum:**

We hope you are sufficiently masochistic to read the paper we (Irene Gullo *et al*) are writing on this subject.

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# AMR Seminar #70

## Case – 21

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

**Clinical History:** A 43 year-old man presented with a 25 cm. (by CT exam) retroperitoneal mass centered around the left upper quadrant of the abdomen with involvement of the midbody and antrum of the stomach as well as about 75% of the pancreas coursing all along the superior border of the pancreas from the distal tail to the pancreatic neck, to the hilum of the spleen, and to a large proportion of the mesentery. He underwent radical resection of the mass along with distal pancreatectomy, splenectomy and adjuvant external beam radiation. All of this occurred 8 years ago.

**Pathology:** Your slides show in most areas a proliferation of bland, monotonous cells having oval to elongated nuclei that are dispersed in stroma that is alternatively minimally fibrotic to areas having large foci of fibrous scarring. A minor portion of this tumor shows foci displaying marked nuclear hyperchromasia, and cellular anaplasia/nuclear pleomorphism along with typical and atypical mitotic figures. Interestingly, these unquestionably malignant cells appear to be randomly interspersed/dispersed among the much more banal appearing fibroblastic cells, rather than completely obliterating them and forming a single focus of anaplastic cells expanding in a centrifugal fashion.

A broad panel of immunostains was performed by the pathologist handling the case, but suffice it to say that the sarcoma was only diffusely positive for CD34 and bcl-2. STAT-6 was not available in 2008.

**Diagnosis:** Malignant solitary fibrous tumor, dedifferentiated.

**Comment:** Subsequent to his radical surgery in 2008, he developed a pathologically documented liver metastasis in 2012 that was treated with microwave ablation. Histologically, the metastatic focus showed even greater nuclear pleomorphism than his original retroperitoneal tumor and had a mitotic count of 8 mf/10 hpf with many anaplastic cells. In 2015, CT exam revealed 2 new low-attenuation lesions in the liver likely representing metastatic disease thought to be unresectable. He started treatment with Bevacizumab and Avastin in 2015. He has never had a recurrence in the retroperitoneum. He is now 8 yrs. post-diagnosis and has no lesions other than the 2 stable ones in his liver that have not been biopsied.

Although I am not an advocate of the term 'dedifferentiated' for reasons outlined long, long ago (>30 yrs.) by Drs. AM Rywlin and JA Robb, I guess that terminology is here to stay as it is now being used for a wide variety of neoplastic lesions. Nonetheless, I thought this was an example of so-called dedifferentiated SFT as outlined in papers by current and prior members of the club. At the risk of possibly offending someone, I am citing only one of the current reviews on the subject by club member Cyril Fisher and his colleagues.

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# AMR Seminar #70

## Case – 22

**Contributed by Saul Suster, M.D.**

(Case kindly contributed by Dr. Maritza Guerrero, General Hospital "Luis Vernaza", Guayaquil, Ecuador).

**Clinical History:** A 32 year old man from Ecuador with no significant past history was seen for severe abdominal pain and diarrhea. An endoscopic examination was performed which showed and edematous and congested bowel with abundant mucus and petechial ulcers. Random biopsies were performed.

**Pathologic findings:** The bowel biopsy shows numerous larval structures in the wall of the bowel mucosa.

**Diagnosis:** Hyperinfection with *Strongyloides stercoralis*.

**Comment:** Strongyloidiasis is a common infection in underdeveloped countries with tropical climates. The disease is caused by a nematode, *Strongyloides stercoralis*. The life cycle of the parasite includes larva passing from feces to the soil where they infect man and penetrate through the skin. Once the larva penetrates the skin, they travel to the lungs where they break out of pulmonary capillaries into the alveolar spaces. Here they develop into adolescent worms that migrate up the bronchi, are swallowed and mature into mature females in the intestines. In hyperinfection the gastrointestinal symptoms of cramping and diarrhea can be severe and may be followed by paralytic ileus and malabsorption. The histology shows adult female worms lodged in the crypts where they deposit eggs that hatch and liberate larvae into the lumen. Longstanding infection may lead to bowel fibrosis.

This is a rather common infection in South America but we do not get to see this type of pathology here and I thought it would be a rare treat for most of the members to get to see some tropical pathology unrelated to neoplasia.