AMR Seminar #68

Case – 1

Contributed by: Carlos E. Bacchi, M.D. (CB 11911/15)

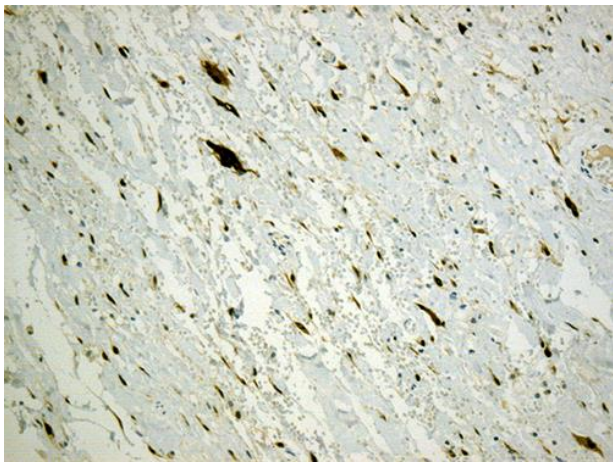
Clinical history: This is a very recent case of a 56-year-old white female with pelvic and retroperitoneal mass. Excision of the mass was performed. This is the only paraffin block sent by the referral pathologist.

Pathological Findings: This neoplasm has two distinctive histological components. In the periphery of the tissue, there is a mature adipocytic proliferation with some variantion in cell size with some fat cells showing nuclear atypia. There are also presence of fibrous septa with hyperchromatic stromal cells sometimes associated with some inflammatory cells. Lipoblasts are not easily found. The other compoment of the neoplasm has a nodular-type of growth and is formed mainly by lymphoid cells including mature lymphocytes, plasm cells, eosinophils and hitiocytes. There is also, vessel proliferation of post-venules type and deposition of delicate hyalin material through out this part of the tumor. Among these hematolymphoid cells there are numerous large cells with very enlarged nuclei, coarse chromatin, sometimes with prominent nucleioli. In some areas, these cells are isolated and others they are formed groups of two or three and often associated with the hyalin material. Few of those cells show some features of RS cells. Immunohistochemistry study revealed expression, in the stromal atypical cells present in both components, of CDK4, MDM2 and p16 (see images).

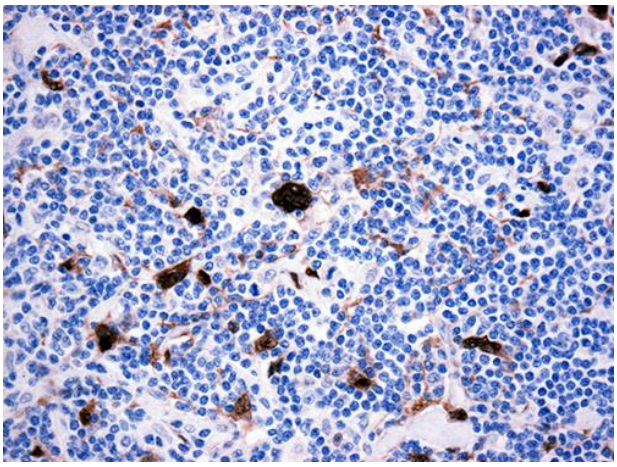
Diagnosis: Well-differentiated lipossarcoma with areas of exuberant hematolymphoid infiltrate mimicking reactive lymphoid infiltrate or hemaopoietic neoplasm including Hodgkin's lymphoma.

Comment: I found this case very interesting as I have never seen a well-differentiated liposarcoma with such an exuberant hematolymphoid component. In fact, if the biopsy had represented only the lymphoid component I believe that the diagnosis of well-differentiated liposarcoma would be very difficult to reach. The case was sent to me in order to rule out lymphoma as the pathologist who referred the case missed the more fibroadipocytic part of the neoplasm. In the paper by Chris Fletcher (AJSP, 1997), it is stressed that the presence of inflammatory pseudotumor areas can easily be confused with no sarcomatous process. In this particular case, I think the lymphoid part of the tumor is mimicking more like reactive lymphoid tissue and/or lymphoma than inflammatory pseudotumor. I would like very much to hear the opion of the soft tissue pathology experts about this case.

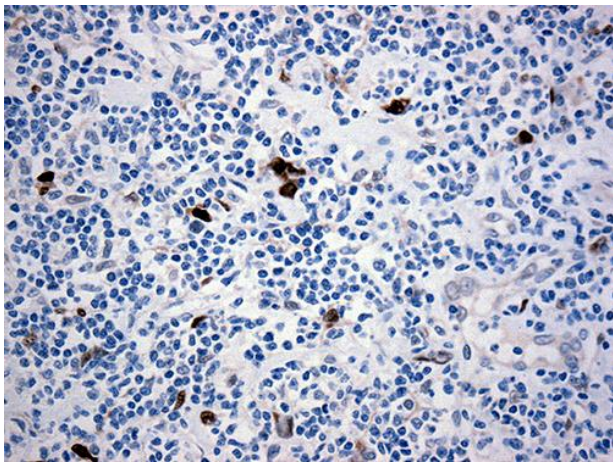
CDK4

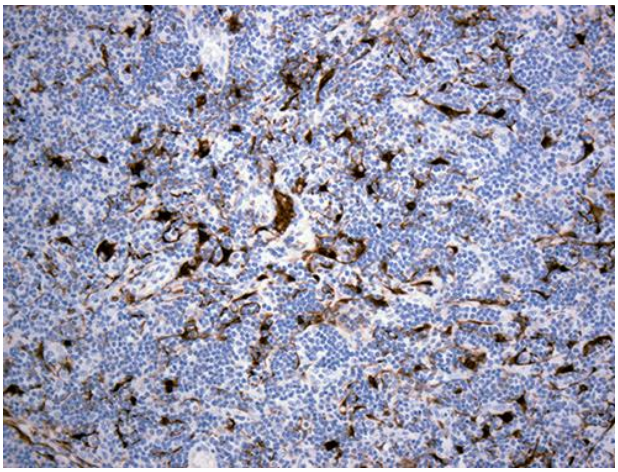


CDK4



MDM2 **P16**





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AMR Seminar #68

Case – 2

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

Clinical History: This concerns a 61 year old woman who was stated to have CIN III (presumably based on a biopsy not performed in our hospital) and who underwent excision of the posterior lip of the cervix for a "cauliflower like lesion".

Pathology Description: The gross specimen consisted of a 2x1.8 cm mucosal fragment said to have a "granular papillary appearance". Histological examination shows at one end of the section a proliferation of highly dysplastic immature epithelial cells totally replacing the mucosa consistent with CIN III/high grade squamous intraepithelial lesion (according to recent but debated terminology or carcinoma in situ which the more elderly members of the group would recognize). A bit inwards the proliferation of the high grade dysplastic cells is surmounted by atypical cells but showing some degree of maturation (consistent with CIN II which would now be referred to as high grade squamous epithelial lesion- HSIL; the differentiation from CIN III is now felt to have no clinical utility). These areas show en bloc nuclear and cytoplasmic positivity for p16 and extensive Ki-67 positivity as expected. The middle of the slide is very interesting: this shows a spiky condylomatous lesion whose lower layers are composed of small basal type squamous epithelial cells which show on careful examination intercellular bridges and without the nuclear atypia shown in the classical HSIL portion. More superficially there is overt squamous differentiation with cytologic atypia, numerous mitoses, and on the surface, florid parakeratosis. While not prominent I think one can make the case that at least focally there are koilocytic changes. In this portion the p16 is debatable: there are a few small foci of strong en bloc staining but the majority of the lesion shows weak and equivocal staining that I'm not sure is diagnostic. It is important to emphasize that there was no evidence of invasion anywhere in this specimen.

Diagnostic considerations: The question that arises is whether we're dealing with a unique biological event with differing histological phenotypes or with a "collision" between two separate events. The CIN III/HSIL is unequivocal. While this is classically composed of immature cells with limited maturation if any, the mere presence of keratinization does not rule the diagnosis out. In fact: HSIL with keratinization is described in the latest AFIP fascicle on tumors of the cervix, vagina, and vulva (fourth series (2010), fascicle 13), pg 88, and illustrated in figures 5-26 (pg 89) and 5-41 (pg 100); on pg 175 (fig 7.05) of the latest WHO " Blue Book" (WHO Classification of Tumors of Female Reproductive Organs, ed. R. Kurman et al, IARC, Lyon France 2014); and in the LAST position paper ("The lower anogenital squamous terminology standardization project for HPV associated lesions", Arch. Pathol. Lab. Med. 136: 1266-1297; see text pg. 1278 and fig. 7 pg 1279). So maybe this is an HSIL with focal keratinization, supported by the fact that I at least don't see any sharp demarcation between the keratinizing and non keratinizing component- rather both these elements seem to be in continuity with one another. However, keratinizing HSIL as depicted in the above references is typically a flat lesion composed of high grade dysplastic cells with the rather abrupt appearance of an overlying layer of parakeratosis (which may be mere degenerative changes). In this case the keratinizing lesion shows architectural features typical of condyloma and the keratinization is an expected outgrowth of a gradually maturing epithelium.

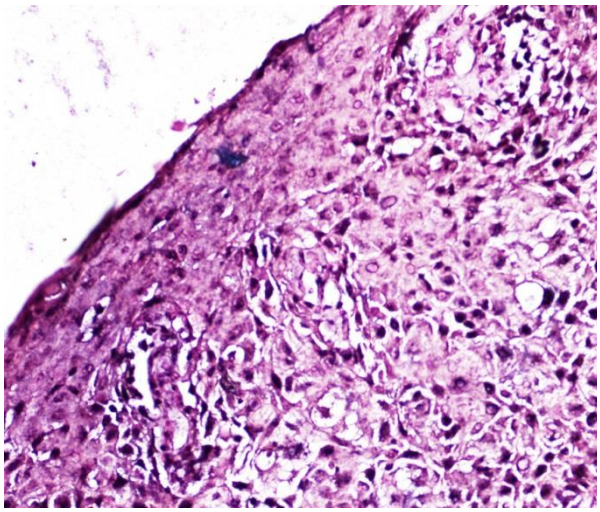
I thought this would be a great case for HPV typing so I enlisted the assistance of Dr Jerry Nuovo of Ohio State University who was kind enough to perform the in-situ hybridization studies using a consensus probe for multiple HPV subtypes (6,11,16,18,30,31,33,35,42,43,44,45,51,52,56,68,and 70) . As expected the portion showing conventional features of HSIL was strongly positive for high risk HPV types 31/35/51. However the condylomatous lesion was totally negative for any HPV, including the low risk subtypes usually associated with condylomas!

Dr Nuovo directed me to an article he had previously written with Dr Paul Wakely concerning keratinizing neoplasia of the cervix (C. Morrison et al, "Highly differentiated keratinizing squamous cell carcinoma of the cervix", Am J Surg. Pathol. 2001: 25, 131-1315). This is a report of 5 cases of keratinizing squamous cell carcinomas of the cervix (as it happens including a case of verrucous carcinoma of the cervix which I had previously sent him) which were all negative for HPV by standard in-situ hybridization and confirmed by PCR in situ hybridization. The cases included in this report differ from the case presented here in that the latter showed no invasion and included an HPV positive HGSIL component, whereas this finding was absent in the cases included in the report. But it does broach the issue of and provide a precedent for squamous cervical neoplasia unrelated to HPV.

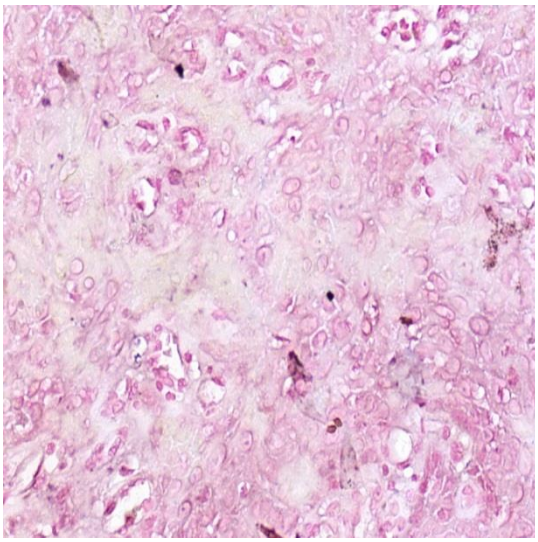
So this is apparently a "collision" between two apparently unrelated phenomena, a high grade SIL related to HPV and the other a condylomatous lesion in which HPV was not detected. Asides from the latter being unrelated to HPV, it is still possible that it does contain HPV of the type included in the consensus probes used but present in copy numbers insufficient for detection by the methodology used (this issue was in fact brought up in the above AJSP reference). Another possibility is that the condylomatous lesion results from an HPV type not included in the probe. In a paper published in 2013 (H. Johannsen et al, "Metagenomic sequencing of "HPV negative" condylomas detects putative HPV types", Virology 2013: 440, 1-7) swabs from clinically detected condylomas that were considered to be HPV negative (presumably by conventional HPV ISH though this was not spelled out in the article at least per my reading of it) were subjected to metagenomic sequencing. While some cases showed recognized HPV types known to be associated with condylomas (HPV 6 but also 58 and 66) but not picked up by the conventional method, some cases were positive only for beta- and gammapapilloma viruses previously identified only in healthy skin or in cutaneous lesions such as basal or squamous cell carcinomas (the full text of the article is online on the journal website for anyone interested in further details which I don't understand in any case). So causative viruses of certain genital lesions may go undetected depending on the methodology used.

Subsequently, further surgery was performed with the classical high grade SIL persisting multifocally in the trachelectomy specimen (in the cervix and vagina) where it reached the surgical margins, and in additional excisions from the vagina where it also reached the margins. There was no further evidence of the keratinizing squamous lesion in these subsequent specimens. Ultimately the prognosis depends on the ability to control the high grade SIL and prevent it from turning into invasive carcinoma. The exact identity of the keratinizing lesion is moot and at this point I think is academic, and the case is presented in that spirit for your examination and comments.

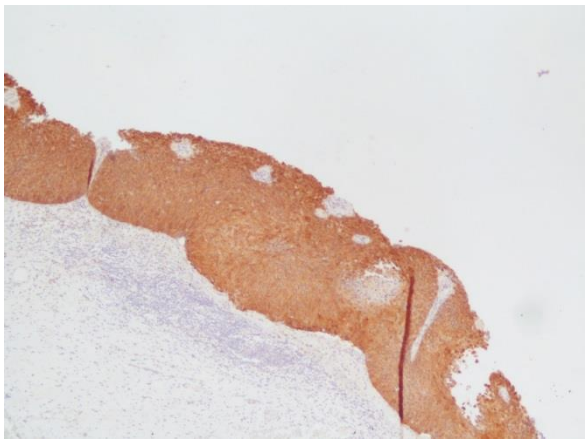
Final diagnosis: HPV associated high grade SIL (CIN III) and dysplastic condylomatous lesion of uncertain etiology (HPV not proven).



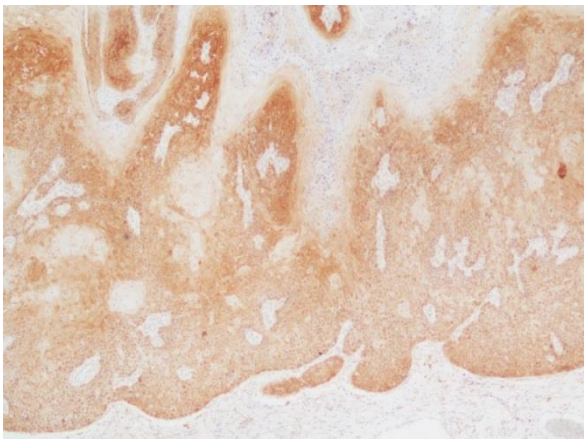
High grade SIL positive for HPV (courtesy of Dr Nuovo)



Condylomatous lesion negative for HPV (courtesy of Dr Nuovo)



P16 immunohistochemical stain shows diffuse "en-bloc" positivity of high grade SIL lesion



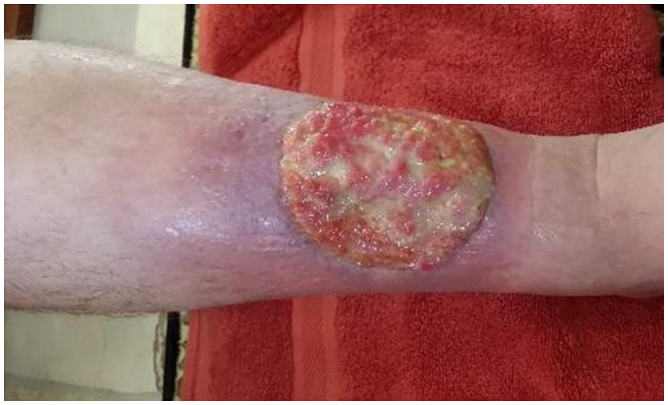
P16 immunohistochemical stain of condylomatous lesion- mostly weak and non-diagnostic

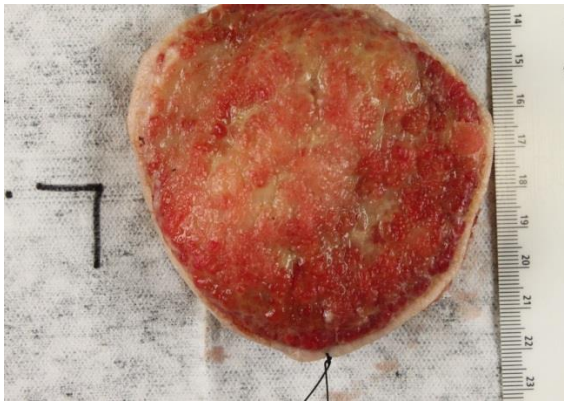
AMR Seminar #68

Case – 3

Contributed by: Kumarasen Cooper, M.D.

Clinical History: This is a 66 year old man with a large tumor on his anterior leg. (Please view the gross (clinical) and resection images before the glass slides). The lesion measures 2.6 x 7.0 cm. Of note is that he has a history of oropharyngeal carcinoma in 2008 for which he was treated appropriately. The clinical concern was for metastatic squamous cell carcinoma from his oropharynx.





Imaging Studies: The imaging demonstrated an irregular infiltrative cutaneous/subcutaneous mass involving the anterior aspect of his left leg. The mass abutted the anterior aspect of the distal tibial metaphysis with local periosteal reaction but without cortical destruction. Surrounding and distal edema of the subcutaneous tissue was noted.

Pathology: A local excision of the mass was performed (see gross photograph). The lesion comprises a spindle cell proliferation arranged in bundles with varying degrees of collagenization (more on the deeper aspect of the lesion) with scattered reparative type blood vessels and mononuclear inflammatory cells. Rare mitotic figures were present but no atypia was seen. The spindle cells were positive for smooth muscle actin and negative for nuclear beta-catenin, nuclear STAT6, MUC 4, keratins, EMA, CD 34 and S-100.

Proffered Diagnosis: Proliferative myofibroblastic lesion (following application of a black salve agent).

Discussion: In April 2014 he noted a small raised "spot" on his anterior leg. He thought it was a cancer and initiated a treatment of "black salve" (purchased on line from the Philippines). This involved a 7 day application followed by a period of skin erosion, scabbing and healing. Initially he felt that the treatment was going well, but then a pink lobular mass sprouted (clinical and gross photographs) which concerned him and he sought medical help in Philadelphia (he lievs in Florida but travels here for his medical care). My theory is that the corrosive agent initiated this reparative myofibrobalstic lesion.

Attached below is a publication highlighting the use of black salves and escharotics in the "self-treatment" of cancer.

The extract below gives some helpful background entitled "Don't use corrosive cancer salves (escharotics)" by **Stephen Barrett, M.D.**

Link http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/eschar.html
Many salves, pastes, poultices, and plasters have been applied directly to tumors with the hope of burning them away. Zinc oxide, bloodroot, and several other herbs are common ingredients. Some marketers claim that corrosive agents (sometimes called "black salves") can "draw out" the cancer. In recent years, scientists have found chemicals that can destroy certain superficial skin cancers. Except for these, however, corrosive agents are worthless against cancer and cannot be legally marketed for that purpose in the United States.

Corrosive salves are often referred to as "escharotics" because they produce a thick, dry scab called an "eschar" on the skin. Their use to treat cancer dates back hundreds of years, perhaps even to ancient times. Their use was fairly common during the 18th and 19th centuries. If a tumor is confined to the superficial layers of the skin, it would be possible to burn it off with a corrosive salve or paste. Unfortunately, products capable of accomplishing this can also burn the surrounding normal tissue and result in unnecessary scarring. For superficial cancers—for which the cure rate with standard treatment is nearly 100%—it makes much more sense to use standard methods that can destroy the cancer with little or no damage to the nearby tissues. Some salves are also promoted for treating herpes, venereal diseases, diabetes, and lupus.

Some currently marketed escharotics contain bloodroot (*Sanguinaria candensis*), zinc chloride, or both. However, because cancer salves are not manufactured under government supervision, it may not even be possible to know what is in them. People who use such products without benefit of medical consultation run additional risks. Untrained individuals may incorrectly conclude that a growth is cancerous when it is not. Skin cancers that can spread should be medically investigated to see whether they have done so, and some of these require extensive treatment even though they might not look dangerous to the naked eye. In addition, although escharotics may appear to destroy cancers on the surface of the skin, the user will not be able to tell whether cancer remains under the skin where it can continue to grow without immediate detection.

J Cutan Pathol 2008; 35: 404–406
doi: 10.1111/j.1600-0560.2007.00816.x
Blackwell Munksgaard, Printed in Singapore

Journal of
Cutaneous Pathology

Histopathologic findings and diagnostic difficulties posed with use of escharotic agents for treatment of skin lesions: a case report and review of the literature

Escharotic agents have been used as alternative therapy for treatment of skin cancer and skin problems for centuries. Internet web sites such as online health product stores and eBay have made them widely available to the general public. The use of these agents carries risk of incomplete removal of tumor, damage of surrounding healthy tissues and marked scarring with poor cosmetic outcome. We report the case of a 27-year-old man who presented with history of moles and self-treatment with an escharotic agent containing bloodroot in order to document the histopathologic findings of topical bloodroot treatment, and to show the clinical consequences that may occur in the unsuspecting public. To the best of our knowledge, the histological features following use of bloodroot (*Sanguinaria canadensis*) have not yet been documented.

Moran AM, Helm KF. Histopathologic findings and diagnostic difficulties posed with use of escharotic agents for treatment of skin lesions: a case report and review of the literature.
J Cutan Pathol 2008; 35: 404–406. © Blackwell Munksgaard 2007.

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Alternative as well as unconventional therapies have been used since the beginning of recorded history and have also been used as an adjunct in conventional medicine.[1] Escharotic agent use for the treatment of skin cancer has most notably been used in conventional medicine by Mohs for *in situ* fixation of tissue prior to micrographic surgery.[2] Today, the popularity of alternative medicine treatments and ease of access to unconventional remedies through the Internet has resulted in suboptimal patient self-treatment in an age where conventional therapies provide remarkable success rates for skin cancer treatment, including clinical cure rates of 99% for primary basal cell carcinoma, 94% for recurrent basal cell carcinoma, 97% for primary squamous cell carcinoma and 90% for recurrent squamous cell carcinoma.[3–7]

We present the case of a 27-year-old man with atypical moles on the upper and lower back which were self-treated with 'black salve' (containing bloodroot, *Sanguinaria Canadensis*) to document the histopathologic findings of topical bloodroot treatment for the first time.

Case report

A 27-year-old man presented with history of abnormal appearing moles on the upper and lower back treated with black salve containing bloodroot or *S. canadensis*. Physical examination showed tan skin with 2 cm necrotic ulcers. Elliptical biopsies were performed to evaluate for any underlying cancer. Yellow salve like material was still present on both skin biopsy specimens. Patient was otherwise healthy and did not show any past medical history or family history of melanoma.

On histopathologic examination, excisional biopsy specimens showed marked ulceration,

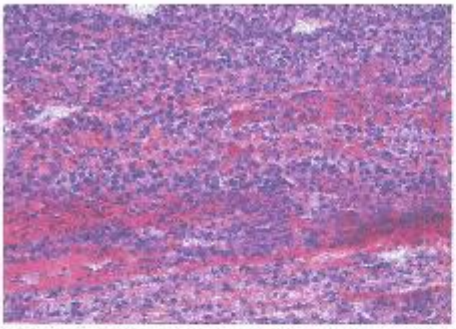

Fig. 1. Extensive tissue necrosis with a diffuse mixed neutrophilic and lymphocytic infiltrate dissecting between collagen bundles and aggregating as large regions. Hematoxylin and eosin. ×100.

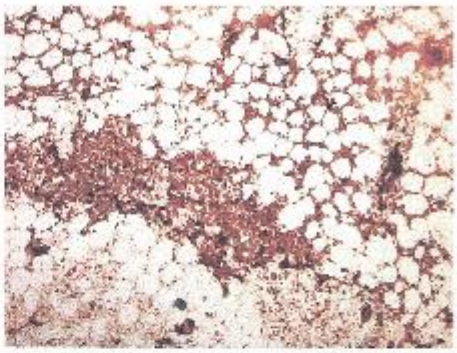

Fig. 3. Diffuse positive myeloperoxidase staining of inflammatory cells within the subcutaneous adipose tissue. Myeloperoxidase. ×40.

extensive tissue necrosis involving the epidermis, dermis as well as subcutaneous tissues with a secondary necrotizing vasculitis. A diffuse mixed neutrophilic and lymphocytic infiltrate was present throughout all layers of the skin and deep subcutaneous tissues (Fig. 1). Inflammatory infiltrate dissected between collagen bundles and also aggregated as large regions in areas of the most prominent necrosis (Fig. 2). AE1/AE3 cytokeratin, melan-A, HMB-45 failed to show residual nevus or epithelium. CD3, CD20, CD30 and LCA were also negative. Myeloperoxidase was diffusely positive and S-100 showed a cluster of positive cells (Fig. 3). In view of negative Melan-A staining, the cluster of S-100 positive cells proved to be dermal dendritic cells. The histology mimicked findings seen in diffuse dermal and subcutaneous diseases such as subcutaneous T cell lymphoma, angiocentric lymphoma, lupus erythematosus panniculitis, polyarteritis nodosa, Sweet's syndrome, Marked cell carcinoma, infectious agents, spider bite and pressure ulcer.

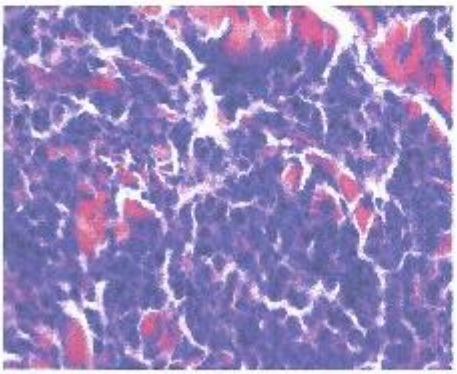

Fig. 2. Large aggregations of inflammatory cells in areas of most prominent tissue necrosis within deep dermis. Hematoxylin and eosin. ×200.

Discussion

As the availability of escharotic agents increases, there will be an increase of patient's using them. Dermatologists and dermatopathologists ought to be aware of the pathophysiology, clinical and histological picture as well as possible consequences resulting from their use.

S. sanguinaria has been shown in studies to induce selective apoptosis in cancer cells through inhibition of transcription factor nuclear factor κB activation, inhibitor of kappa B-alpha phosphorylation and degradation.[6,7] Data from another study had shown the involvement of the mitochondrial pathway and Bcl-2 family of proteins during apoptosis of immortalized keratinocytes.[10] In addition, sanguinarine causing cell cycle blockade and apoptosis of prostate carcinoma cells through cyclin kinase inhibitor-cyclin-cyclin-dependent kinase machinery modulation has also been shown.[11]

Clinically, the paste induces a necrotic eschar formation which heals with extensive scarring. Histologically, sanguinaria induces an extensive necrosis with brisk deep mixed inflammatory response. Histopathologic analysis of an escharotic plaque following use of zinc chloride had also shown dense acute and subacute inflammation with extensive tissue necrosis extending deep to involve fat in one article, similar to what we had observed with *S. canadensis*.[9] Pathologists should be aware that extensive tissue necrosis could be caused by an escharotic agent.

There has been recent outcry among the dermatologic community regarding the use of

escharotic agents for self-treatment of skin cancer as a result of unregulated access to escharotic agents on the Internet. Detrimental patient outcomes following indiscriminate use have been well documented.[2–11] In addition to residual tumor following use of escharotic agents,[4,12] other adverse affects include severe scarring, and even metastasis.[13]

Clinical history from the dermatologist in the pathology report stating possible escharotic agent use is paramount. In addition, pathologists should be aware that tissue necrosis with a diffuse interstitial infiltrate could be secondary to an escharotic agent to avoid possible pitfalls in misdiagnosis.

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AMR Seminar #68

Case – 4

Contributed by: Manuel Sobrinho Simões, M.D.

Clinical History: 76-year-old female with a history of long standing goiter that has recently started growing fast causing slight dysphagia and apparently invading the local structures of the neck. A clinical diagnosis of "anaplastic carcinoma" was made (no FNAB) and the patient was submitted to a quasi-total thyroidectomy with bilateral lymphadenectomy.

Macroscopy: The surgical specimen – classified by the surgeon as "total thyroidectomy and left lymphadenectomy" – weighed 44g and included 11 lymph nodes, the largest measuring 8mm. There was a separate specimen – "right lymphadenectomy" – weighing 2 g and including 4 lymph nodes, the largest measuring 7mm.

The left lobe measured 6.0x4.5x4.0 cm and was almost totally occupied by a large, poorly circumscribed tumour that invaded the anterior and posterior margins of the specimen. The tumour had a multinodular appearance and a central fibro-calcified nodule that is represented in the slide. The right lobe measured 3.3x2.0x1.5cm and had no lesions at all (Not even lymphocytic thyroiditis). The 15 lymph nodes (11+4) displayed only reactive changes (No metastasis).

Diagnosis: The case was sent to us to confirm the tentative diagnosis of Oncocytic variant of poorly differentiated thyroid carcinoma, extensively invasive. I agreed with most of the points made by the colleague who sent the case and advanced the diagnosis of "**Widely invasive, oncocytic (Hürthle cell) carcinoma, NOS, with abundant lymphoid infiltration and prominent angioinvasion".**

In order to progress in the characterization of the tumour we asked for two representative paraffin blocks (for performing immunohistochemical and molecular studies).

Comments: I must confess I decided to select this case for the sake of discussing a number issues that recurrently pop in whenever facing an oncocytic thyroid tumour. If one excludes the vexing problems of PTC nuclei *versus* non-PTC nuclei and the diagnosis of the equivocally invasive encapsulated follicular patterned (papillary and follicular) tumours, oncocytic neoplasms raise the most frequent diagnostic and/or prognostic problems in thyroid pathology. As you will see later on I was right for the wrong reasons.

For the sake of keeping things as real as possible, I decided to disclose the text I had written before receiving the results of the ancillary studies.

Is it an oncocytic variant of papillary, follicular or poorly differentiated carcinoma?
Despite the existence of many papillary patterned areas the nuclei are not of the PTC-type. It is not a poorly differentiated oncocytic carcinoma for the following reasons: the cells have abundant cytoplasm at variance with the small size of the oncocytic cells of poorly differentiated oncocytic carcinomas; mitoses are scarce, and that is the reason why the cells have abundant cytoplasm stuffed with mitochondria (if there were frequent cell divisions the number of mitochondria would be reduced); and, finally, no necrotic foci were observed. We think the best name for cases like this is "Oncocytic carcinoma, NOS".

What about the lymphoid infiltration?
It is quite frequent to see benign and malignant oncocytic thyroid tumours on a background of Hashimoto thyroiditis. At first we thought this might be the case in "our" tumour but the right lobe was rather small and totally normal. The prominent lymphoid infiltration (even with germinal centers) appears to be secondary to the neoplastic process and is mainly located inside vessels. We do not recall seeing such a picture in an oncocytic carcinoma (It is not a Warthin-like thyroid carcinoma).

How to classify the tumour in terms of degree of invasion?

Since the tumour invaded the perithyroid tissues (and had positive margins) it is not important to decide whether or not it should be classified as widely invasive. We decided to go for "widely invasive" because there is a central fibro-calcified nodule that may represent the original tumour. At variance with common follicular carcinomas in which it is usually easy to separate minimally (encapsulated) carcinoma from widely invasive neoplasms, oncocytic carcinomas tend to display a multinodular growth pattern without exhibiting a clear cut centrally located tumour.

What about the metastatic pattern?
Regardless of the classification of oncocytic carcinomas into the papillary or follicular subcategory, they tend to give rise to nodal metastases and blood born metastases in the lungs and bone. This metastatic pattern provides an additional reason to diagnose cases like the present one as Oncocytic carcinoma, NOS. Taking into consideration the prominent angio and perineural invasion we would expect to see nodal metastases in this case. We can not rule out, however, the existence of nodal metastases in the central compartment since only the lateral compartments were resected .

What about prognosis?
This case has a number of very negative prognostic parameters: Incompleteness of surgery, old age of the patient, large size and extrathyroid extension of the tumour and prominent signs of lympho-vascular invasion.

With such a series of guarded prognostic factors it is probably useless to look for additional cytomorphological and/or molecular data. In a less dreadful situation we would look for the presence and extension of hobnail/micropapillary areas in case of an oncocytic variant of papillary carcinoma, and for the occurrence of TP53 and TERT promoter mutations. (Although the frequency of TERT promoter mutations seems to be lower in oncocytic thyroid tumours than in their non-oncocytic counterparts).

RET/PTC rearrangements are quite frequent in benign and malignant oncocytic neoplasms and BRAF V600E mutations are similarly prevalent in classic PTC and in oncocytic variant PTC and do not carry *per se* any prognostic meaning. Finally, it is generally acknowledged that HRAS and NRAS mutations play a less important role in oncocytic thyroid tumours than in their non-oncocytic counterparts (This case has been sent for consultancy a week ago and we do not have yet the results of the genetic study).

Mitochondrial DNA deletions/rearrangements and/or mutations are present in every benign and malignant oncocytic neoplasm presumably leading to a higher mitochondrial division rate and an increased number of abnormal mitochondrial but no significant diagnostic and/or prognostic meaning has been ascribed to mtDNA mutations .

A last point to address the responsiveness to radioactive iodine (RAI). Reduced or no responsiveness to RAI is one of the most important prognostic/predictor factors in thyroid cancer. In a study of about 400 cases of well differentiated thyroid carcinomas that after one (or more than one) recurring episodes lost the responsiveness to RAI we found oncocytic transformation in 3/5 of them (Sobrinho-Simões et al, unpublished observations). The putative role played by mitochondrial DNA mutations and NIS alterations in the loss of responsiveness to RAI of oncocytic thyroid neoplasms remains to be firmly established.

References: (On oncocytic thyroid tumours – **Please read the postscript**)
Tallini G et al. Frequent chromosomal DNA unbalance in thyroid oncocytic (Hurthle cell) neoplasms detected by comparative genomic hybridization. Lab Invest 79:547-555, 1999.

Cheung CC et al. Molecular basis of Hürthle cell papillary thyroid carcinoma. J. Clin. Endocrinol Metab 85:878-882, 2000.
Maximo V et al. Hurthle cell tumours of the thyroid. A review with emphasis on mitochondrial abnormalities with clinical relevance. Virchows Arch 437: 107-115, 2000.

Soares P et al. BRAF mutations and RET/PTC rearrangements are alternative events in the etiopathogenesis of PTC. Oncogene 22:4578-4580, 2003.

DeLellis RA et al. WHO Classification of Tumours. Pathology and genetics of tumours of endocrine organs. Lyon: IARC Press, 2004.

Trovisco V et al. BRAF mutations are associated with some histological types of papillary thyroid carcinoma. J Pathol 202:247-251, 2004.

Trovisco V et al. Type and prevalence of BRAF mutations are closely associated with papillary thyroid carcinoma histotype and patients' age but not with tumour aggressiveness. Virchows Arch 446: 589-595, 2005.

Motosugi U et al. Thyroid papillary carcinoma with micropapillary and hobnail growth pattern: a histological variant with intermediate malignancy? Thyroid 19:535-7, 2009

Maximo V et al. Mitochondria and cancer. Virchows Arch 454; 481-495, 2009.

Asioli S et al. Papillary thyroid carcinoma with prominent hobnail features: a new aggressive variant of moderately differentiated papillary carcinoma. A clinicopathologic, immunohistochemical, and molecular study of eight cases. Am J Surg
Pathol 34:44-52, 2010

de Vries MM et al. RET/PTC rearrangement is prevalent in follicular Hürthle cell carcinomas. Histopathology 61:833-843, 2012.

Nikiforova MN et al. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. J Clin Endocrinol Metab 98:E1852-1860, 2013.

Melo M et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. J Clin Endocrinol Metab 99:E754-765, 2014.

Postscript: (Almost) final diagnosis

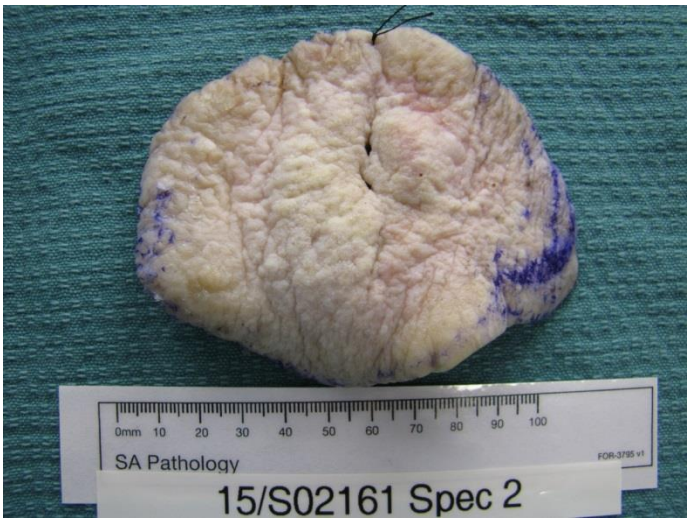
After having written this stuff I got the immunostained slides (the molecular study is not ready yet) and the neoplastic cells are negative for TTF1 and Thyroglobulin (There is not any technical problem because the internal control is expressively positive). As many (all?) of you have probably guessed half an hour ago, **It is not a primary thyroid tumour**. We still do not know what it is – please send your suggestions – but I have learned once again the most important lesson on thyroid pathology: Whenever facing a peculiar tumour start by searching for TTF1, TG and calcitonin.

AMR Seminar #68

Case – 5

Contributed by: Phil Allen, M.D.

Case History: Female aged 93, a resident of a nursing home. Excision of a lesion on the left lower leg. The specimen consisted of a roughly ovoid piece of skin 95x75mm x18mm thick with an ill-defined, non-ulcerated area of nodularity measuring 50x50 mm and a central depression measuring 7x1 mm (see photograph below). Serial slicing revealed a deep dermal and subcutaneous cavity measuring 25x20 mm immediately beneath the depressed area. The cavity was lined by dark tan tissue. No previous biopsies or excisions had been performed in this area.



Intact gross specimen showing the non-ulcerated, central, depressed area which is surrounded by poorly defined skin nodularity.

The circulated section shows irregularly acanthotic but histologically benign skin, dermal elastosis, in keeping with the patient's age, and a moderately differentiated squamous cell carcinoma arising in the wall of an epidermoid cyst located in the deep dermis and subcutis. The histologically benign portion of the cyst wall exhibits the same irregular acanthosis that is present in the overlying epidermis and at one point, the strands of proliferating acanthotic epithelium from the cyst are almost in continuity with the strands growing down from the overlying epidermis, raising the possibility that the large epidermoid cyst arose from cystic transformation of a deeply penetrating tongue of epidermal acanthosis. In some of the other sections that were not circulated, there are several small superficial squamous lined cysts, all widely separated from the larger epidermoid cyst and the carcinoma. The association of the abnormal, multinodular skin overlying the carcinoma suggests that the initial abnormality in this case was the florid, irregular acanthosis of the skin with its tongues of bland squamous cells growing down into the dermis and undergoing central cystic change. I do not have easy access to PCR to investigate the possibility of this being a human papilloma virus associated condition.

Squamous cell carcinomas arising from epidermoid cysts of the skin are very rare. I can only find two recent references,[1,2] although squamous carcinomas more commonly arise in intracranial epidermoid cysts[3] as well as in ovarian dermoid cysts.

Has anyone seen at a case like this before and is it likely that the human papilloma virus combined with the patient's advanced age were triggers for this most unusual tumor?

References:

Morritt AN; Tiffin N; Brotherston TM. Squamous cell carcinoma arising in epidermoid cysts: report of four cases and review of the literature. J Plast Reconstr Aesthet Surg, 2012;65:1267-9.

Pusiol T; Zorzi MG; Piscioli F. Squamous cell carcinoma arising in epidermal and human papillomavirus associated cysts: report of three cases. Pathologica (Italy), 2010;102:88-92.

Raghunathan A; Barber SM; Takei H; Moisi MD; Mukherjee AL; Rivera AL; Powell SZ; Trask TW. Primary intracranial sarcomatoid carcinoma arising from a recurrent/residual epidermoid cyst of the cerebellopontine angle: a case report. Am J Surg Pathol 2011; 35:1238-43.

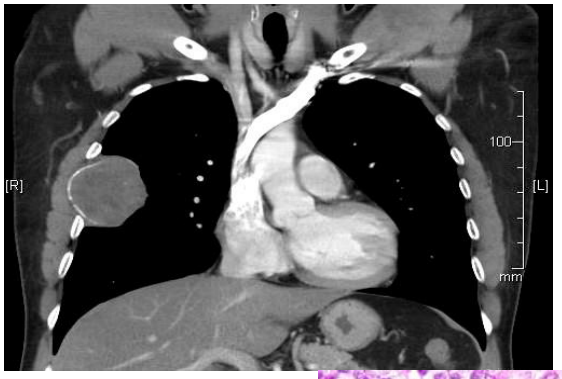
AMR Seminar #68

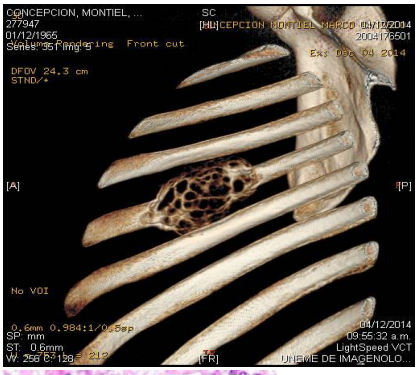
Case – 6

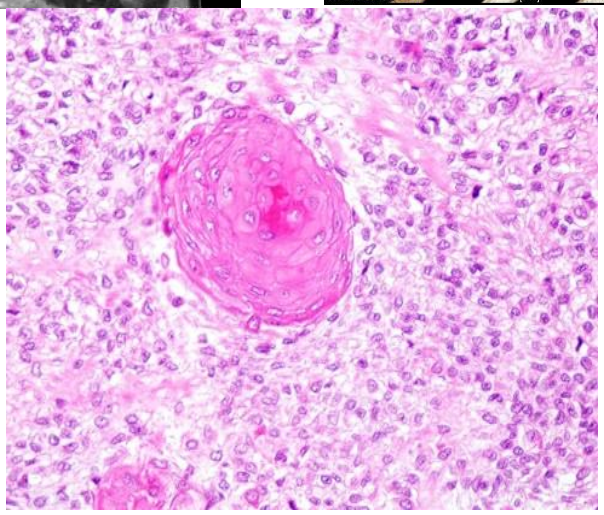
Contributed by: Hugo Domínguez Malagón, M.D.

Clinical History: A 49 year-old male with a tumor in the right chest dependant of the 5th rib, the tumor grew over the span of several weeks. Radiologically a lucent, well-delimited expansive lesion was discovered. The tumor was resected in block.

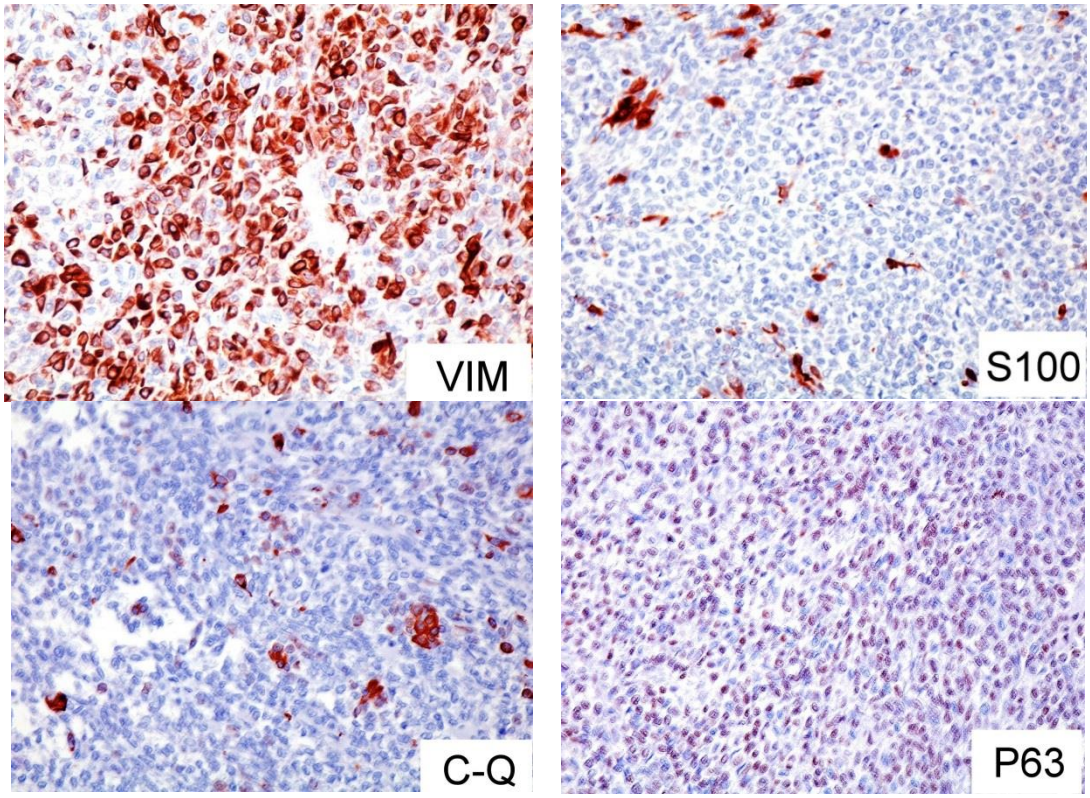
Histology: The neoplasia is formed by well delimited polygonal cells with moderate amount of clear cytoplasm, a few islands of keratinocytes (not seen in your slide) are scattered among the tumor cells (see figure). They show ovoid to indented nuclei with finely granular chromatin and small nucleoli, there are up to 3 mitosis per HPF







Immunohistochemistry: The clear cells are positive for P63, Vimentin and S100 (focal), the keratinocytes and some clear cells reacted with Keratin AE1-AE3. Negative for actin, TLE-1, CD56 and CD99.



Diagnosis: Myoepithelioma (myoepithelial carcinoma) of bone.

Discussion: Myoepithelioma is a neoplasm which has been described in several exta-salivary sites, soft tissue is uncommon location and exceptional in bone, with few cases reported to date. The molecular basis has been already mentioned in the last seminar by Cyril Fisher, and some molecular variants by Antonescu and Chris Fletcher in recent publications (Genes Chromosomes Cancer. 2015 Feb;54(2):63-71, Genes Chromosomes Cancer. 2010 Dec;49(12):1114-24), it is one of many tumors that share EWSR1 rearrangement which is very "promiscuous".

My intention was to share a case of bone.

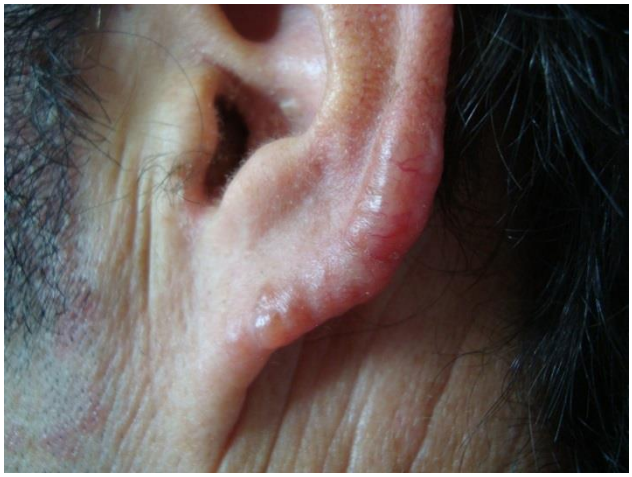
AMR Seminar #68

Case – 7

Contributed by: Jerónimo Forteza Vila, M.D.

Clinical History: 40 years old man with atypical LLC in 2009, bilateral cervical and supraclavicular lymphadenopathies in 2012. Splenomegaly.

In 1997 asymptomatic nodules in both ears. The nodules were erythematous, coalescent lesions with a rosary-bead appearance.

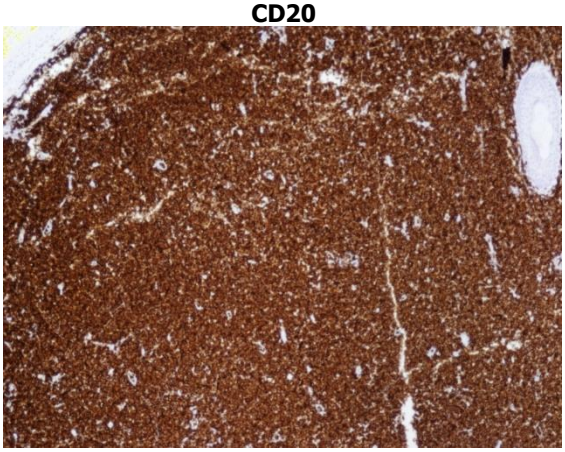


Histology: Diffuse proliferation of small lymphocytes. A slighter large than a normal lymphocyte, with clumped chromatin, usually a round nucleus, and occasionally a small nucleolus.

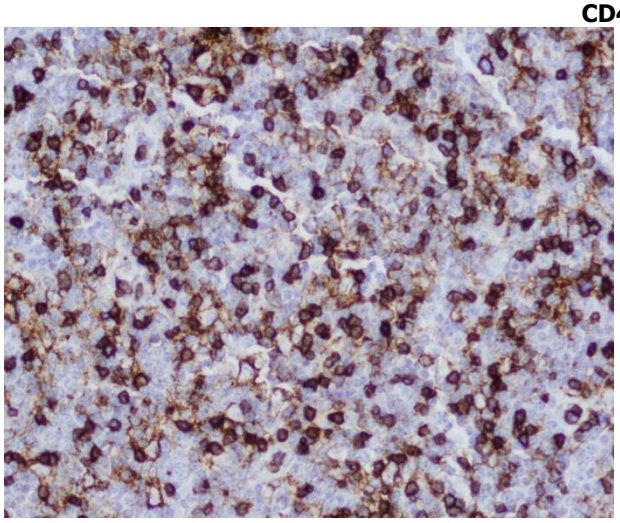
Very low mitotic activity.

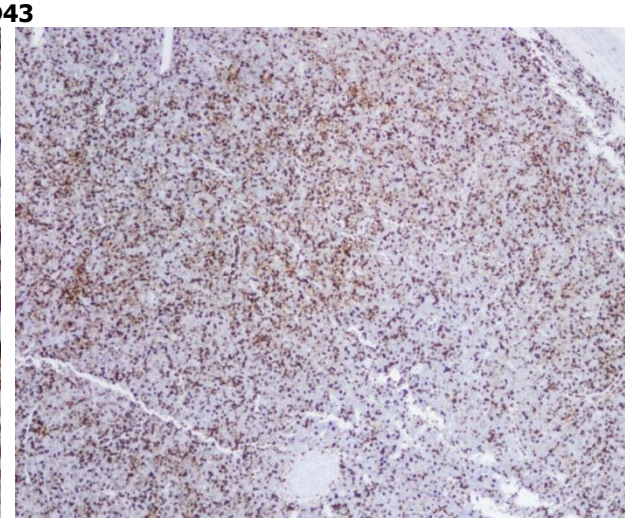
There's no epidermotropism.

CD20

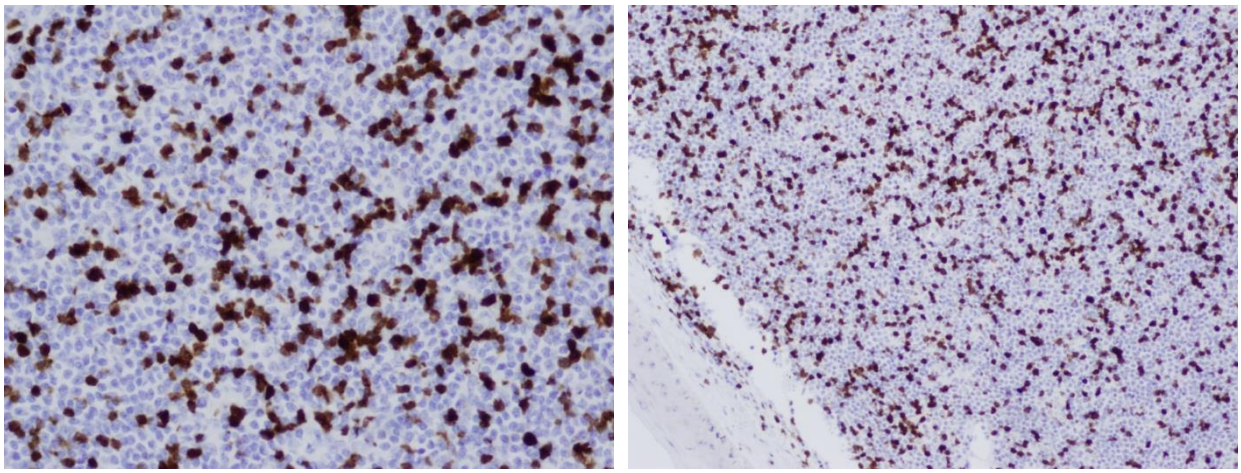


CD43

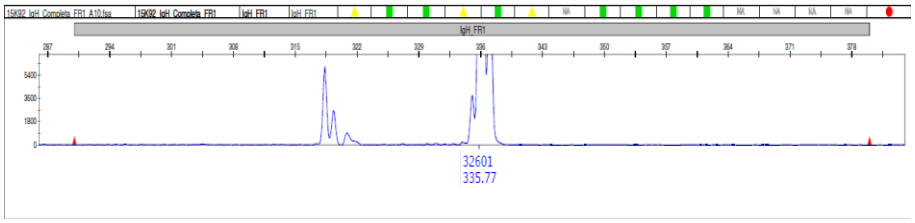




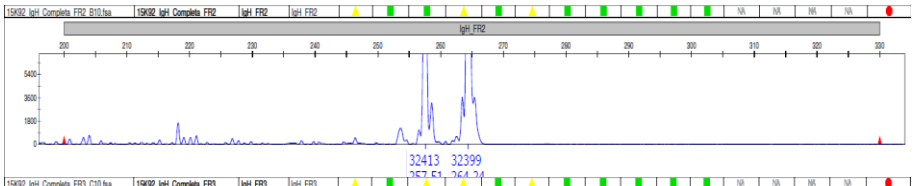
ZAP70



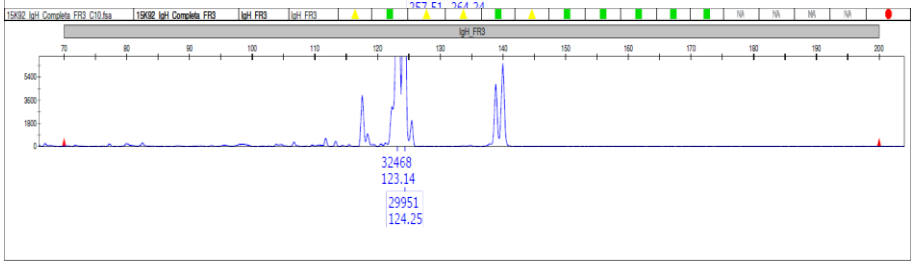
Secuenciación IgH



FR1: Monoclonal

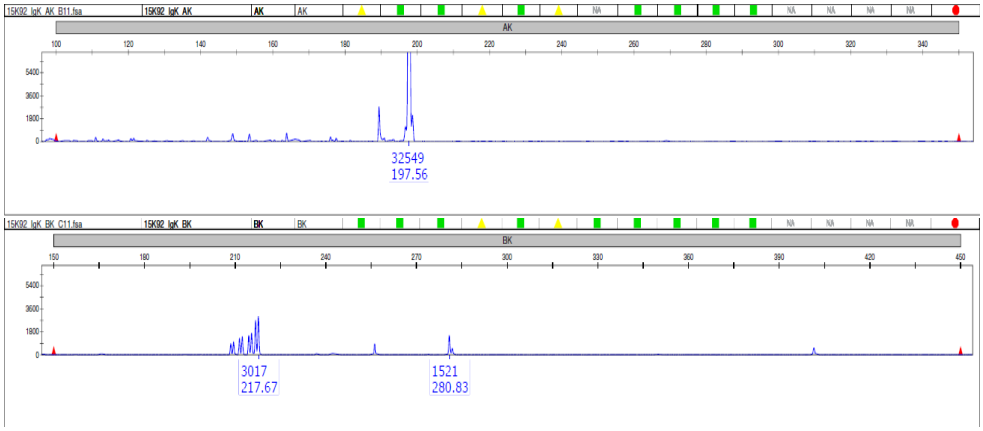


FR2: Biclonal



FR3: Monoclonal

Secuenciación IgK



IgK 1: Monoclonal

IgK 2: Policlonal

Secuenciación TCR Gamma

TCRG 1:Policlonal

TCRG 2: Policlonal

Immunohistochemistry: Positivity for CD20, CD43, CD5 and ZAP70. Ki67 shows a proliferation activity of 20-30%.

Rearrengement: Monoclonality IgH and IgK and policlonality TCRgamma

Diagnosis: PATIENT WITH B-CELL CHRONIC LYMPHOCITIC LEUKAEMIA WITH POSTERIOR INFILTRATION BILATERAL CAULIFLOWER EAR

References: "Bilateral cauliflower ear as the presenting sign of B-cell chronic lymphocytic leukemia" . Kimdem et al.

AMR Seminar #68

Case – 8

Contributed by: Masaharu Fukunaga, M.D. (H15 6975 #2)

Case History: A 48-year-old, gravida 0, para 0, female, who was pointed out to have a left ovarian tumor three years ago, presented with abdominal discomfort. MRI and physical examination indicated a multicystic ovarian tumor. The laparoscopic examination revealed a subserosal cystic mass in the uterine body and the mass was enucleated. The ovaries looked normal.

Macroscopic features: A multicystic mass measuring7x9x20mm in the myometrium and it contained serous liquid.

Immunohistochemistry: Lining cells were diffusely positive for calretinin and D2-40, focally positive for WT1. They were negative for BerEP4.

Diagnosis: Benign multicystic mesothelioma (BMCM)（mesothelial inclusion cyst)

Comments: Histology is very simple; cyst walls were lined by a monolayer of ciliated columnar or cuboidal cells with round nuclei and eosinophilic cytoplasm. Hobnail cells and focal papillary proliferation were observed, but neither atypia nor mitotic figures were seen. No stromal invasion or solid proliferation was found. Differential diagnosis includes adamantinoma, adenomyosis, endosalpingiosis and papillary mesothelioma. The lining cells in the present case were microscopically and immunohistochemically of mesothelial nature. This lesion is sometimes called "cystic adenomatoid tumor".

About 170 cases of BMCM were reported. The majority of them (about 80%) developed in females, usually between their 20^{th} to 50^{th} year of life. This lesion develops on serous membranes, mostly on the peritoneum. Isolated cases of extra-abdominal location were reported in the spermatic cord, peritesticular issues, inguinal region, uterus, pleura, pericardial sac and retroperitoneal space. Cysts can float in the abdominal cavity.

MBCM are believed to be associated with endometriosis or pelvic inflammatory disease as well as present or past abdominal surgery (in 30-66% of patients). It shows a considerable tendency towards multiple recurrences. The phenomenon is estimated to occur in 50-80% of cases. BMCM may be a reactive process. Laparoscopic surgery is useful to treat this type of lesion.

References:

Bernstein EM, et al. Benign multicystic mesothelioma: a case report of three sisters. Rare Tumors, 1:w46, 2009.

Urbanczyk K et al. Mesothelial inclusion cysts (so-called benign cystic mesothelioma):a clinicopathologic analysis of six cases.

Pol J Pathol 56:81-87, 2005.

Chan JKC et al. Composite multicystic mesothelioma and adenomatoid tumor of the uterus: different morphological manifestation of the same process? Histopathology 6:43-48, 1996.

AMR Seminar #68

Case – 9

Contributed by: Thomas Krausz, M.D.

Case History: A 72-year-old woman presented with abdominal pain. CT exam revealed a renal mass and extensive retroperitoneal lymphadenopathy. Her previous medical history is notable for endometrial carcinoma diagnosed 6 years prior. She underwent a complex retroperitoneal resection, which included nephrectomy.

Pathology: *Gross examination* disclosed a 10 cm mass involving the kidney. *Histologic analysis* revealed involvement of the renal parenchyma and sinus by a tumor with a predominantly tubulocystic architecture (focally papillary). The neoplastic cells exhibit significant phenotypic variability in many respects: cell shape ranging from polygonal to hobnail; cytoplasm ranging from clear to eosinophilic and granular; significant nuclear pleomorphism, with nuclear position either central or eccentric and bulging into lumina (hobnail cells). Mitotic figures are readily identified, and the tumor overall exhibits a high-grade appearance.

The principal diagnostic considerations for a kidney tumor with this morphology are collecting duct carcinoma (CDC) and clear cell RCC. However, two points arguing against CDC in this case are: 1) prominence of hobnail cells, which are usually limited in CDC, and 2) very little stromal desmoplasia. As for clear cell RCC, the lack of a rich vascular network argues against the diagnosis. Although there is focal papillary architecture, the overall tubulocystic architecture combined with the high-grade tumor appearance make papillary RCC and translocation-associated RCC considerably less likely.

Immunohistochemistry demonstrated the following profile: strong expression of PAX8, CK7, AE1/AE3, and AMACR; no expression of c-kit, CAIX, or TFE3. This immunoprofile is not a perfect match for the aforementioned top considerations. Further inquiry into the patient's history revealed that her prior endometrial carcinoma was of the clear cell type, which fits nicely into the above morphologic and immunophenotypic profile.

Final Diagnosis: Müllerian/uterine clear cell carcinoma metastatic to kidney

Discussion: Uterine clear cell carcinoma is very rare among endometrial carcinomas, comprising 2–5% of cases (Offman 2012). Reports of this tumor type metastasizing to the kidney are virtually non-existent. The reverse scenario in which clear cell carcinoma of kidney metastasizes to the gynecologic tract is better described but still rare, with only 20–30 cases existing in the literature (Sountoulides 2011). A single case report of clear cell carcinoma simultaneously involving the uterus and the kidney was ultimately traced to a kidney primary (Ho 2011).

Without a clear clinical history, the morphologic diagnosis is problematic. Immunohistochemistry can be misleading, as PAX8 and HNF-1β are both expressed in RCC and gynecologic clear cell carcinoma. HNF-1β is a relatively new marker that has been used to support the diagnosis of gynecologic clear cell carcinoma; it is a transcription factor normally expressed in the GI tract and kidney as well as in secretory endometrium and in the endometriotic tissues associated with clear cell carcinoma (Offman 2012). The key to the diagnosis rests on a heightened index of suspicion (e.g., tip-off from clinical history), which permits consideration of clear cell carcinoma from the gynecologic tract. Only then can immunohistochemistry can be effectively applied to resolve the differential, with the aid of PAX2 (Offman 2012) and CD10 (Ho 2011). INI-1 immunohistochemistry may also be considered, as its loss has been described in a subset of collecting duct carcinomas (Agaimy 2014).

References:

Offman SL, Longacre TA (2012) Clear cell carcinoma of the female genital tract (not everything is as clear as it seems). Adv Anat Pathol 19;296-312.

Sountoulides P, Metaxa L, Cindolo L (2011) Atypical presentations and rare metastatic sites of renal cell carcinoma: a review of case reports. J Med Case Reports 5;429

Ho CK et al (2011) A rare case of renal and uterine clear cell carcinoma: which is the primary tumour? Central European Journal of Medicine 6;247-249

Agaimy A (2014) The expanding family of SMARCB1(INI1)-deficient neoplasia: implications of phenotypic, biological, and molecular heterogeneity. Adv Anat Pathol 21:394-410.

AMR Seminar #68

Case – 10

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

History: An 8-month-old boy with abdominal distension and severe anemia. In clinical work-up, a solid-cystic large abdominal mass is seen and is considered unresectable. He was treated with chemotherapy (vincristine, actinomycin and cyclophosphamide), and operated at 6 weeks.

Macroscopically a multicystic specimen with large hemorrahagic, necroso and other solid white areas was received. The size was larger than 18x15 cm.

After surgical resection, the patient relapsed at 2 weeks, with a retroperitoneal mass, which grew rapidly into the entire abdominal cavity. For 5 months he was undergoing treatment with various chemotherapeutic, complicated with various infections and he died at 8 months for disseminated disease and sepsis.

In the microscopic study, after chemotherapy, foci of atypical spindle cell malignant proliferation and extensive areas of necrosis and hemorrhage are observed.

In the immunohistochemistry study, only positivity for vimentin was observed. The proliferative index (Ki 67) is over 75%. The rest of immunohistochemical studies, including S-100 protein, EMA, CK7, AE1-AE3, CK5, C-Kit, CD31 and CD34 were negative.

In the molecular study, by PCR, the translocation of infantile fibrosarcoma, ETV6-NTRK3 was positive while the translocations of Ewing sarcoma and synovial sarcoma were negative.

Comment: The infantile fibrosarcomas are extremely rare. These tumors tend to be located in distal parts of the limbs, but have also been reported at the abdomen. Characteristically, the tumors grow quickly, are ill-defined and are accompanied by hemorrhagic areas and necrosis. From the histological point of view is a tumor with fibrosarcomatous pattern with pretty, moderately atypical spindle cells and oval or fusiform nuclei. They can show a prominent vascular pattern and eventually become a sarcomatous pleomorphic neoplasia.

Immunohistochemically it described positive for vimentin and occasionally to actin, and is negative for the vast majority of the markers of mesenchymal tumors. At the molecular level, it is typical reciprocal translocation t (12;15) (p13; q25) resulting from the merger of the ETV6 and NTRK3 genes. Remember that this translocation is not specific to children fibrosarcomas and can also be seen in other tumors such as mesoblastic nephroma and secretory breast carcinoma.

The differential diagnosis is given the age of patients with embryonal rhabdomyosarcoma or vascular tumors. In superficial tumors, also with dermatofibrosarcoma protuberance and giant cell fibroblastoma but histopathological features and, immunohistochemical and molecular studies are quite distinctive.

The prognosis is relatively good if surgical excision is complete. However, infant fibrosarcomas, particularly in the abdominal location, have a tendency to local recurrence and partially respond to current chemotherapy protocols as happened with our patient.

AMR Seminar #68

Case – 11

Contributed by: Alberto Cavazza, M.D.

History: An immunocompetent, asymptomatic 36 year old woman was incidentally found to have bilateral pulmonary nodules, randomly distributed, small (up to 8 mm) and well-circumscribed. A videothoracoscopic surgical excision of some of the nodules was performed.

Pathologic findings: We received 4 small pieces of subpleural lung tissue, each containing a small, rounded nodule. At histology, the nodules consisted in eosinophilic, acellular necrosis with an inflammatory rim containing scattered giant cells. Ziehl-Neelsen and Grocott stains were negative.

Diagnosis: Chickenpox-related pulmonary nodules.

Further clinical informations and follow-up: One year previously, the patient had a severe chickenpox (from her son) with fever, asthenia and cutaneous manifestations, but without pulmonary symptoms. PCR performed on paraffin sections detected varicella zoster DNA inside lung nodules. The patient remained asymptomatic, and she is alive and well 4 years after surgery.

Comment: Varicella pneumonitis is uncommon and may be lethal in immunocompromised patients, leading to diffuse alveolar damage or to necrotic/hemorrhagic nodules with a bronchiolocentric or miliary distribution. In the immunocompetent host, varicella infection in the lung may present as healed chickenpox granulomas, as the case I am presenting here, an unusual but probably under-recognized phenomenon. They prevail in young to middle aged adults with a previous history of chickenpox infection, with or without pulmonary symptoms: the patients are frequently young parents who took the infection from their children. In our brief series, the delay between infection and discovery of the pulmonary nodules varied from 8 to 37 months. The lesions are generally an incidental finding in a CT scan of the chest performed for another reason, and they present as multiple small (< 1cm) nodules, well-circumscribed and sometimes calcified, randomly dispersed through the lungs. The nodules are generally PET-negative. Metastases are frequently the main clinico-radiologic consideration, although an experienced radiologist can suspect the disease (sometimes strongly enough to avoid a surgical biopsy).

Histology shows small necrotic nodules, rounded and well-circumscribed, randomly distributed in an otherwise unremarkable lung. With time, necrosis tends to calcify. The nodules are bordered by a fibro-inflammatory rim, with or without a granulomatous component generally consisting in scattered giant cells: notably, granulomas outside the nodules are absent. Sometimes a peripheral palisading of histiocytes is present, simulating a rheumatoid nodule. Obviously, special stains for mycobacteria and fungi have to be performed and are negative.

Probably the main point is the following: how much these findings are specific and allow to differentiate chickenpox-related nodules from other, more trivial, granulomatous infections? In my opinion, tiny necrotic nodules within normal lung, in the correct clinico-radiological scenario, are not fully specific but are characteristic enough (at least in the part of the world were I live) to suggest the possibility of chickenpox-related nodules and to ask the clinician to query the patient for a previous varicella infection. If all the clinical, radiological and pathological data fit, molecular analysis is not necessary. In case of doubt, PCR performed on paraffin material is a sensitive and specific technique to detect varicella zoster DNA in the necrotic nodules, further confirming the diagnosis.

Reference:

Rossi G et al. Chickenpox-related pulmonary granulomas in immunocompetent adults. Clinicopathologic and molecular features of an underrated occurrence. Am J Surg Pathol 2012;36:1467-1502.

AMR Seminar #68

Case – 12

Contributed by: Brian Rubin, M.D.

Clinical History: The patient was a 50 year old woman who presented with a large mass involving the subcutaneous and deep soft tissues of the left lower leg. She had an additional large mass involving the subcutis of the left groin and thought to be matted lymph nodes clinically. She underwent a left, below the knee amputation and a separate resection of the groin mass. She received radiation therapy to the groin post-operatively. Two months after the leg and groin resections there was a large local recurrence in the groin followed by a hemipelvectomy with a positive margin. Two months later the patient developed lung metastasis. She died a short time later. All told, she survived about 6 months from the time of diagnosis until she died; a very aggressive clinical course.

Gross Pathology: On sectioning, the leg mass from the below the knee amputation was lobulated, pink and fleshy. There was numerous smaller satellite lesions scattered around the larger mass. The tumor was described as "crawling" along blood vessels, nerves and fascial planes. The groin mass was similar in appearance.

Histology: Histologically, the lesion is variably cellular with alternating areas with a more myxoid stroma and a vaguely multinodular architecture. The tumor cells are arranged singly or in clusters or sheets. The lesional cells are large, predominantly epithelioid with a smaller number of lesional spindle shaped cells with abundant eosinophilic cytoplasm and more or less centrally located nuclei. The nuclei have dense chromatin and there is an occasional prominent nucleolus. There is prominent nuclear pleomorphism. Mitotic figures number up to 7/10 HPF and there are atypical mitotic figures. Necrosis was identified in other slides, involving about 5-10% of the neoplasm.

Immunohistochemistry: Immunohistochemical studies revealed the lesional cells to be negative for cytokeratins AE1/AE3 and CAM 5.2, EMA, S100, smooth muscle actin, desmin, CD34, MITF, MelanA and HMB45.

Diagnosis: Epithelioid Variant of Myxofibrosarcoma.

Discussion: I submitted this case because this variant of myxofibrosarcoma (MFS) is not very well known and it is clinically important since it has a terrible prognosis.

There is essentially one paper describing the epithelioid variant of MFS (Nascimento et al. –Chris Fletcher senior author) and I have essentially abstracted the paper in this discussion. In their paper, they reviewed 570 cases of MFS to identify 17 cases of epithelioid MFS (3% of total). Of the 17 cases, nine patients were men and eight were women. The age range was 43-89 years with a median of 63.5, similar to conventional MFS. Most patients presented with a mass and their duration of symptoms ranged from 1-24 months. Two-thirds of cases arose in the subcutis and one-third was deep. Eight cases arose on the lower extremities and six cases were on the upper extremities. There was one case each on the neck, scalp, and trunk. Tumor size ranged from 2 to 15 centimeters (median 6.75).

Histologically, the tumors showed a multinodular growth pattern. Like conventional MFS, the nodules had alternating cellular and myxoid areas. The myxoid areas tended to have curvilinear blood vessels, around which tumor cells frequently condensed. Myxoid areas also frequently contained muciphages. Necrosis was present in 11 of 17 cases (64.7%) and the extent was variable. Mitotic figures ranged from 2-58 per 10 HPF (median 12). Nuclear pleomorphism, one of the hallmarks of MFS, was present in all cases. The majority of the tumors had an infiltrative growth pattern, typical of MFS. Notably, and what sets these cases apart histologically from conventional MFS, the tumors contained a variable proportion of epithelioid cells. The epitheloid cells were described as having "round, centrally or eccentrically placed nuclei, vesicular chromatin, prominent, inclusionlike nucleoli and moderate to large amounts of eosinophilic, somewhat granular cytoplasm". The epithelioid cells were present in both the cellular and myxoid areas. The extent of the epithelioid areas was focal (approximately 25% of the tumor cells) in one case, comprised between 25% to 75% of the tumor (multifocal) in 3 tumors and was diffuse (> 75% of the tumor) in 13 cases. So the great majority of cases had >75% epithelioid cytomorphology.

Immunohistochemically, very rare cells were positive for Pan-K (2 cases), desmin (1 case) and smooth muscle actin (1 case). S100 was negative in all cases.

Grading of cases according to the "Fletcher" grading system (Mentzel et al.) revealed 14 cases (82.3%) to be high-grade, 2 cases to be intermediate grade (11.8%), and 1 tumor (5.9%) to be low grade. Follow-up data was available for 14 patients (range 2-240 months; median 16 months). Ten patients (71.4%) developed local recurrence. Seven patients (50%) developed metastasis (5 to lung and 2 to retroperitoneum). The case I presented had metastasis to lymph nodes, which has not been reported in the epithelioid variant before. However, I wonder if the cases in Fletcher's series with retroperitoneal metastasis were actually lymph node metastasis. I e-mailed Chris to ask about this and he wasn't sure about those cases but he has seen additional cases since he published his paper with lymph node metastasis. He also mentioned that in the Mentzel paper cited below that 5 cases of typical MFS metastasized to nodes. While he suspects that the epithelioid variant of MFS metastasizes to lymph nodes more often, the numbers are too small to prove it. Despite short follow-up, 5 of 14 patients died of disease (35.7%), which is high for MFS, supporting a worse prognosis for this subtype.

Differential Diagnosis: Due to its lack of immunoreactivity, epitheloid MFS is a diagnosis of exclusion. The differential diagnosis includes other epithelioid neoplasms including carcinoma, melanoma, myoepithelial carcinoma, pleomorphic rhabdomyosarcoma,pleo morphic liposarcoma and PEComa.

Summary: The epithelioid variant of MFS is rare but its recognition is important due to a poor prognosis. As illustrated in this case, unlike most other sarcomas, it has potential to metastasize to lymph nodes.

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Nascimento AF, Bertoni F, Fletcher CD. Epithelioid variant of myxofibrosarcoma: expanding the clinicomorphologic spectrum of myxofibrosarcoma in a series of 17 cases. *Am J Surg Pathol*. 2007;31:99-105.

Mentzel T, Calonje E, Wadden C, et al. Myxofibrosarcoma: clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. *Am J Surg Pathol.* 1996;20:391-405.

AMR Seminar #68

Case – 13

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

History: A 62 y/o man underwent total thyroidectomy for non-familial medullary thyroid carcinoma. At the same surgical procedure, a 2.0 gram peri-thyroidal mass was removed. There is no history of prior radiation therapy.

Pathology: This enlarged parathyroid gland shows focal oncocytic metaplasia, but the most exciting feature is the scattered population of markedly enlarged chief cells with enormously oversized nuclei having some degree of pleomorphism, and intense hyperchromasia, but lacking mitotic activity. None of the cells in this parathyroid stained for calcitonin, CEA, or synaptophysin. A second parathyroid gland removed at the same procedure was completely normal histologically.

Diagnosis: Parathyroid Adenoma With Bizarre Cells Occurring In A Patient With Medullary Thyroid Carcinoma.

Comment: I submitted this case not because it is diagnostically challenging, but thinking that members of the club would enjoy seeing a good example of endocrine cytologic 'atypia'. I'm sure everyone has encountered this phenomenon, but this is one of the more striking examples to cross my microscope stage. Dr. DeLellis states that this microscopic finding may be seen in up to 25% of all parathyroid adenoma cases, and its presence in fact "may be used as a point in favor of the diagnosis of adenoma rather than hyperplasia or carcinoma." I am not aware of any association of parathyroid gland adenoma having striking cytologic atypia with medullary thyroid carcinoma.

Selected Reference:

DeLellis RA. Parathyroid adenoma and its variants. In: Rosai J, DeLellis RA, Carcangiu ML, et al. (eds.). Tumors of the Thyroid and Parathyroid Glands. AFIP Atlas of Tumor Pathology, series 4, vol. 21. p. 513-42. ARP Press, Silver Spring, MD, 2014.

AMR Seminar #68

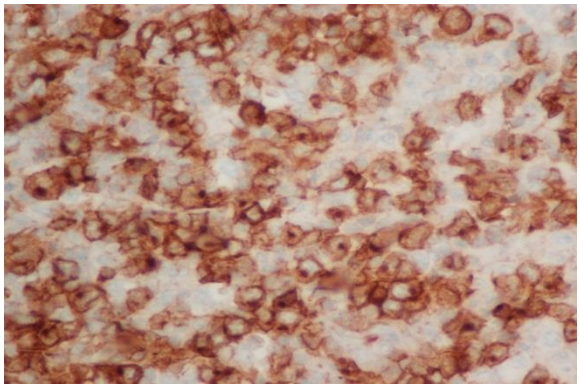
Case – 14

Contributed by: James A. Strauchen, M.D.

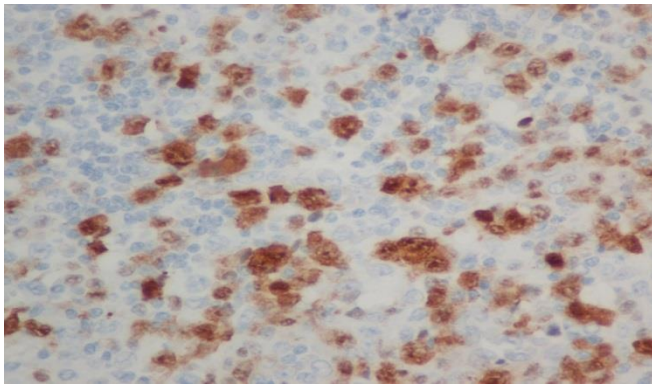
History: A 32 year old woman physician presented with right arm pain. Eventually PET/CT scan showed hypermetabolic lymphadenopathy in the right axilla. An ultrasound-guided core needle biopsy was inconclusive and excisional biopsy was performed.

Pathology: The specimen consisted of yellow lobulated fat measuring 4 x 3 x 1 cm containing several tan, fleshy, lymph nodes lymph nodes measuring up to 2.9 cm in greatest dimension. Microscopically, sections showed lymph node with capsular fibrosis and a patchy infiltrate involving the lymph node and perinodal fat. The infiltrate is composed of a mixed population of inflammatory cells and larger cells with lobular nuclei and abundant pale cytoplasm. Immunohistochemical stains demonstrate these to be positive for CD30 and ALK (see Images).

CD30



ALK-1



Diagnosis: Anaplastic large cell lymphoma, ALK positive, mimicking an inflammatory lesion of lymph node.

Comment: This case is reminiscent of a series of 4 cases reported by Cheuk et al in the AJSP in 2000 as "hypocellular anaplastic large cell lymphoma mimicking inflammatory lesions of lymph nodes" (see Reference). As they indicate, a high index of suspicion is required since there is a striking resemblance to inflammatory pseudotumor of lymph node and the atypical cells are easily overlooked. I had one previous case in a child in which I also considered an inflammatory lesion of lymph node. Immunohistochemical staining for CD30 and ALK is diagnostic (see Images).

Reference: Cheuk W, Hill RW, Bacchi C, Dias MA, Chan JK. Hypocellular anaplastic large cell lymphoma mimicking inflammatory lesions of lymph nodes. Am J Surg Pathol 2000; 24:1537-43.

AMR Seminar #68

Case – 15

Contributed by: Franco Fedeli, M.D.
(courtesy of Dr. Antonina Parafioriti – Milan, Italy)

Clinical History: A 35-years-old woman was subjected to our physician's observation for the presence of a few months appeared supraclavicular swelling.

TC scan revealed a 5cm supraclavicular mass without involvement of neck and mediastinum lymph nodes.
The lesion underwent to needle biopsy and subsequently to excision.
Macroscopically, tumor was well demarcated and whitish in color, but at microscopic examination it was possible watching the tumor spreading into normal tissue. Histologically, the lesion was composed of cords and strands of clear looking cells in a hyalinized stroma. Such elements showed to be diffusely positive for vimentin, MUC4 and focally for EMA. Cytokeratin was negative.

Diagnosis: Sclerosing epithelioid fibrosarcoma

Comments: Sclerosing epithelioid fibrosarcoma (SEF) was described by Meis-Kindblom et al. in 1995 (1). It is currently considered by the WHO to represent a distinct variant of fibrosarcoma.

The most frequent tumor sites are lower extremities/limb girdle and trunk, followed by upper extremities, head and neck and abdominal/inguinal region. SEF typically occurs in middle-aged adults, mean age 47 years, but shows a wide age distribution, range 14-87 years, and it has no apparent sex predilection.

As described by Meis-Kindblom and colleagues (1) in their series of 25 cases, SEF is a well circumscribed lesion with pushing margins, although focally infiltrative into the adjacent soft tissue or bone.

Overall, it is a relatively hypocellular and strikingly hyalinized lesion. At higher magnification, the neoplasm consist of distinct nests, strands and cords of small cells with a scant amount of clear cytoplasm. The individual tumor cells have round, oval or fusiform nuclei that are variably angulated. The chromatin pattern is finely stippled to vesicular, and nucleoli tend to be small and basophilic. The extracellular matrix consist of amorphous to ropey strands of deeply acidophilic collagen, and in some areas it is arranged in delicate lace-lake strands reminiscent of osteoid. In addition, most of the tumors display more cellular zones characteristic of conventional fibrosarcoma, as well as prominent myxoid areas, reminiscent of low-grade fibromyxoid sarcoma (LGFMS); today such lesions are considered hybrid LGFMS/SEF tumors.

The median mitotic rate is 4 mitoses per 10 HPF.

Interestingly, the original report noted expression of epithelial markers in a significant subset of cases, with EMA and CK expression in 50% and 14% of studied cases, respectively, other than vimentin positivity in all of the lesions. In addition, more recently MUC4 has been identified as a sensitive marker for SEF, being present in 78% of the lesions with diffuse distribution and moderate to strong intensity, as well as in LGFMS, in a study by Doyle and colleagues (2).

Cell morphology allows for the wide differential diagnosis including benign, pseudosarcomatous, and malignant proliferations; these include nodular fasciitis, myositis ossificans, fibromatosis, hyalinizing leiomyoma, fibrous

histiocytoma, lobular or signet ring cell carcinoma, sclerosing lymphoma, granulocytic sarcoma, ossifying fibromyxoid tumor, synovial sarcoma and small cell osteosarcoma.

Follow-up indicates that SEF is an aggressive tumor, with persistent disease or local recurrence in more than 50% of patients, a metastatic rate between 43% and 86%, with approximately one-third of patients alive with the disease, and a mortality because of the tumor between 25% and 57%. The most frequent site of distant tumor manifestation is the lung followed by osseous lesions to multiple bones and pleura/chest wall. Of note is the finding of lymph node metastasis; this potential for lymph node metastasis is shared by other phenotypically epithelioid malignant soft-tissue tumors, such as epithelioid sarcoma and epithelioid malignant peripheral nerve sheath tumor (3).

Wide surgical excision is the mainstay of therapy and long-term follow-up is indicated, because some patients develop local recurrence or metastatic disease late in their course. The role of systemic treatment remains unclear.

References:

1. Meis-Kindblom JM, Kindblom LG, Enzinger FM. Sclerosing Epithelioid Fibrosarcoma. *Am J Surg Pathol.* 1995;19:979-993.

2. Doyle LA, Wang WL, Dal Cin P, et al. MUC4 is a sensitive and extremely useful marker for sclerosing epithelioid fibrosarcoma: association with FUS gene rearrangement. *Am J Surg Pathol*. 2012; 36:1444–1451.

3. Antonescu CR, Rosenblum MK, Pereira P, et al. Sclerosing epithelioid fibrosarcoma: a study of 16 cases and confirmation of a clinicopathologically distinct tumor. *Am J Surg Pathol*. 2001;25:699–709.

AMR Seminar #68

Case – 16

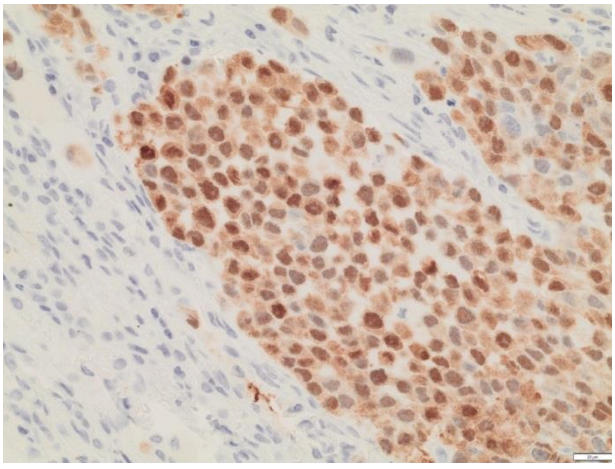
Contributed by: Göran Elmberger, M.D.

Case history: A 73-year-old female with a 30 mm sized peripheral lung nodule in RUL. Underwent lobectomy with a diagnosis of NSCLC NOS. Immuno performed with TTF1-/p63+ phenotype.

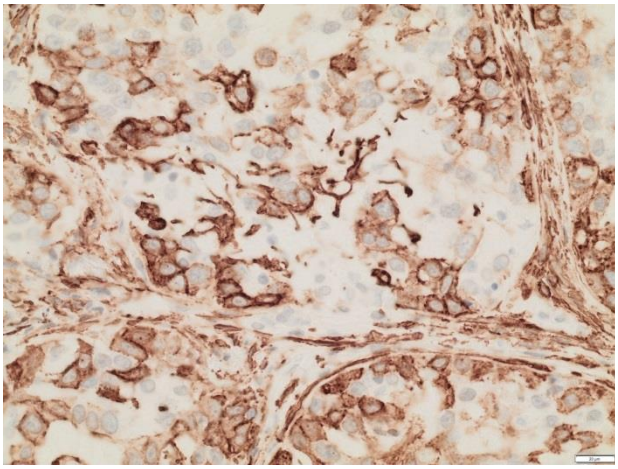
I got a phone call from a young pulmonary medicine specialist that wanted to inquire further about one lobectomy case that one of my colleagues in general pathology signed out. The specific question was if I could give any further details on the diagnosis that read non-small cell lung carcinoma. Since this was a resection specimen I thought this was a reasonable demand – we actually should not use this terminology for cases resected – sp I ordered slides and report out. Except for the detail of the diagnosis case was exemplary handled including a rather large IHC panel …. My first thought seeing the case and IHC was poorly differentiated non-keratinizing squamous cell carcinoma based on IHC including TTF1 – and p63 +. However, taking a closer look I started to suspect something unusual going on here…

Pathological Findings: Microscopy revealed a diffusely and multinodular growing infiltrative carcinoma with a rather low-grade atypia. Tumor seemed to fill alveolar spaces leaving remnants of TTF1 positive pneumocytes behind. Various architectural patterns including a dominating solid, but also trabecular, reticular, and focally cribriform pattern could be seen. Likewise various cytological differentiations like epitheloid, plasmacytoid and clear cell could be appreciated. Stromal features were merely fibrotic hyaline with concentric lamellae surrounding tumor cell islands in a way reminiscent of myoepithelial tumors. A focal comedo-like necrosis was noteworthy but I could not document any squamous differentiation in routine histology. No definitive evidence for pre-existing myoepithelioma or PA. After my suspicion that we indeed could be dealing with a MECA additional IHC was ordered.

Extended IHC confirmed a myoepithelial phenotype including S100+ and SMA+/- without any evidence of luminal-ductular differentiation. Proliferation rate was focally high – 60 % in Ki-67.



S100



SMA

A molecular predictive panel including KRAS, EGFR and ALK was found negative and performed under primary diagnosis of NSCLC.

Diagnosis: Myoepithelial carcinoma (MECA) of the lung. pT1bN0R0.

Follow-up: Case is recent and only 3 months follow up presently NOD. In my report I stated that myoepithelial primary carcinoma of the lung is unusual and recommended checking history and status including H&N and breast. No evidence of other primary or metastases at the present time.

Discussion: Myoepithelial neoplasms represent a clinically, behaviourally and histologically varied group. These have been well characterized in the salivary glands but are increasingly documented in a range of other sites, including those in which myoepithelial cells are normally found in relation to various ductal structures (such as the skin, lung, breast and larynx) and also where myoepithelial cells are usually absent, such as superficial and deep soft tissues and bone. Myoepithelial neoplasms account for only 1.0–1.5 % of all salivary gland tumors. Their unifying feature is the morphologic and immunohistochemical evidence of myoepithelial differentiation, but this encompasses a large spectrum of different histological appearances and varying immunoprofiles.

Primary salivary gland–type lung cancer is rare and represents less than 1% of all lung tumors. This group of tumors derives from small salivary glands in the respiratory system and mainly includes mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), epithelial–myoepithelial carcinoma (EMC) and carcinoma ex pleomorphic adenoma (CEPA). Salivary gland–type lung cancer was mostly reported in small series or described in case reports because of its low incidence. Thus, relatively little is known about their precise clinical, radiological, and pathological features. Consequently, no consensus on optimal therapeutic strategy is available.

Patient demographic information, clinical presentation, and radiological appearance lack characteristic features and pathological examination is the exclusive means to distinguish salivary gland–type lung cancer from other pulmonary lesions. However, salivary gland–type lung tumors are easily misdiagnosed as common lung cancers in pathology, due to their rarity and sometimes subtle morphological evidence for myoepithelial differentiation. Generally myoepithelial IHC markers are not included in the analyses of poorly differentiated tumors. For samples obtained from endoscopy or pneumocentesis, diagnosis may be difficult based on the limited size of the tissue.

The first case of MECA of the lung was described by Higashiyama et al in 1998 and to date, there are approximately 10 cases of MECA reported in the English literature. Most tumors were endobronchial and a few were peripherally located. Tumors ranged in size from 1.5 to 13 cm with a mean size of 4.3 cm.

The currently accepted diagnostic criteria for MECA are exclusive myoepithelial differentiation (morphologic and immunohistochemical) and clear-cut evidence for malignancy such as tumor infiltration.

A variety of growth patterns can be observed, with a diffuse sheet like arrangement of tumor cells being the most common followed by a multinodular growth pattern.

A range of histomorphological patterns (solid, trabecular, reticular, fascicular, dissociated) and cytological types (epitheloid, spindle, stellate, plasmacytoid, hyaline, clear cell, vacuolated, signet ring cell-like and rhabdoid) have been recognized. Frequently these histological patterns and cell types are mixed within the same tumor. Myxoid and/or hyaline extracellular matrix in varying proportions and necrosis are frequently present. Pseudoglandular structures may be seen, but true ductal lumens should not be accepted according to present definition. Tumor metaplastic changes in the form of squamous metaplasia occur frequently. Sebaceous metaplasia and chondroid stroma is very rarely seen.

In a substantial fraction of MECA's unequivocal evidence of a pre-existent benign tumor can be found. Most commonly the underlying tumor is a pleomorphic adenoma but sometimes a myoepithelioma can be found.

Morphologic heterogeneity is the hallmark of neoplastic myoepithelial cells. Because of this, the recognition of "myoepithelial differentiation," at the histologic level, remains difficult. Some of the histologic features that are found to be characteristic of myoepithelial differentiation are the presence of more than one morphologic cell type within a tumor, the multinodular architecture with hypercellular peripheral rims and hypocellular myxoid, comedo-like necrosis of nodule centres and the accompanying myxoid and hyalinised matrix components.

A confounding issue regarding the diagnostic criteria of malignancy in myoepithelial tumors remains. Traditionally, the histologic features that are considered helpful in discriminating benign and malignant myoepitheliomas include cytologic atypia, tumor infiltration, and mitotic rate. The presence of tumor infiltration into adjacent tissues is the most reliable and should be considered the minimum requirement for diagnosis of MECA. Other histologic features that signify malignancy include frequent mitotic figures and necrosis. Cytologic atypia may or may not be present and should not be considered as a prerequisite for malignancy in myoepithelial tumors. Recently Nagao et al suggested that assessment of cell proliferative activity may be helpful in the differential diagnosis between benign and malignant myoepitheliomas, and that more than seven mitoses per 10 HPFs or a Ki-67 labelling index of more than 10% is diagnostic of MECA.

Immunohistochemistry is essential to identify myoepithelial cells and reactivity for CK's and at least one of the other myoepithelial markers, including S100, vimentin, calponin, p63, glial fibrillary acidic protein, CD10, SMA, maspin, smooth muscle myosin heavy chains or D2-40, is required for diagnosis. In MECA staining results with individual markers is highly variable and no single marker is 100 % sensitive or specific. Therefore, a combined use in a broad panel of these putative myoepithelial markers should be stressed when MECA is a morphologic consideration.

Recently, a study by Skalova et al has demonstrated that clear cell MECAs of salivary gland harbor EWSR1 rearrangement in a subset of cases and therefore may be genetically related to EWSR1-rearranged cutaneous myoepithelial tumors.

Unusual variants like the secretory (Bastaki), rhabdoid (Thway) and anaplastic (Petersson) has lately been suggested in the literature.

High grade transformation in MECA has been reported by Ogawa in one case with loss of myoepithelial markers and acquisition of p53 positivity in undifferentiated carcinoma component.

The differential diagnosis of MECA includes a wide range of neoplasms, depending on the predominant cell type. It is sometimes difficult to differentiate MECA showing epitheloid morphologic characteristics from other salivary gland neoplasms showing myoepithelial differentiation, especially adenoid cystic carcinoma, polymorphous low-grade carcinoma, and others. Demonstration of luminal differentiation by CEA or EMA immunostaining favors diagnosis of adenoid cystic carcinoma. In tumors with clear-cell morphologic characteristics, the differential diagnosis includes hyalinising clear-cell carcinoma, epithelial-MECA, and metastatic renal cell carcinoma. Melanoma, high-grade lymphoma, or plasmacytoma must be ruled out when the tumor shows plasmacytoid differentiation. With spindle cell morphologic characteristics, the most common differentials are sarcomatoid squamous carcinoma, spindle cell melanoma, and schwannoma. At times, diagnosis of MECA remains challenging, with many factors contributing to the challenge.

Frequently there is confusion between 'myoepithelioma', 'MECA' and 'epithelial-MECA' of the lung. MECA and epithelial-MECA are distinguished by the presence or absence of ductal cells. This histological separation is of outmost importance for the patient's prognosis. As pointed out by Nguyen et al. in a recent review of 23 cases of pulmonary epithelial-myoepithelial tumors, these neoplasms are low-grade lesions without recurrences or metastasis described after resection. Separation of MECA from myoepithelioma of the lung is also prognostically important, and this is primarily based on cellular atypia, infiltrative growth, necrosis and high proliferative activity. Both of these tumors consist exclusively of myoepithelial cells with or without malignant histological features, respectively. Tanahashi et al. reviewed the only four cases of myoepithelioma of the lung in the literature. All these tumors had a low mitotic rate (<1/10 HPFs) and the patients presented no recurrence or metastasis after surgical resection.

In the lung the most obvious and difficult differential diagnosis amongst non-myoepithelial tumors would be squamous cell carcinoma as recently defined in WHO 2015 based on p63 positivity in an undifferentiated tumor. If a small biopsy, limited number of IHC stains are used or a pathologist not experienced in salivary gland pathology is signing out the case this mistake would be very understandable. In present case luckily first pathologist stopped at NSCLC for some reason and in the end the correct detailed diagnosis could be established.

All patients with pulmonary MECA's underwent surgical resection by wedge resection, lobectomy, or pneumonectomy. 90 % of cases showed metastases, involving the lung, liver, brain, or soft tissue. Findings in limited cases suggest that mitotic activity and the presence of necrosis may be useful prognostic markers of MECA's of the lung. Thus, one might suspect that pulmonary MECA has a worse prognosis than NSCLC on a stage for stage comparison.

Our case represents our infamous man from Istanbul or as I start to view cases – every case is a cancer of unknown primary until proven otherwise…

I think case also illustrates the value of still trying to be broad as a pathologist. It certainly gets harder by each new WHO classification that adds constantly new entities in an ever growing list to each organ system. Luckily many of the tumors occur in more than one organ even if the relative frequency is varying.

Conclusions:

- MECA of the lung is a high-grade tumor with poor prognosis and close surveillance for local-regional recurrence and distant metastasis is warranted for these patients due to the propensity for local and regional recurrence
- A high index of diagnostic suspicion and confirmation via a number of IHC markers used in panels are necessary for the important diagnosis of MECA
- Morphologic heterogeneity is the hallmark of neoplastic myoepithelial cells and thus the recognition of "myoepithelial differentiation" at the histologic level, remains difficult
- The most reliable criterion for diagnosis of malignancy in myoepithelial tumors is infiltration of surrounding tissues but a number of other histological features such as atypia, necrosis and high proliferative rate are also indicative
- In MECA of the lung one need to rule out metastasis from other organs
- A risk of using smaller samples and IHC panels is that one easily can miss uncommon tumors

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AMR Seminar #68

Case – 17

Contributed by: Maria Pia Foschini, M.D.

Case history: 19922\13: Section from a brain lesion of a 39 year old woman, heavy smoker. The patient showed also a lung nodule.

Clinical history: A 39 year old woman, with a history of heavy smoke, presented with symptoms related to cerebral hypertension. NMR showed a centrally necrotic nodule, suggestive for metastasis. The patient underwent extensive search, that evidenced a nodule located in the upper lobe of the right lung.

Fine needle aspiration cytology was performed on the lung nodule, resulting in a scanty amount of neoplastic cells, interpreted as "non-small cell lung carcinoma, possibly adenocarcinoma".

As the patient's symptoms were mainly related to the brain nodule, the neurosurgeons decided to remove it. After the histological diagnosis of brain metastasis, consistent with lung origin, chemotherapy was administered. Nevertheless, in spite of the chemotherapy the lung nodule progressed, invaded the pleura resulting in massive pleural effusion. Therefore the patient underwent thoracoscopic biopsy of the lung nodule.

Pathology: Brain nodule: The nodule measured 2 cm. in greatest axis, and was smooth in consistency. The slide is from the brain nodule.

On histology it was composed of markedly atypical spindle cells. Atypical mitoses and areas of necrosis were present.

On immunohistochemistry the neoplastic cells were strongly positive for CK7 and vimentin. Rare neoplastic cells were positive for CK 14 and smooth muscle actin. Negativity was obtained for progesterone receptor, p63, GFAP, CK 5`6, MART/1 and CD34.

The peural biopsy showed the typical features of epithelioid mesothelioma, with a focal spindle cell proliferation. On immunohistochemistry it was strongly positive for calretinin. Fig.s 1,2,3)

Thereafter, Calretinin was performed on the brain nodule that resulted positive (Fig.s 4-7).

Diagnosis: Brain metastasis of nodular mesothelioma with sarcomatoid features.

Comment: The present case is a summary of several rare features encountered in malignant mesotheliomas.

Mesothelioma usual presents as a pleural plaque, but on rare occasions it can appear as an intraparenchimal nodule (1). Asioli et al (1) described two cases of malignant mesothelioma, presenting as intraparenchymal nodules and simulating lung carcinomas. Differential diagnosis was based on the morphological and immunohistochemical profile. Unfortunately, in the present case, the small amount of cells available from the lung nodule FNA did not allow a detailed morphological study.

Malignant mesotheliomas can present a great variety of histological features, among which sarcomatoid features are comprised (2). Diagnosis of malignant mesothelioma, in addition to the morphological and immunohistochemistry, can be supported by specific chromosomal translocations (3).

In the present case, the morphologic features observed in the brain nodule are those of a poorly differentiated, spindle cell neoplasm. Therefore, even if Calretinin is positive, the mesothelial nature could be argued. Nevertheless, the pleural

biopsy showed typical features of malignant mesothelioma, with conventional epithelioid areas. Therefore the brain lesion can be reasonably considered the metastasis.

Malignant mesothelioma is a highly aggressive tumour, with high mortality rate, mainly due to local invasiveness. Metastases can occur mainly to the liver and bones. Brain metastases from mesothelioma have been reported (4,5). Nevertheless, in most of the cases, the brain metastasis appeared in patients with a well-known history of mesothelioma, therefore the diagnosis was not difficult.

Nevertheless, as the present case, even if on rare occasion, the metastatic lesion can be the presenting symptom of malignant mesothelioma (6)!

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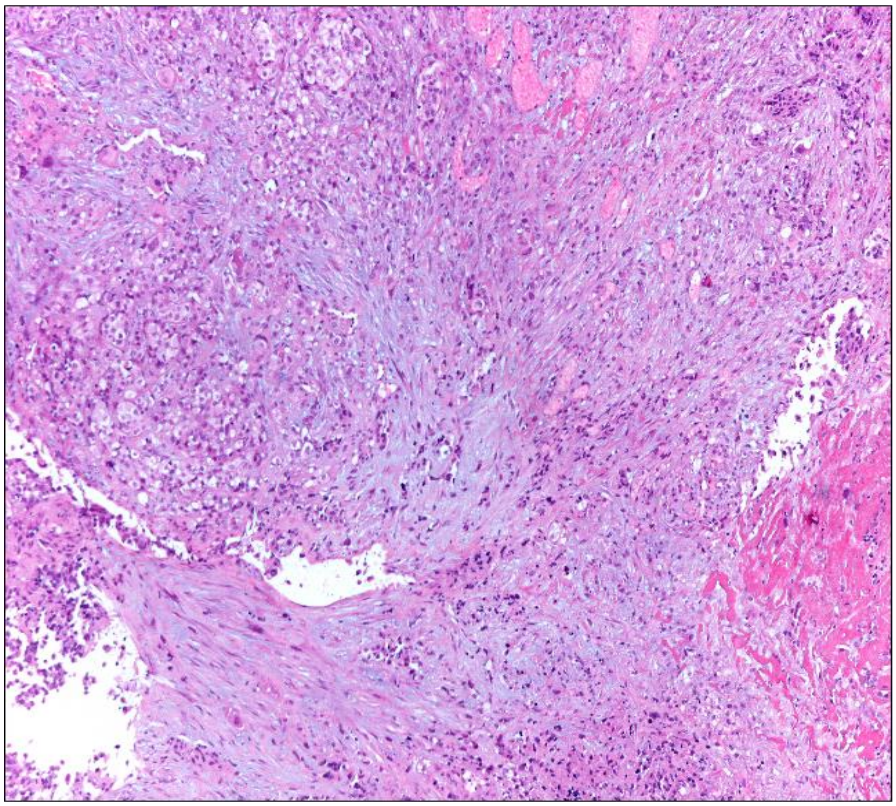


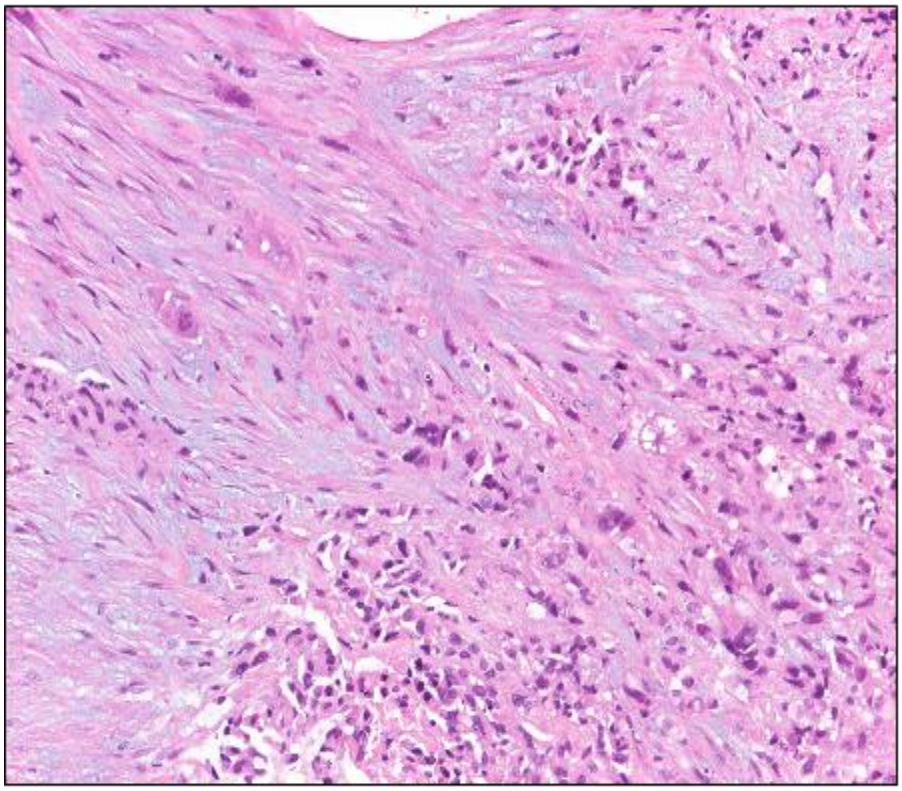


Fig. 1, 2: Histology of the lung nodule

Fig. 3: Calretinin positivity in the lung nodule

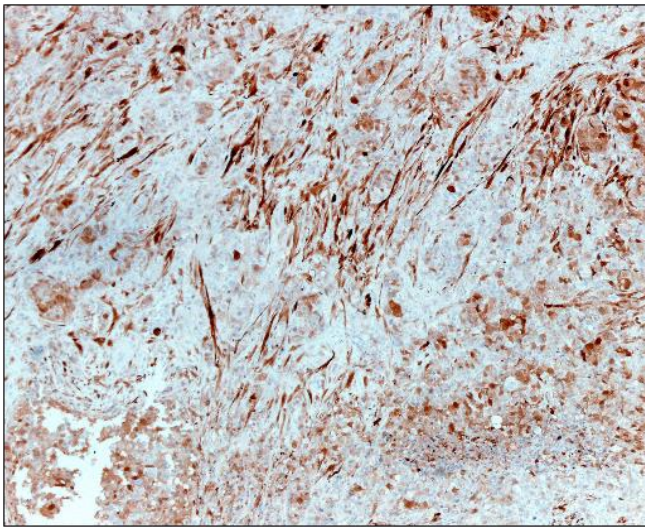


Fig. 4: Brain nodule: H&E features

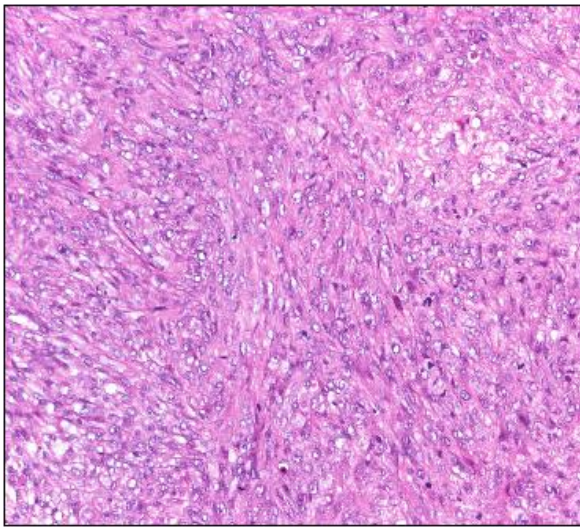


Fig. 5: Brain nodule: CK 7 positivity

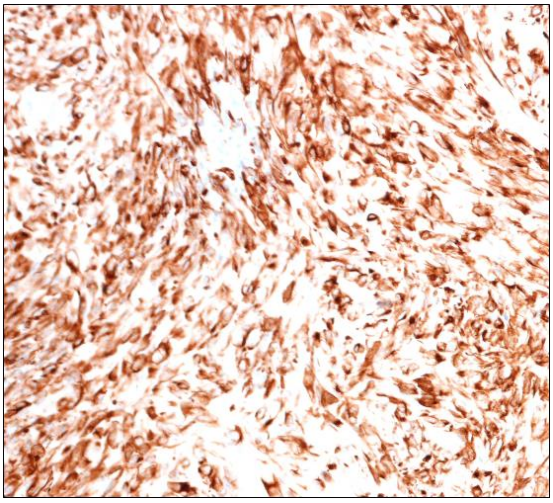


Fig. 6: Calretinin positivity in the brain nodule

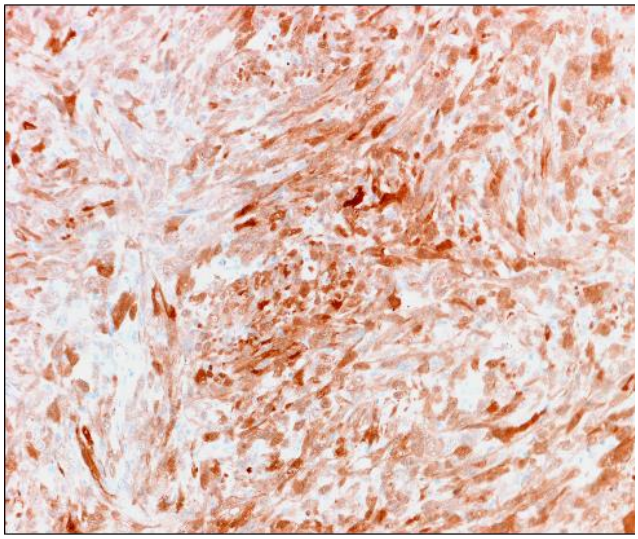
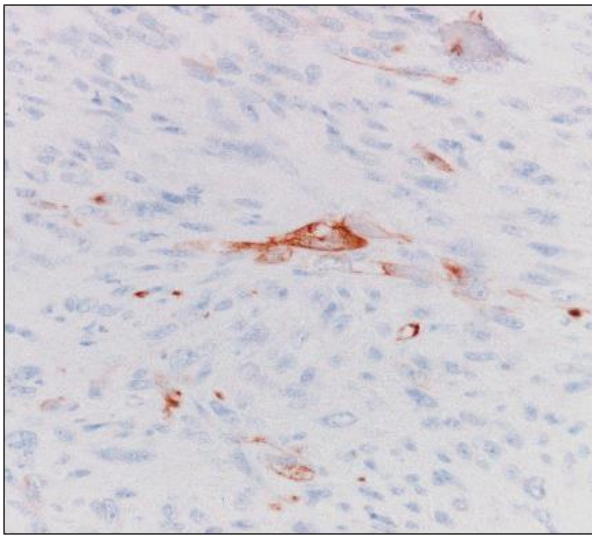


Fig. 7: CK 14 is positive in rare cell of the brain nodule



AMR Seminar #68

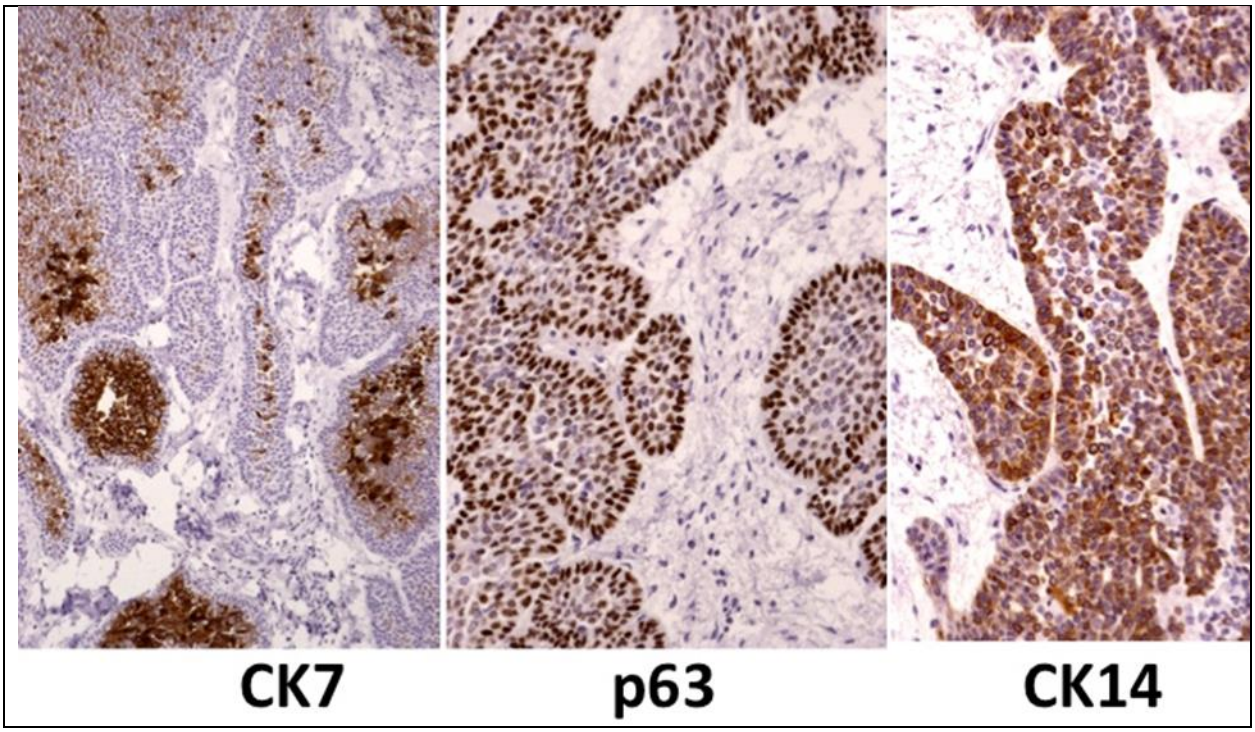
Case – 18

Contributed by: Giovianni Falconieri, M.D.

Case history sheeth: A 71 year-old woman was admitted to the hospital for a left upper lobe opacity discovered during oncologic follow up for ductal carcinoma of breast of usual type, pT1cN0. Lobectomy was carried out. The tumor measured 2.7 x 2 cm and grew predominantly within the lumen of the bronchial lumen although the surrounding lung parenchyma was clearly infiltrated.

Histologic features: The tumor has basically a mixed pattern of growth i.e. polypoid yet with obvious microscopic features of invasion of the bronchial wall and pulmonary parenchyma. Along to squamous features it showed a basaloid pattern with peripheral palizading of small, cuboidal cells with hyperchromatic nuclei at the stromal interface reminding cutaneous basal cell carcinoma. On the other hand, inner cells were larger, with moderate amount of eosinophilic cytoplasm. poorly defined cell borders, and clearer nuclei with inconspicuous nucleoli. Focal areas of coagulative necrosis were recognized. Regional lymph nodes were free of tumor. There was no evidence of metastatic disease. Medical follow up is uneventful at 1 year.

Immunohistochemistry. Tumor cells were positive for cytokeratins with high-molecular weight cytokeratins being expressed by the basaloid cells, paralleled by p63 immunopositivity. A decreased gradient of intensity was seen in the non-basal areas in which a focal yet convincing immunoreaction for CK7 was noted. Other stains such as TTF1, ER, S100 protein, neuroendocrine markers, h-caldesmon were negative



Comment: On the overall, this neoplasm possesses an exophytic, papillary and endobronchial configuration reminding the "papillary endobronchial squamous cell carcinoma" of the lung, a known variant of bronchial squamous cell carcinoma. Nonetheless, there are several unusual features which do not go very well along to that entity: it has a remarkable basaloid configuration, a fibroepitheliomatous appearance and a biphasic cell population with basaloid and squamous features.

Due to the interpretive issues, this case was sent to dr Suster for a diagnostic opinion. Dr Suster basically shared out thoughts and privileged a descriptive diagnosis of "**endobronchial basaloid-squamous cell carcinoma**", suggesting to circulate the case in this seminar to obtain additional opinions.

Have any Club Member seen a case like?

AMR Seminar #68

Case – 19

Contributed by: Anais Malpica, M.D.

Case #2 (S15-6523): A 34 year-old female underwent a myomectomy for a two-month history of uterine bleeding. A 6.0 x5.0 x 4.0 cm fragmented "myomectomy specimen" was received.

Dx: Endometrial stromal sarcoma with myxoid features, low grade

IHC: CD10 +/PR +/ caldesmon neg/ desmin neg

Discussion: The predominance of myxoid and/or fibrous features in a low grade endometrial sarcoma can represent a diagnostic challenge. Attention to the histological features can facilitate the proper diagnosis as some case can show focal areas with the typical appearance of a low grade endometrial stromal sarcoma. Fibromyxoid low grade endometrial stromal sarcoma may be associated with a high grade endometrial stromal sarcoma .

Immunohistochemical studies show that this tumor is positive for CD10 and PR and shows a variable expression of desmin, SMA and h-caldesmon. The most common genetic alteration seen in this neoplasm is the JAZF1-SUZ12 gene fusion. Of note, MDM2 amplification has been found in these neoplasms.

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AMR Seminar #68

Case – 20

Contributed by: Anais Malpica, M.D.

Case #1 (S14-80866): A 63 year-old female presented with a six-month history of pelvic pain. Physical examination revealed a right pelvic mass. The patient underwent a TAHBSO. A 15.0 x 7.5 x 6.5 cm cystic, red brown, hemorrhagic fluid filled right ovary was found.

Dx: Microcystic stromal tumor

IHC studies: CD10 +/ vimentin +/ inhibin neg/ calretinin neg

Discussion: This rare neoplasm, first described in 2009 by Irving and Young, is currently included in the most recent WHO classification of ovarian tumors under the sex-cord stromal tumors-pure stromal tumors category.

Patients' age range from 26 to 63 years (mean 45) and the most common presentation is a pelvic mass. Hormonal manifestations are rare. This neoplasm is unilateral, ranges in size from 2 to 27 cm (mean size, 8.7 cm) and is confined to the ovary. Grossly, it is typically solid and cystic; however, it can be either solid or predominantly cystic. Microscopically, it shows a variable combination of microcysts, solid areas and fibrous stroma. The cells are bland, round to oval or spindle with fine chromatin and a low mitotic index. Foci of bizarre nuclei can be found. Immunohistochemically, this tumor is characterized by a + CD10, a + vimentin and a negative EMA. Inhibin, calretinin, ER and PR are usually negative. More recently, diffuse nuclear expression of FOXL2 and WT-1 as well as nuclear expression of SF-1, β-catenin and cyclin D1 have been reported. So far, no cases with recurrences have been documented.

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AMR Seminar #68

Case – 21

Contributed by: Volkan Adsay, M.D.

Clinical History: 43 year old male, with a history of ulcerative colitis (pan-colitis; diagnosed one year earlier, had been on 5-ASA and 6-Methylprednisolone without good response, and was also intermittently on prednisone).

Patient was admitted with abdominal pain and bloody diarrhea with concern for "acute flare". The patient was started on prednisolone again, with escalating dose, but did not respond well and in the meantime, liver enzymes started rise. Patient was febrile, and developed hypotension. Hemoglobin dropped over the course of several days.

Total colectomy was performed.

Microscopic examination: The colon showed extensive mucosal ulcerations. Many of the ulcers were broad-based of the type that is commonly seen in ulcerative colitis, and had fissure configuration. Uninvolved mucosa showed signs of chronic colitis consistent with the patient's known IIBD of ulcerative colitis type.

Within the ulcers, there were scattered degenerative-appearing cells with a distinctive purple color which were highlighted by an immunostain for herpes virus. Immunohistochemical stains for cytomegalovirus and adenovirus were negative. There were no definitive features to suggest Crohn's disease such as terminal ileal involvement, granulomata, or transmural inflammation unassociated with ulceration.

Diagnosis: Herpetic ulcerations of colonic mucosa in a patient with active ulcerative colitis undergoing intensive suppressive treatment.

Discussion: I must say I selected this case for 3 reasons: 1) I generally find myself sending only tumor cases, which is clearly what excites most of us surgical pathologists, 2) This case is a rather unusual manifestation of a rather straightforward condition herpes, but occurring in the colon; ie., the "man from Istanbul phenomenon", and 3) Many of us often get frustrated with the disinterest of some of the young generation pathologists in morphology, but this was a diagnosis due to the persistence of one of our young colleagues.

With this patient's history of "ulcerative colitis", one could easily dismiss the extensive ulceration seen in this patient as a sign of idiopathic inflammatory bowel disease (IIBD). And frankly, when this case was shown at our consensus conference, this was our initial impression, and we were ready to move on to the next case. In fact, if it weren't to one of our young but exceptionally skilled colleagues pointing out that the degenerative looking cells amidst the ulcers have some features of virally infected cells. We were initially skeptical especially because these cells did not look like CMV or other viral inclusions that we typically see in the colon, but the more we stared at them, the more we got convinced that they may be viral-associated. And indeed immunostain for Herpes was clearly positive in several of these ulcers, matching to those suspect cells. We conceded that this is an unusual occurrence of herpes inclusions in the colon. We see herpes in the anus all the time, but it is rather uncommon in the colon. Of course, how much this herpes is contributing to the formation of these ulcers is very difficult to determine; it is possible that many of these ulcers could still be due to the IIBD (and other factors due to treatment) but punctate nature of the ulcers reminded us the necrosis herpes causes in the liver. Therefore, it is possible that herpes may be a major factor in the process, rather than being a mere passenger.

And, of course, as usual, a member of the AMR club, Dr. Cooper already had a very nice example of this phenomenon documented in the literature (see references) along with electron microscopic verification.

Look forward to your comments.

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AMR Seminar #68

Case – 22

Contributed by: Saul Suster, M.D.

Case: C15-0342 – Case contributed by Dr. Howard Epstein, Hoag Memorial Hospital, Newport Beach, CA.

Clinical History: A 75 year old man was seen for chest pain and was found to have a large anterior mediastinal mass. A mediastinoscopic biopsy was diagnosed as carcinoma. The patient had no significant previous history or evidence of tumor elsewhere. A median thoracotomy with complete resection of the tumor was done. A well-circumscribed, 9.4 x 5.7 x 4.8 cm. lobulated, partially encapsulated mass was removed.

Pathologic Findings: The tumor was composed of a spindle cell proliferation displaying scattered foci of abrupt squamous differentiation with clearing of the cytoplasm (Fig. 1). Scattered dilated perivascular spaces could be identified. Several foci contained clusters of large cells with abundant eosinophilic cytoplasm displaying a somewhat "rhabdoid" morphology. The large rhabdoid cells had small dark nuclei devoid of atypia or mitotic activity (Fig. 2). Immunohistochemical stains showed strong positivity of the spindle cells for cytokeratin AE1/AE3 (Fig. 3) and nuclear positivity for p63 (Fig. 4). The large rhabdoid cells were positive for both markers but stained strongly positive for desmin (Fig. 5) and showed focal nuclear staining for myogenin (Fig. 6).

Diagnosis: Rhabdomyomatous thymoma.

Discussion: Rhabdomyomatous thymoma is a rare thymic epithelial neoplasm described by Dr. Cesar Moran (Am J Surg Pathol 17:633-636, 1993). The tumor is characterized by islands and small clusters of large, benign appearing rhabdoid cells scattered throughout the lesion. The origin of the rhabdomyomatous cells is unknown, but has been observed in other neoplastic processes in the thymus and in association with myasthenia gravis. This particular case, although well-circumscribed, the tumor already showed infiltration into perithymic fat and in a few areas it was already displaying cytologic atypia with mitotic activity. In addition, the MIB-1 stains showed an increased proliferation index compared with conventional thymomas (>15% positive nuclei), and CD117 was also positive. This, coupled with the foci of squamous differentiation, qualify this tumor as an *atypical thymoma with rhabdomyomatous differentiation* (i.e., a WHO type B-3 thymoma, spindle cell variant). I hope the group will enjoy this case – this is only the 2nd. one I've seen so far.

(see pictures next page)

Fig 1

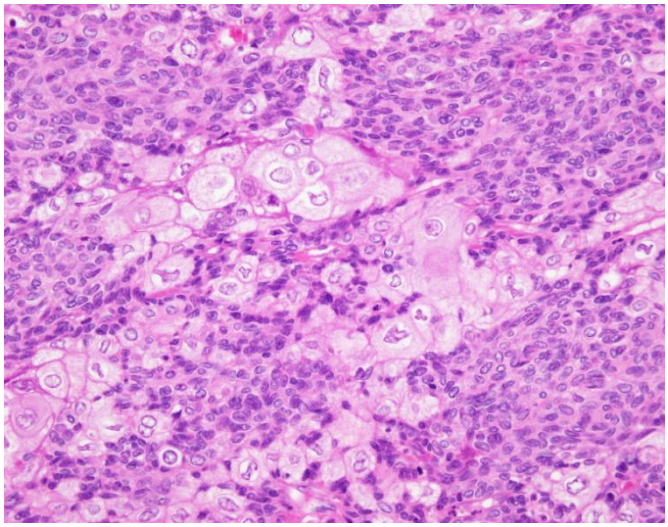


Fig 2

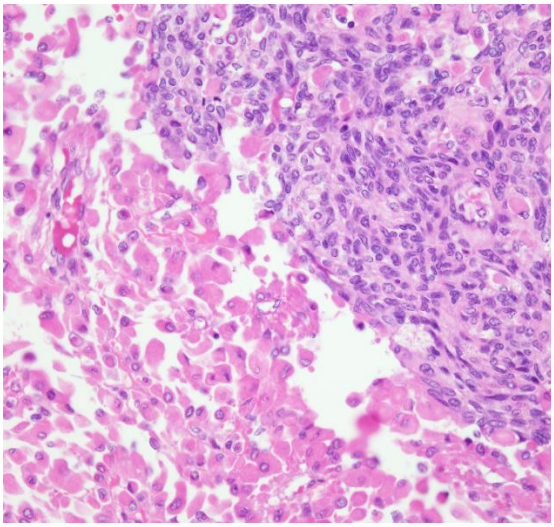


Fig 3

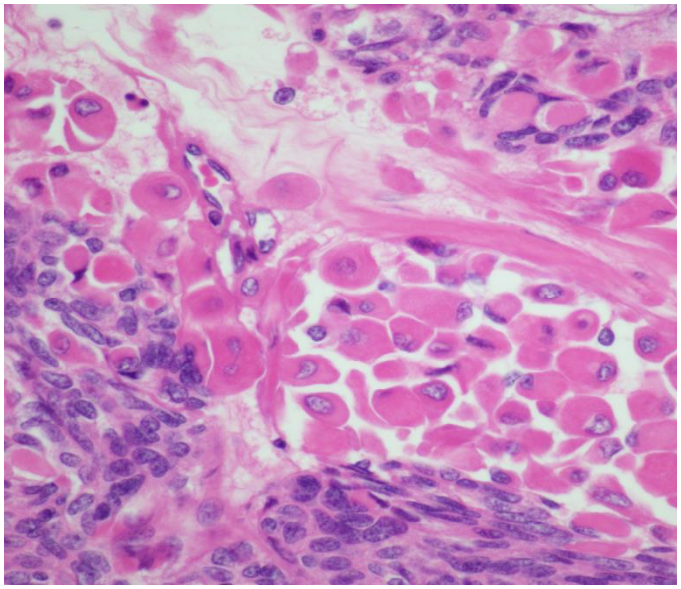


Fig 4

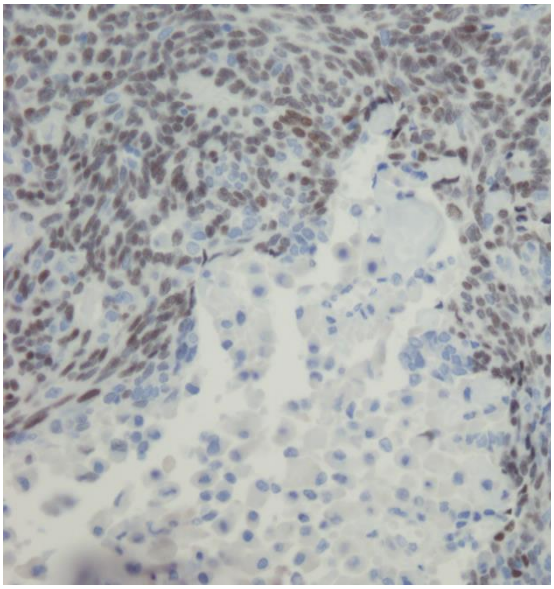


Fig 5

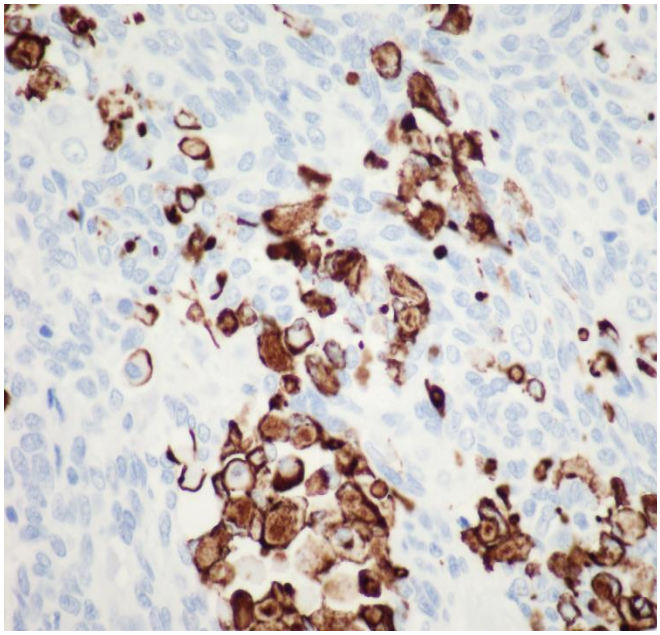
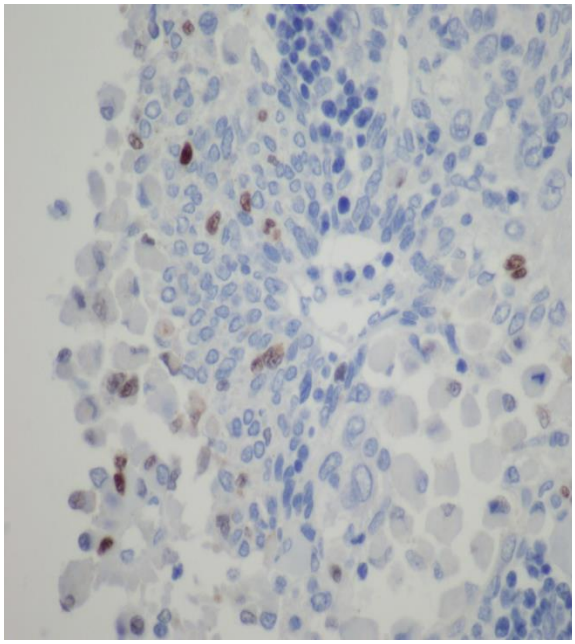


Fig 6



AMR Seminar #68

Case – 23

Contributed by: Bruce M. Wenig M.D.

Clinical History: 47 year old man presented with an enlarging neck mass. No other significant contributing history and/or information.

Histologic Findings: High-grade malignant neoplasm characterized by spindle-shaped and epithelioid appearing cells with pleomorphic vesicular to hyperchromatic nuclei, small to enlarged eosinophilic nucleoli and a variable amount of eosinophilic cytoplasm. There is marked nuclear pleomorphism, increased mitotic activity including atypical mitoses and (focal) necrosis. Overall, there is an absence of specific cellular differentiation. In association with the neoplastic proliferation there is myxoid appearing stroma as well as delicate vascularity including foci of plexiform appearing vessels. In addition, there are foci showing fascicular growth without associated myxoid stroma. The neoplastic proliferation extensively involves the resected thyroid gland seen in and around residual nonneoplastic thyroid parenchyma. Lymph-vascular invasion was also present (which may or may not be in your slide). The neoplasm was also present in extrathyroidal tissues specifically within perithyroidal soft tissue approximating but not involving a normocellular parathyroid gland. There was also involvement of several lymph nodes without extranodal extension. These lymph nodes were within soft tissues that were not adjacent to the thyroid gland so felt to represent metastatic tumor rather than direct invasion into the involved lymph nodes. Immunohistochemical staining showed the neoplastic cells to be reactive for vimentin and desmin, focally positive for thyroglobulin and cytokeratins (CAM5.2, OSCAR) but negative for TTF1, PAX8, AE1/AE3, p63, EMA, MUC4, muscle specific actin, smooth muscle actin, myogenin, myoglobin, MDM2, CDK4, CD31, FLi1, ERG, calcitonin, synaptophysin, S100 protein and HMB45. A proliferation rate of >50% was seen by Ki67 staining.

Diagnosis: High-grade myxoid sarcomatous neoplasm possibly representing undifferentiated (anaplastic) thyroid carcinoma.

Discussion: The findings in this case are clearly those of a high-grade malignancy. Histologically and to some extent the IHC staining suggests a possible diagnosis of a sarcoma, albeit an unclassifiable myxoid sarcoma. Further, the involvement of perithyroidal soft tissues raise the possibility that this neoplasm is a sarcoma originating in the soft tissues of the neck secondarily involving the thyroid gland. However, there are findings that raise the possibility that this neoplasm is a primary thyroid malignancy within the spectrum of undifferentiated (anaplastic) thyroid carcinomas. Such findings include extensive involvement of the thyroid gland, presence of lymph-vascular invasion, presence of nodal metastasis, presence of positive thyroglobulin, albeit focally, and cytokeratin staining. However, the overall histologic findings are not usual for undifferentiated (anaplastic) thyroid carcinoma. Further, the relatively young age of the patient factors also weighs somewhat against a diagnosis of undifferentiated (anaplastic) thyroid carcinoma. Nevertheless, for the reasons cited I diagnosed this case within the spectrum of undifferentiated (anaplastic) thyroid carcinoma but would appreciate the opinions from the group. Thank you.

AMR Seminar #68

Quiz Case -1

Contributed by: Saul Suster, M.D.

Case: A 78 year old male presented with soft tissue mass in the neck. He had no previous pertinent medical history or evidence of tumor elsewhere. A wide excision was done. The tumor was located in the subcutaneous tissue above the fascia and focally infiltrating the skin, and measured 4.5 cm in greatest diameter. The cut section was solid and glistening with a yellow tan color.