AMR Seminar #76

Case – 1

Contributed by: Abbas Agaimy, M.D.

Clinical History: A 54-year-old male with a clinical history of rheumatoid arthritis presented with a recently rapidly growing subcutaneous soft tissue mass in the dorsum of his left foot. Based on clinical impression of a benign or inflammatory process, the mass was first removed non-radically. As this is a very recent case (submitted for second opinion just two weeks ago), no details regarding the extent of the lesion, duration etc. are available yet and radical resection was pending.

Macroscopic Features: Multiple tissue fragments measuring > 7cm in aggregate. The cut-surface was extensively necrotic with areas of brownish discoloration and focal yellowish appearance.

Histological and Immunohistochemical Findings: The main part of the lesion was composed of extensively necrotic high-grade undifferentiated malignancy composed of large epithelioid and rhabdoid cells disposed into diffuse solid sheets. The nuclei have vesicular chromatic and prominent centrally located macronucleoli. Binucleation and multinucleation were seen occasionally. There is brisk atypical mitotic activity. At the periphery, a prominent component was seen, composed of bland fascicles of slender spindled cells infiltrating and entrapping increased amount of normal looking fat. These cells contained prominent cytoplasmic hemosiderin. This spindle cell hemosiderotic component blended with areas of ectatic thin-walled vessels surrounded by prominent amorphous hyaline material and interspersed areas of pleomorphic bizarre looking cells with intranuclear pseudoinclusions.

IHC showed strong CD34 expression limited to the spindle cell and the hyalinizing angiectatic components but was negative in the large cell rhabdoid malignant areas. All components were negative with melanocytic, myogenic and other lineage-specific markers. Due to the prominent rhabdoid morphology, one representative block was stained with the SWI/SNF markers. Loss of SMARCA4 was observed in the large cell undifferentiated component, retained in the remainder. All other SWI/SNF components tested (SMARCB1/INI1, ARID1A, PBRM1 & SMARCA2) showed retained expression in all of the lesional components.

Diagnosis: SMARCA4-deficient large cell (rhabdoid cell) undifferentiated sarcoma originating from preexistent hybrid HFLT/PHAT.

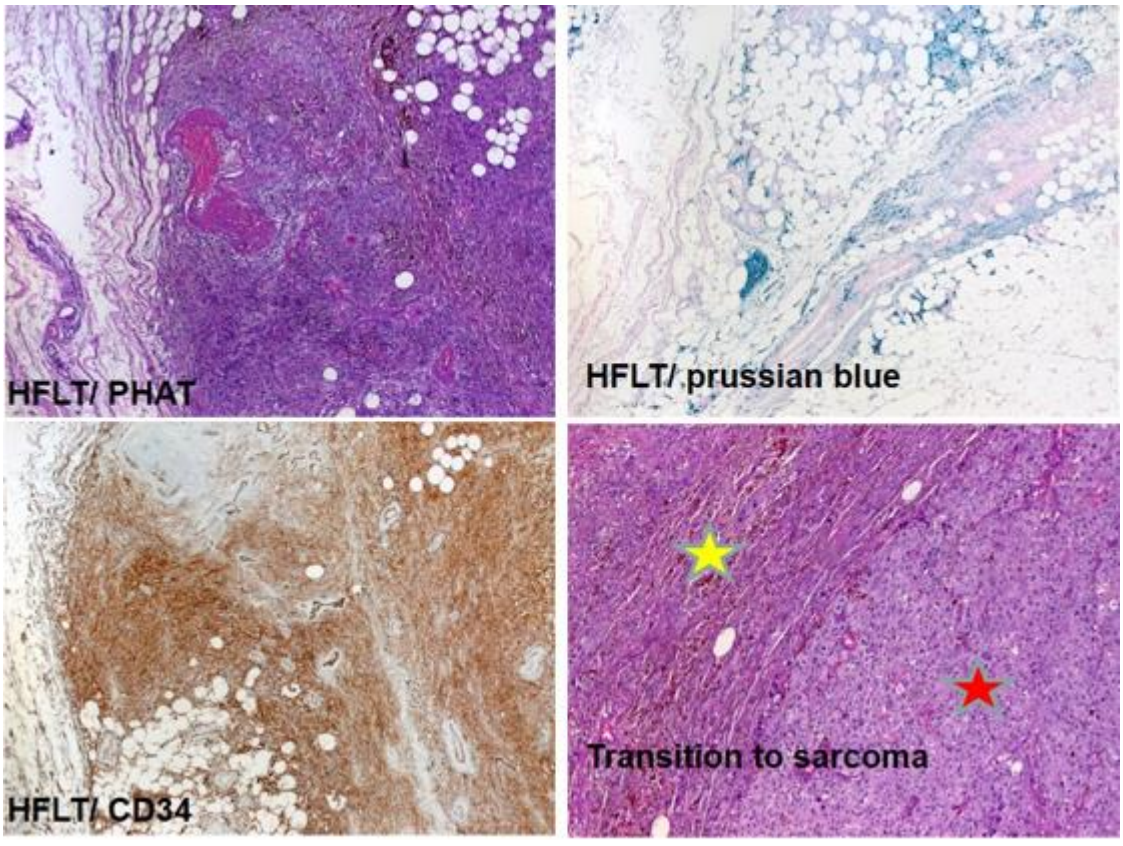
Comments: Hemosiderotic fibrolipomatous tumor (HFLT) is a rare low-grade soft tissue neoplasm first described by Marshal-Taylor & Fanburg-Smith in 2000 as "hemosiderotic fibrohistiocytic lipomatous lesion" of likely reactive nature [1]. Browne & Fletcher then suggested the neoplastic nature of this lesion in 2006 in a reported on 13 additional cases and coined the current name, "HFLT" [2]. HFLT develops mainly in the ankle/foot region of middle-aged patients with a local recurrence rate of up to 50%. Histology shows bland spindle cells infiltrating into fat and containing prominent cytoplasmic hemosiderin. The stroma shows variable myxoid changes and inflammation.

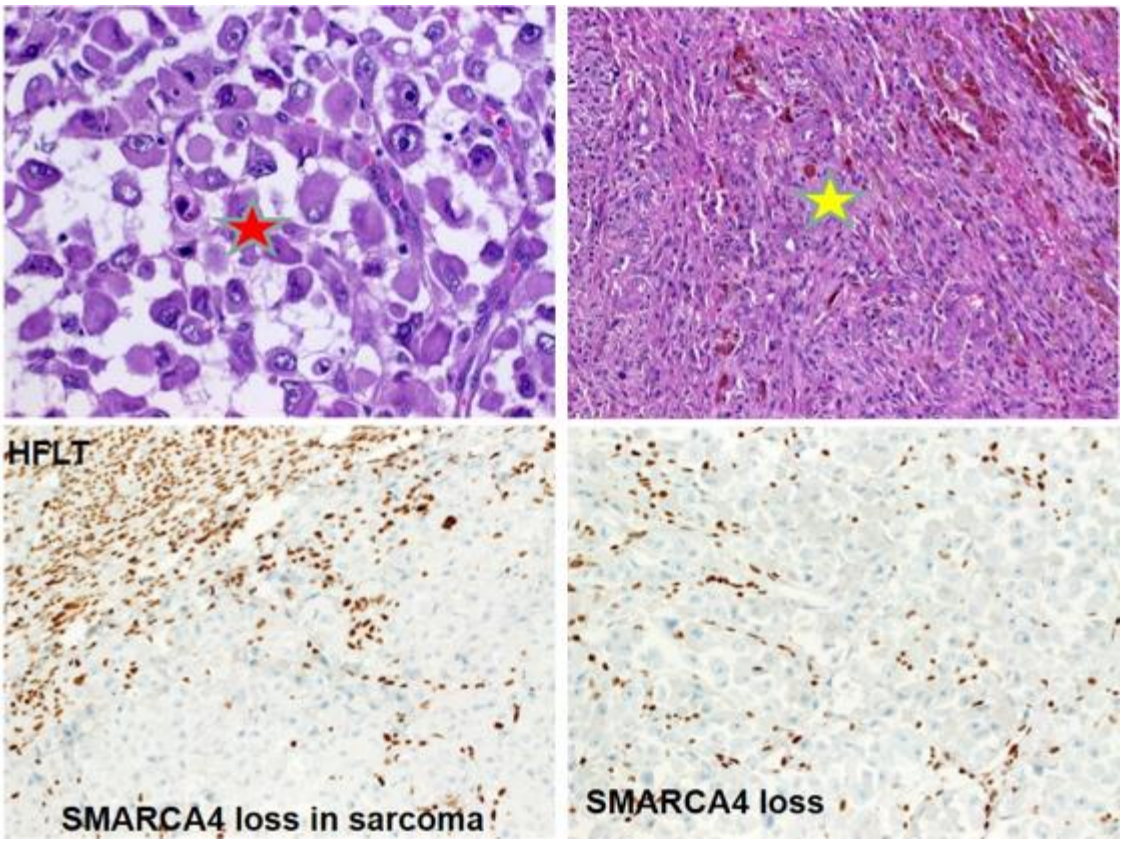
Pleomorphic hyalinizing angiectatic tumor (PHAT) is another rare locally aggressive low-grade soft tissue neoplasm first described by Smith, Fisher and Weiss in 1996 [3]. PHAT displays ectatic thin-walled vessels surrounded by prominent amorphous hyaline material and interspersed areas of pleomorphic bizarre looking cells with intranuclear pseudoinclusions. Similar to HFLT, PHAT occurs as slowly growing subcutaneous soft tissue mass mainly in the lower extremity of middle-aged to older adults. In 2004, Folpe & Weiss described a series of 41 PHATs and recognized a distinctive preexistent lesion identical to HFLT at the periphery of PHAT, which they referred to as "early PHAT" [4]. In same series, genuine HFLTs were found to contain foci identical to PHAT. The relationship between HFLT and PHAT was then strengthened by genetic studies highlighting frequent detection of a t(1;10) (p22;q24) translocation resulting in fusion of the TGFBR3 to MGEA5 [5-8]. Rare fusion variants were reported recently [9]. Myxoinflammatory fibroblastic sarcoma (MIFS) is another low-grade sarcoma that was proposed to be linked to HFLT. The genetic studies suggest PHAT and MIFS represent distinctive progression forms of HFLT, but data on this aspect is however still controversial

and emerging [10,11]. It seems that the unifying feature of hybrid HFLT/PHAT with or without a sarcoma component is the presence of the HFLT component, which correlates with underlying TGFBR3-MGEA5 gene fusion.

Origin of sarcoma ex "HFLT/PHAT" is rare with putative 10 cases reported so far, most were either myxofibrosarcoma-like or MIFS-like [12-17]. Other sarcoma types (reported as undifferentiated pleomorphic sarcoma) are exceedingly rare. The current case represents such an occurrence with the peculiarity and novel aspect of being epithelioid sarcoma-like undifferentiated associated with SMARCA4 loss. This case illustrates:

a. The close link between the undifferentiated rhabdoid phenotype and the SWI/SNF pathway deficiency.
b. That the mere phenotype is not sufficient to name a tumor (e.g. in the current case as epithelioid sarcoma), but the morphological and genetic context is more important.
c. The importance of thorough sampling, in the current case missing the HFLT/PHAT component would have resulted into a descriptive diagnosis of "undifferentiated sarcoma" or as "SMARCB1 proficient SMARCA4-deficient proximal epithelioid sarcoma.
d. The SWI/SNF loss heralds a highly aggressive phenotype irrespective of the anatomic site, and
e. The spectrum of "sarcoma ex HFLT/PHAT" may vary phenotypically based on the secondary genetic hit superimposed on a preexisting TGFBR3/MGEA5 gene fusion.





References:

1. Marshall-Taylor C, Fanburg-Smith JC. Hemosiderotic fibrohistiocytic lipomatous lesion: ten cases of a previously undescribed fatty lesion of the foot/ankle. Mod Pathol. 2000 Nov;13(11):1192-9.
2. Browne TJ, Fletcher CD. Haemosiderotic fibrolipomatous tumour (so-called haemosiderotic fibrohistiocytic lipomatous tumour): analysis of 13 new cases in support of a distinct entity. Histopathology. 2006 Mar;48(4):453-61.
3. Smith ME, Fisher C, Weiss SW. Pleomorphic hyalinizing angiectatic tumor of soft parts. A low-grade neoplasm resembling neurilemoma. Am J Surg Pathol. 1996 Jan;20(1):21-9.
4. Folpe AL, Weiss SW. Pleomorphic hyalinizing angiectatic tumor: analysis of 41 cases supporting evolution from a distinctive precursor lesion. Am J Surg Pathol. 2004 Nov;28(11):1417-25.
5. Antonescu CR, Zhang L, Nielsen GP, Rosenberg AE, Dal Cin P, Fletcher CD. Consistent t(1;10) with rearrangements of TGFBR3 and MGEA5 in both myxoinflammatory fibroblastic sarcoma and hemosiderotic fibrolipomatous tumor. Genes Chromosomes Cancer. 2011 Oct;50(10):757-64.
6. Carter JM, Sukov WR, Montgomery E, Goldblum JR, Billings SD, Fritchie KJ, Folpe AL. TGFBR3 and MGEA5 rearrangements in pleomorphic hyalinizing angiectatic tumors and the spectrum of related neoplasms. Am J Surg Pathol. 2014 Sep;38(9):1182-992.
7. Zreik RT, Carter JM, Sukov WR, Ahrens WA, Fritchie KJ, Montgomery EA, Weiss SW, Folpe AL. TGFBR3 and MGEA5 rearrangements are much more common in "hybrid" hemosiderotic fibrolipomatous tumor-myxoinflammatory fibroblastic sarcomas than in classical myxoinflammatory fibroblastic sarcomas: a morphological and fluorescence in situ hybridization study. Hum Pathol. 2016 Jul;53:14-24.
8. Liu H, Sukov WR, Ro JY. The t(1;10)(p22;q24) TGFBR3/MGEA5 Translocation in Pleomorphic Hyalinizing Angiectatic Tumor, Myxoinflammatory Fibroblastic Sarcoma, and Hemosiderotic Fibrolipomatous Tumor. Arch Pathol Lab Med. 2019 Feb;143(2):212-221.

9. Rougemont AL, Berczy M, Lin Marq N, McKee TA, Christinat Y. Targeted RNA-sequencing identifies FBXW4 instead of MGEA5 as fusion partner of TGFBR3 in pleomorphic hyalinizing angiectatic tumor. Virchows Arch. 2019;475(2):251-254.
10. Boland JM, Folpe AL. Hemosiderotic Fibrolipomatous Tumor, Pleomorphic Hyalinizing Angiectatic Tumor, and Myxoinflammatory Fibroblastic Sarcoma: Related or Not? Adv Anat Pathol. 2017 Sep;24(5):268-277.
11. Michal M, Kazakov DV, Hadravský L, Agaimy A, Švajdler M, Kuroda N, Michal M. Pleomorphic hyalinizing angiectatic tumor revisited: all tumors manifest typical morphologic features of myxoinflammatory fibroblastic sarcoma, further suggesting 2 morphologic variants of a single entity. Ann Diagn Pathol. 2016 Feb;20:40-3.
12. Kazakov DV, Pavlovsky M, Mukensnabl P, Michal M. Pleomorphic hyalinizing angiectatic tumor with a sarcomatous component recurring as high-grade myxofibrosarcoma. Pathol Int. 2007 May;57(5):281-4.
13. Elco CP, Mariño-Enríquez A, Abraham JA, Dal Cin P, Hornick JL. Hybrid myxoinflammatory fibroblastic sarcoma/hemosiderotic fibrolipomatous tumor: report of a case providing further evidence for a pathogenetic link. Am J Surg Pathol. 2010 Nov;34(11):1723-7.
14. Solomon DA, Antonescu CR, Link TM, O'Donnell RJ, Folpe AL, Horvai AE. Hemosiderotic fibrolipomatous tumor, not an entirely benign entity. Am J Surg Pathol. 2013 Oct;37(10):1627-30.
15. Rekhi B, Adamane S. Myxoinflammatory fibroblastic sarcoma with areas resembling hemosiderotic fibrolipomatous tumor: a rare case indicating proximity between the two tumors. Indian J Pathol Microbiol. 2014 Oct-Dec;57(4):647-8.
16. Etchebehere RM, Almeida ECS, Santos CDT, Micheletti AMR, Leitão AS. Sarcomatous transformation of a hemosiderotic fibrohistiocytic lipomatous tumor: a case report. Rev Bras Ortop. 2016 Nov 16;52(3):366-369.
17. Hallin M, Miki Y, Hayes AJ, Jones RL, Fisher C, Thway K. Acral myxoinflammatory fibroblastic sarcoma with hybrid features of hemosiderotic fibrolipomatous tumor occurring 10 years after renal transplantation. Rare Tumors. 2018 Jun 20;10:2036361318782626.

AMR Seminar #76

Case – 2

Contributed by: Gerald Berry, M.D.

Case History: The patient is a 63-year old man who was undergoing a mitral valve repair for severe mitral regurgitation. At the time of surgery, a 2.5 nodule was identified in the mediastinum and it was excised. Preoperatively, the patient was noted to have hypercalcemia; it resolved after surgery to low-normal levels.

Pathologic Findings: The nodule was presumed to be a lymph node by the surgeon. At the time of intraoperative examination, it was noted to be an encapsulated, lobulated 2.5 x 2 x 1.2 cm nodule with a gritty yellow-tan consistency. Microscopically, it displays a clear-cell neoplasm composed of large polygonal cells with clear-to-foamy cytoplasm and prominent "endocrine anaplasia". Foci of degeneration with calcification are present but we did not identify capsular or vascular invasion or brisk mitotic activity and a rim or normal parathyroid tissue was seen in some sections (may be absent in some of the recut slides).

Diagnosis: Mediastinal water-clear parathyroid adenoma

Comments: I thought this was a nice example of an uncommon variant of parathyroid neoplasia in an infrequent location. The cytologic features are alarming but appear to be degenerative in nature. With short follow-up, the patient remains well.

References:

1. Bai S et al. Water-clear parathyroid adenoma: report of 2 cases and literature review. Endocr Pathol 2012; 23:196-200.
2. El Hussein S et al. Water clear adenoma of the parathyroid gland: a forgotten cause of primary hyperparathyroidism. Int J Surg Pathol 2017; 25:384-88.

AMR Seminar #76

Case – 3

Contributed by: Justin Bishop, M.D.

Clinical History: A 49-year-old man with a large, slowly growing cystic neck mass and no known primary tumor. A neck dissection was performed.

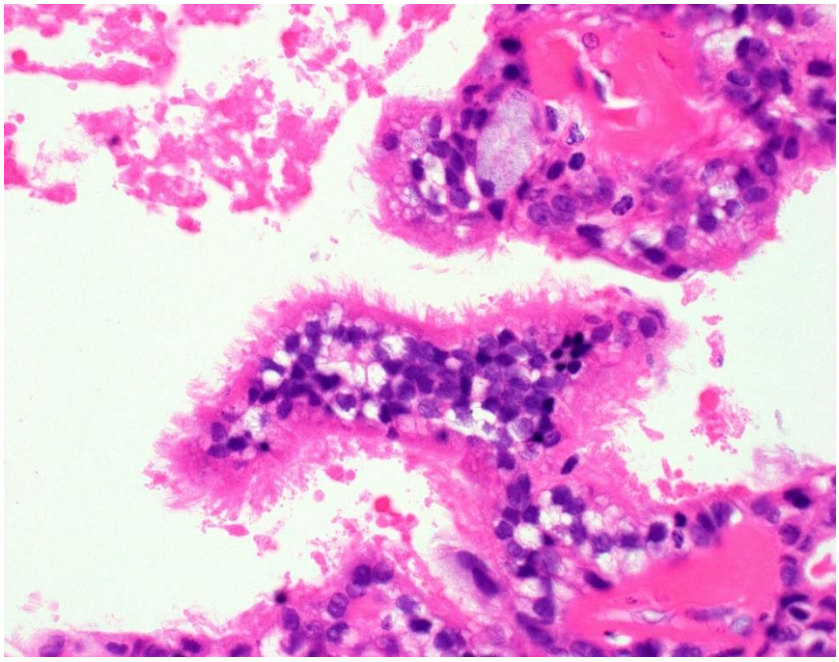
Macroscopic Features: Numerous grossly positive lymph nodes were noted in level 2A. The cut surfaces of these lymph nodes demonstrated heterogeneous areas containing mucoid material and yellow-tan soft tissue.

Gross photograph of the cystic lymph node, post-fixation.

Histological and Immunohistochemical Findings: A total of 5 of 54 lymph nodes (all of which were in level 2A) were positive for tumor. The positive lymph nodes contained consisted of a large multiloculated cysts filled with pink proteinaceous material and lined by predominantly tubulopapillary epithelium. The epithelium lining the cysts was comprised of a mixed population of intermediate cells with clear cytoplasm, squamoid cells, mucinous cells, and eosinophilic columnar cells with terminal bars and numerous well-formed cilia. The tumor nuclei were small, round and monotonous with inconspicuous nucleoli. Mitotic figures were rare.

The tumor was p16 negative by immunohistochemistry. Break apart FISH was positive for the MAML2 rearrangement.

No primary tumor was found on clinical and radiographic examination. The patient is currently alive with no evidence of disease 6 months after treatment.



Microscopic photogram of ciliated tumor cells.

Diagnosis: Metastatic low-grade mucoepidermoid carcinoma, ciliated variant.

Comments: Until relatively recently, chromosomal rearrangements in human neoplasms were believed to be limited to hematologic malignancies and sarcomas. Over the past few years, several salivary gland tumors have been shown to harbor defining gene fusions including mucoepidermoid carcinoma (*CRTC1-MAML2* or *CRTC3-MAML2*), adenoid cystic carcinoma (*MYB-NFIB* or *MYBL1-NFIB*), secretory carcinoma (*ETV6-NTRK*3), clear cell carcinoma (*EWSR1-ATF1*), and polymorphous adenocarcinoma (*PRKD1-3* partnered with various genes). In the case of secretory carcinoma, the discovery led to the recognition of an entirely new tumor type, but in most cases the finding of a recurring translocation has given pathologists a diagnostic "gold standard," allowing them for the first time to truly appreciate the complete histologic spectrum of a given salivary gland neoplasm. In effect, the detection of a tumor-specific gene fusion facilitates accurate tumor classification even in those peculiar variants that phenotypically deviate from its more conventional form.

The histologic spectrum of mucoepidermoid carcinoma (MEC) now includes a variant with cilia. Because they are restricted to the fully differentiated glandular cell, the microscopic detection of cilia has historically been taken as compelling evidence of a benign process, particularly in cytologic material. There are only rare reported cases of ciliated carcinomas, mostly in the gynecologic and gastrointestinal tracts. Until recently, the presence of cilia in MEC has been restricted to those rare cases arising in the thyroid gland. I published a single case that was quite similar to this one; in that case, a very small base of tongue primary was found. I suspect that in this case, the primary was base of tongue, but it was never biopsied. I've seen a couple other ciliated examples in the parotid gland as well. All cases I have seen of ciliated MEC have been low-grade, not surprisingly. It is unclear how common cilia are in MEC. If one is not looking for them in an otherwise straightforward case, they are easily missed. Indeed, I wonder how many of our AMR members noticed them on the slide before reading this write-up!

The finding of cilia in MEC may pose diagnostic difficulties. First, the presence of ciliated cells, especially when presenting as a lateral neck mass, raises the possibility of a benign branchial cleft cyst. This distinction is made more difficult by the bland cytomorphology that is typically seen in low-grade cystic examples of MEC. Even more problematic, ciliated MEC could be confused with the newly described ciliated variant of HPV-related oropharyngeal carcinoma. Like our cases of ciliated MEC, ciliated HPV-related carcinoma often presents as a cystic lymph node metastasis in the lateral neck from an oropharyngeal primary site. Confusion with ciliated HPV-related carcinoma is heightened by the observation that many MECs are p16 positive - a surrogate marker of HPV infection for those tumors arising in the oropharynx or presenting as a cervical lymph node metastasis. For ciliated carcinomas of the

oropharynx and lateral neck where MEC and ciliated HPV-related carcinoma are considered in the differential diagnosis, the diagnostic workup should include MAML2 testing and direct HPV testing (e.g. in situ hybridization) and not p16 immunostaining alone. Moreover, at the histologic level, while HPV-related oropharyngeal carcinomas may exhibit foci of cilia and attenuated, bland cystic epithelium, they also demonstrate foci of overtly malignant non-keratinizing squamous cell carcinoma morphology, a feature that is absent in MEC.

References:

1. Bishop JA, et al. MAML2 rearrangements in variant forms of mucoepidermoid carcinomas: ancillary diagnostic testing for the ciliated and Warthin like variants. Am J Surg Pathol. 2018;42:130-6.

2. Bishop JA, Westra WH. Ciliated HPV-related Carcinoma: A Well-differentiated Form of Head and Neck Carcinoma That Can Be Mistaken for a Benign Cyst. Am J Surg Pathol. 2015;39(11):1591-5.

3. Radkay-Gonzalez L, et al. Ciliated Adenosquamous Carcinoma: Expanding the Phenotypic Diversity of Human Papillomavirus-Associated Tumors. Head Neck Pathol. 2016;10(2):167-75.

AMP Seminar #76

Case – 4

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

Short summary of case: 60-year-old woman with longstanding nevus on the chest, flank, and left breast.

Clinical History: This is a 60-year-old woman with a large chest/flank/breast nevus that became apparent around age 7 (yes, I said age 7). A previous biopsy in 2009 was reported as "melanocytic schwannoma" and "cellular blue nevus". She now presents with a growing nodule within the nevus. The nodule was biopsied and then widely excised using wire localization. The surgeon stated that the background nevus extended deeply into the soft tissue (breast tissue in this case).

The specimen measured 5.8 x 4.8 x 4.5 cm. and contained a single black brown well demarcated solid nodule measuring 1.2 x 1.0 x 0.8 cm, 0.8 cm. A few irregular black-brown linear areas around the tumor, 1.2-2.0 cm, were noted. The slides are from the nodule and surrounding breast tissue.

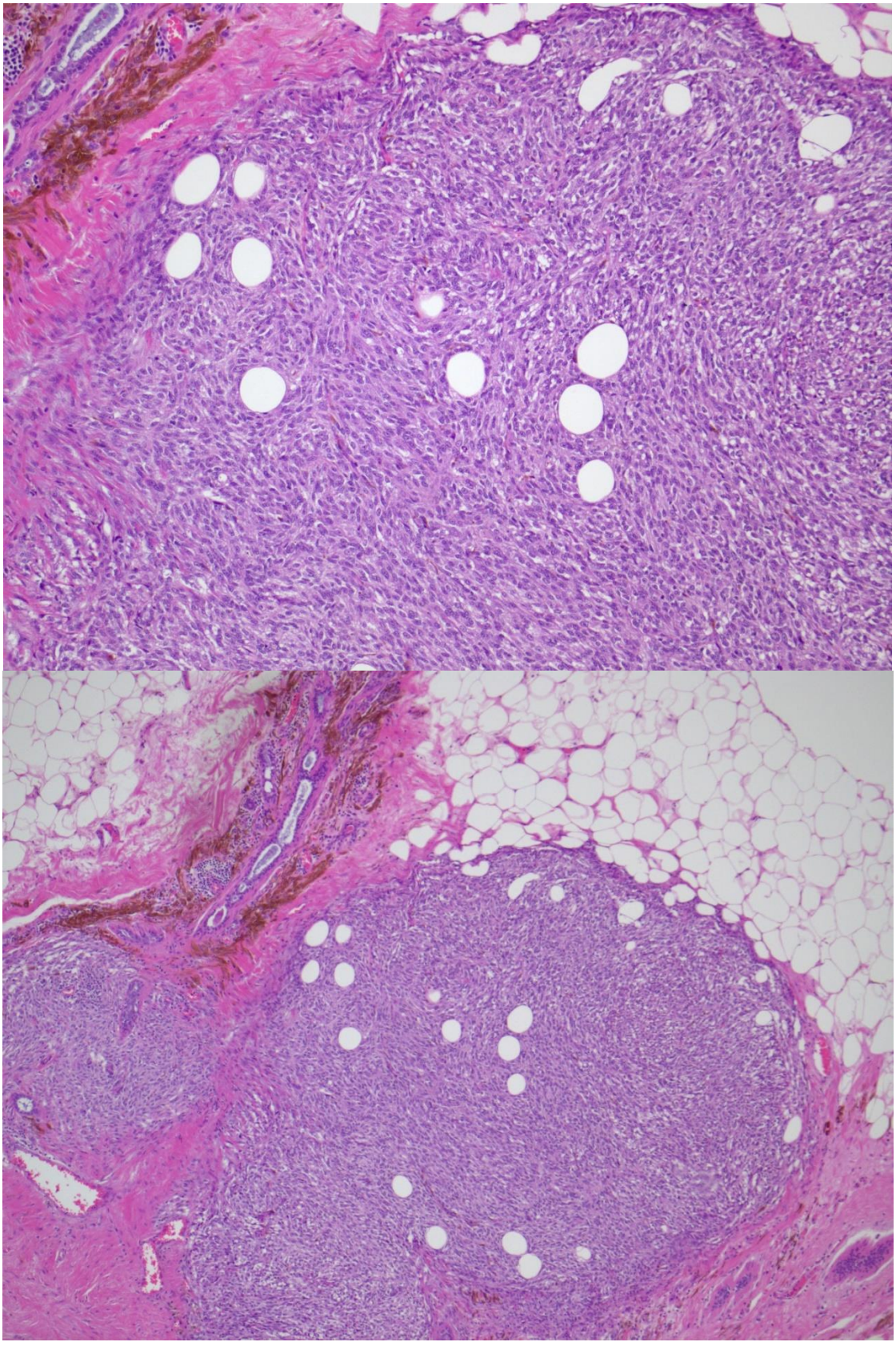
As you will immediately note on the slides, the breast tissue contains a massive amount of pigmented spindle cells and melanophages which have a curious relationship with the glandular breast tissue, growing around it and linearly through septae and even into fat. The nodule is composed of spindle and epithelioid cells with some atypia, prominent nuclei, and numerous mitoses. The cells of the nodule and in the background are positive for Sox10. A larger immunohistochemical panel had been performed on the biopsy and reportedly the lesional cells were diffusely and strongly positive for Sox10, S100, HMB45, and Melan-A and negative for pancytokeratin, AE1/AE3, p63, K903, LMWCK, EMA, CK 5/6, CK7, GATA3, myosin, p16, ER, PR and HER2. Expression of INl-1 and H3K27mc3 were retained. The Ki-67 labeling index was approximately 5%.

Diagnosis: Atypical cellular blue nevus (the nodule) rising in a large cellular blue nevus in breast

Comments: This case was shown to me by my esteemed colleague Dr. David Elder who was kind enough to provide the block and history originally submitted by pathologist Hannah Wu in Newmarket, Ontario. I must confess I have NEVER seen such a lesion in the breast, not even anything close. I was (and still am) concerned about the nodule being a melanoma. Obviously, the nevus has been around for a long time (53 years) – no doubt this would fulfill even the most stringent critic's definition of indolent! The nodule itself is completely and widely excised. I am amazed though at the extent and insidious pattern of the blue nevus coursing through breast tissue. From the sound of it, any attempt at excising the blue nevus itself would be unnecessarily disfiguring.

I really wonder what everyone thinks. Have you ever seen anything like this? Do you think the nodule is a (primary or metastatic) melanoma? Should she have a sentinel lymph node biopsy?

I'm including 2 photos of the nodule because it's barely present on some of the slides.



AMR Seminar #76

Case – 5

Contributed by: Fatima Carneiro, M.D., Ph.D.

Clinical History: A 72-year-old female with large-volume ascites was found to have a thick omental cake on CT image compatible with peritoneal carcinomatosis. So far there was no clinical evidence of neoplasia elsewhere. Omentectomy was performed for diagnostic purpose.

Diagnosis: Epithelioid malignant mesothelioma.

Description: Diffusely involvement of omentum by a malignant neoplasm composed of epithelioid cells with solid and papillary patterns. Focal deciduoid pattern can be seen.

Immunohistochemistry: Positive for Calretinin, CK5, 34BE12, WT1, D2-40

Negative for PAX-8, RE, Desmin, TTF1, S100, Melan-A

AMR Seminar #76

Case – 6

Contributed by: Fatima Carneiro, M.D., Ph.D.

Clinical History: A 37-year-old female with history of monoclonal gammopathy presented with multiple cutaneous nodules in the forearm and face. Excisional biopsy of two nodules was performed.

Diagnosis: Necrobiotic xanthogranuloma.

Description: Subcutaneous lesion composed of histiocytes and multinucleate giant cells, which are of several types, displaying bizarre features and occasionally foamy cytoplasm. There is hyaline necrobiosis and cholesterol clefts can be seen focally.

Immunohistochemistry: Positive for CD68 and CD4

Negative for Cytoqueratins, S100, Melan-A, HMB45 and CD34

Comments: Necrobiotic xanthogranuloma (NXG) is a rare non-Langerhans cell histiocytosis with chronic, indolent, and progressive course. The morbidity and mortality are the result from wound complications and associated disorders. Because of its strong association with monoclonal gammopathy and multiple myeloma (found 80–90% of cases), early recognition of disease is mandatory to monitor and prevent systemic involvements of hematologic malignancies.

AMR Seminar #76

Case – 7

Contributed by: Fatima Carneiro, M.D., Ph.D.

Clinical History: A 32-year-old male with history of recurrent haemoptysis presented with a 5.3-cm hilar mass in the right lung. After several inconclusive biopsies, a right pneumonectomy was performed.

Diagnosis: Angiomatoid fibrous histiocytoma of the right pulmonary hilum with lymph node metastasis.

Description: The lesion comprises a multinodular proliferation of spindle to histiocytoid cells with bland, ovoid vesicular nuclei. There is dense lymphoplasmacytic chronic inflammation, both surrounding and intermingled with the tumor cells, as well as areas of dense fibrosis and some angiomatoid features. No significant cellular atypia or necrosis are identified. Mitotic activity is extremely low. The tumor invades into the walls of the hilar bronchi, artery and vein, exhibiting an impressive endovascular growth. Two peritumoral lymph nodes are involved by the tumor. Focally, it also involves the adjacent lung parenchyma.

Immunohistochemistry: Tumor cells were diffusely positive for CD99, CD68, CD31 and EMA. Focal desmin expression (dendritic pattern) was seen. There was also focal expression for actin, caldesmon and ALK. The neoplastic cells were negative for CK8/18, CD34, dendritic cell markers (CD21, CD23), CD1a and HHV-8. The plasma cells were polytypic.

Molecular study: FISH for EWSR1 was positive.

Comments: Angiomatoid fibrous histiocytoma have only quite recently been recognized to arise primarily in lung. The line of differentiation in these lesions remains poorly understood but, overall, the risk of metastasis is only around 2% and the overall mortality is no more than 1% and therefore the prognosis in most patients is good.

AMR Seminar #76

Case – 8

Contributed by: Alberto Cavazza, M.D.

Clinical Presentation and Histology: This is a case I presented in Bratislava a few years ago. The case refers to a 29-year-old woman who underwent endometrial biopsy for vaginal bleeding. We received abundant grayish and hemorrhagic tissue, that was included completely in 6 blocks. At histology, a few fragments of hypotrophic and partially necrotic endometrium were present, but the majority of the biopsy consisted in a nodular, well vascularized proliferation of cells within a variably myxoid background. The cells were epithelioid to spindle, with mildly atypical nuclei and large eosinophilic cytoplasm, sometimes vacuolated, and were intermixed with a sprinkling of lymphocytes. Necrosis was absent and mitoses were few. At immunohistochemistry, the proliferating cells were diffusely positivity for CD10 and estrogen receptor, focally positive for smooth muscle actin and progesterone receptor, negative for several cytokeratins, desmin and HMB45. At that time a definitive diagnosis was not reached, and the patient underwent hystero-annessiectomy. At surgery, multiple pelvic and omental nodules up to 4 cm in diameter were found, and some of them were excised (your slide). Microscopically, the same cells found in endometrial biopsy comprised the peritoneal nodules and were focally present in the endometrium and in the peri-ovarian tissues.

Diagnosis: Benign decidual proliferation forming tumor-like nodules.

Further Clinical Information and Follow-up: No history of progesterone therapy was elicited, but the patient had a normal delivery 3 years previously and she was still breast-feeding her child. She is alive with no evidence of residual disease 6 years after surgery.

Comments: Ectopic (extra-uterine) decidua is probably physiologic during pregnancy and puerperium, with a frequency approaching 100% if it is carefully searched. It is thought to arise from a progesterone-induced metaplasia of the celomic stroma. Rarely, however, it can occur without a history of partum and in non-pregnant perimenopausal women. The most frequent sites of involvement are pelvis, omentum and appendix; rarely ectopic decidua can be found in other sites including diaphragm, liver, spleen, lymph nodes, kidney and lung. In the vast majority of the cases ectopic decidua is a microscopic incidental finding, but occasionally it can be visible as multiple nodules or plaques on the peritoneal surface, mimicking malignancy. Rare patients may present with abdominal pain, dystocia, intraperitoneal or gastrointestinal bleeding, hematuria or pneumothorax, depending on the involved sites. Ectopic decidua generally does not require any treatment and regresses spontaneously post-partum.
On occasion, several malignancies may have a variably "deciduoid" appearance, but they almost always lack the bland cytology of benign decidua and the distinction is generally not difficult. Obviously, when in doubt immunostains can be helpful: as a note of caution, decidua can express cytokeratins.

References:

1. Malpica A, Deavers MT, Shahab I. Gross deciduosis peritonei obstructing labor: a case report and review of the literature. Int J Gynecol Pathol 2002;21:273-275.
2. Flieder DB, Moran CA, Travis WD, et al. Pleuro-pulmonary endometriosis and pulmonary ectopic deciduosis: a clinicopathologic and immunohistochemical study of 10 cases with emphasis on diagnostic pitfalls. Hum Pathol 1998;29:1495-1503.
3. Rodriguez FJ, Abraham SC, Sendelbach KM, et al. Florid decidual reaction mimicking gastrointestinal malignancy in a primipara woman. Histopathology 2006;49:82-85.
4. Ordonez NG. Deciduoid mesothelioma: report of 21 cases with review of the literature. Mod Pathol 2012;25:1481-1495.

AMR Seminar #76

Case – 9

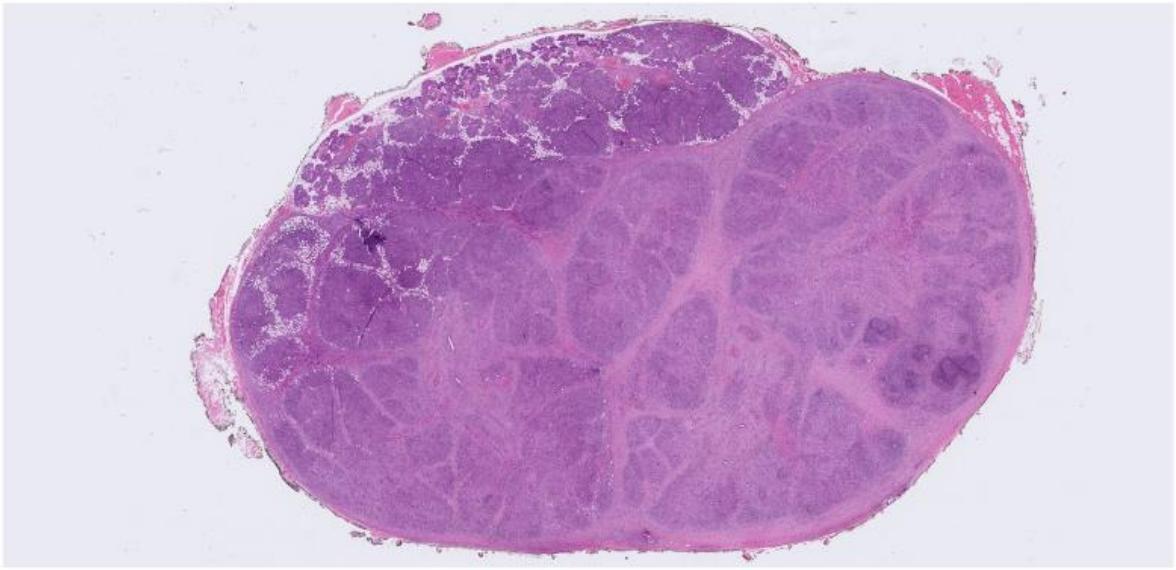
Contributed by: Göran Elmberger, M.D., Ph.D.

Case History: A 71-year-old man with a gradually growing tumor in right submandibular gland. CT suggestive of Warthin's tumor.

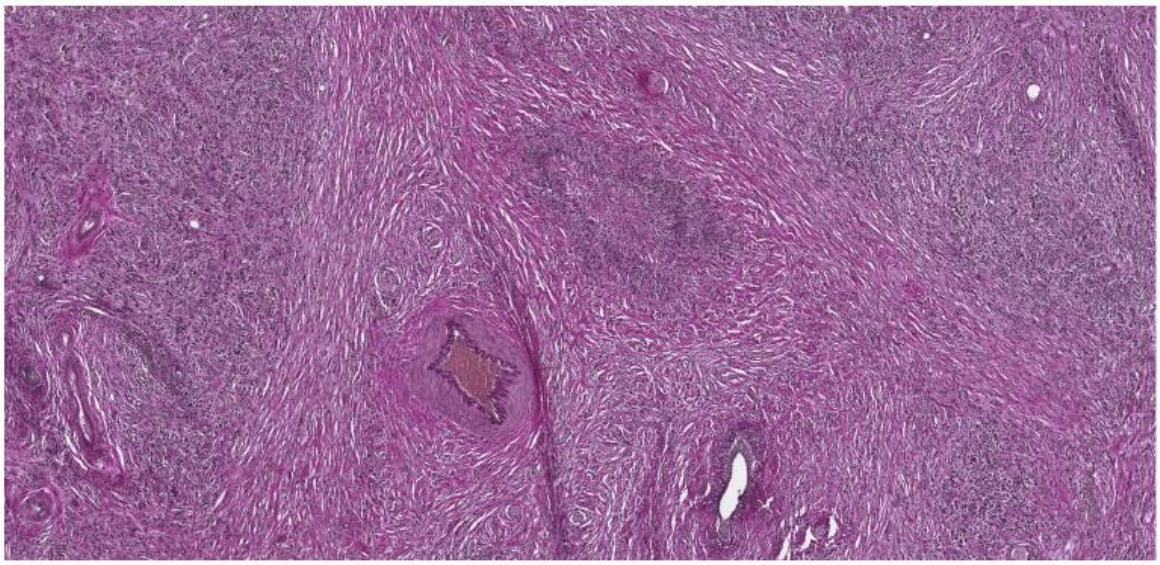
Pathological Findings: Microscopy reveal a well-defined circumscribed lesion involving a proportion of the submandibular gland. There is a preservation of lobular architecture with lobules separated by thickened sclerotic interlobular septa. Storiform-type fibrosis is not a prominent feature. A dense lymphoplasmacytic infiltrate within lobules and extended into fibrosis including sheets of mature plasma cells. Only a few large irregular lymphoid follicles with expanded germinal centers. Some acinar atrophy and replacement of fatty tissue. Obliterative phlebitis can be demonstrated in elastin van Gieson stains. Venous channels are obliterated by dense lymphoplasmacytic infiltrate. Thickened arteries with angiocentric fibrosis without eosinophilia.

Immunohistochemistry show Increased amounts of IGG4 plasma cells with 152 cells per HPF. Ratio IGG4/IGG is > 40%. ALK negative. Plasma cells polyclonal.

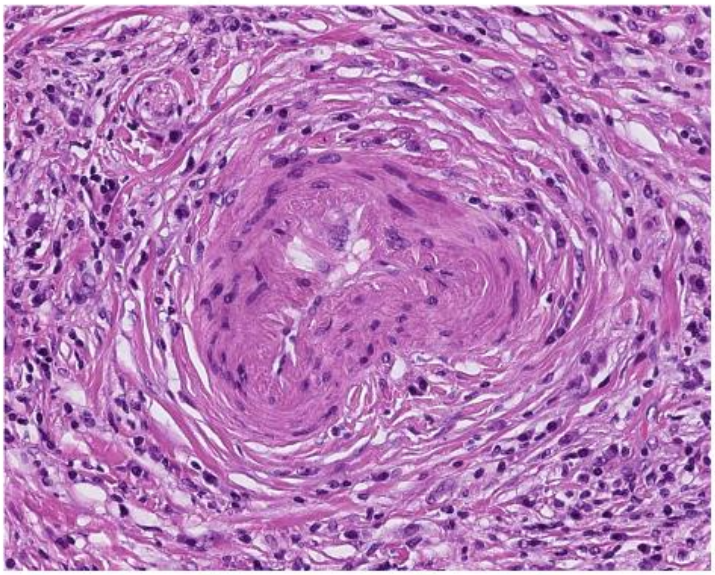
Retained lobular arcitecture and partial involvement



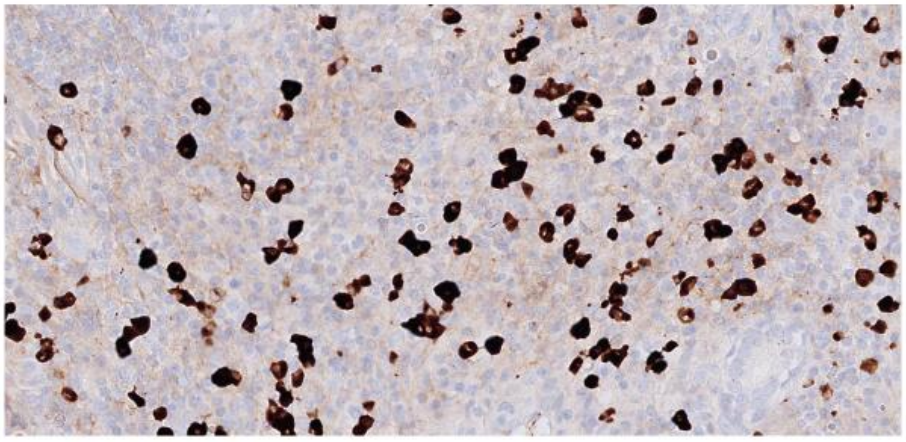
Obliterative endophlebitis Elastin van Gieson



Angiocentric fibrosis



IGG4 IHC 152/HPF



Diagnosis: IGG4-Related Salivary Gland Disease (Chronic Sclerosing Sialadenitis; Kuttner tumor)

Comments: The typical patient with IgG4-RD is a middle aged to elderly male. The incidence and prevalence of IgG4-RD are probably substantially underestimated because recognition of this condition has begun to increase only within the past decade.

IgG4-RD tends to form tumefactive lesions. As a result, patients are often suspected of having a malignancy. IgG4-RD usually presents in a subacute fashion in most patients, without the rapid onset of constitutional symptoms such as fever. IgG4-RD typically comes to medical attention because of single organ involvement, but more widespread disease is often observed following a detailed workup. Involvement by IgG4-RD of different organs can occur either simultaneously or metachronously, with the emergence of one newly affected organ following another.

Spontaneous improvements are reported in a minority of patients, but the majority appear to have slow, indolent progression.

A proportion of patients have symptoms that overlap with allergic conditions. Whether this exceeds the frequency of allergic individuals in the population at large is unclear.

Some patients have long-standing histories of allergy (rhinitis, nasal polyps, asthma, mild eosinophilia) before the full IgG4-RD disease phenotype emerges or is recognized. Mild

to moderate peripheral eosinophilia, sometimes involving up to 20% or more of the circulating white blood cells, is occasionally observed. Elevations in serum IgE concentration, sometimes higher than 10 times the upper limit of normal, are also observed. Whether there is a role for allergens in the pathogenesis of IgG4-RD remains unclear.

Condition	Affected organ(s) or tissue(s)
Eosinophilic angiocentric fibrosis	Orbits, upper respiratory tract
Fibrosing mediastinitis	Mediastinum
Hypertrophic pachymeningitis	Dura mater
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits	Kidney
Inflammatory aortic aneurysm	Aorta
Inflammatory pseudotumor	Orbits, lungs, kidneys, and other organs
Küttner's tumor	Submandibular glands
Mikulicz's syndrome	Salivary and lacrimal glands
Multifocal fibrosclerosis	Orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs
Periaortitis and periarteritis	Aorta and large blood vessels
Retroperitoneal fibrosis (Ormond's disease)	Retroperitoneum
Riedel's thyroiditis	Thyroid
Sclerosing mesenteritis	Mesentery
Sclerosing pancreatitis	Pancreas

In IgG4-RD, the involvement of salivary glands is observed in 27% to 53% of the patients. Several organ-specific conditions, now recognized as different manifestations of IgG4-related sialadenitis (IgG4-RS), were viewed in the past as individual disease entities. For example, Mikulitz disease, a dramatic bilateral painless swelling of parotid, lacrimal, and submandibular glands, was previously linked and not clearly distinguished from Sjögren's syndrome. Prominent submandibular gland involvement, formerly known as Kuttner's tumor, is particularly characteristic of IgG4-RD. IgG4-related sialadenitis must be distinguished from Sjögren's syndrome, which has a predilection for the parotid glands and does not involve the submandibular glands in isolation. Biopsy of the minor salivary glands can be diagnostic of IgG4-RD even if the oral mucosa has an unremarkable clinical appearance.

Histopathological findings in IGG4-RD

Major
Lymphoplasmacytic infiltrate
High percentage of IgG4-positive plasma cells
Storiform fibrosis
Obliterative phlebitis
Mild to moderate tissue eosinophilia
Minor
Germinal centers
Lymphoid follicles
Nonobliterative phlebitis
Obliterative arteritis (usually found in lung)

1. IgG4(+)/IgG(+) plasma cell ratio of > 40% considered cutoff value in any organ.

2. Appropriate cut-off number of IgG4(+) plasma cells varies per organ and for salivary and lacrimal glands > 100 per 10 HPF is considered highly suggestive for diagnosis.

Conclusions:

- IGG4 RD frequently occur in H&N and manifestations in submandibular gland has previously been called chronic sclerosing sialoadenitis (Kuttner tumor)
- Patients with new diagnosis may also suffer from other organ manifestations synchronously or metachronously
- Screening for other organ manifestations at time of diagnosis should be done
- Follow-up may be indicated to early detect new organ manifestations of possibly more dangerous nature
- Effective therapy exists

References:

1. IgG4-related disease. Stone JH, Zen Y, Deshpande V. N Engl J Med. 2012 Feb 9;366(6):539-51.
2. IgG4-related disease. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. Annu Rev Pathol. 2014;9:315-47.
3. Consensus statement on the pathology of IgG4-related disease. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, Klöppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalberse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del Castillo C, Forcione DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Mod Pathol. 2012 Sep;25(9):1181-92.
4. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. Bledsoe JR, Della-Torre E, Rovati L, Deshpande V. APMIS. 2018 Jun;126(6):459-476.
5. IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients. Wallace ZS, Deshpande V, Mattoo H, Mahajan VS, Kulikova M, Pillai S, Stone JH. Arthritis Rheumatol. 2015 Sep;67(9):2466-75.
6. IgG4 related disease of the head and neck. Deshpande V. Head Neck Pathol. 2015 Mar;9(1):24-31.
7. IgG4-related disease in the head and neck. Johnston J, Allen JE. Curr Opin Otolaryngol Head Neck Surg. 2018 Dec;26(6):403-408.
8. Recent advances in knowledge regarding the head and neck manifestations of IgG4-related disease. Takano K, Yamamoto M, Takahashi H, Himi T. Auris Nasus Larynx. 2017 Feb;44(1):7-17.
9. Histopathology of salivary glands. Carubbi F, Alunno A, Gerli R, Giacomelli R. Reumatismo. 2018 Oct 3;70(3):146-154
10. Salivary Gland Pathology in IgG4-Related Disease: A Comprehensive Review. Puxeddu I, Capecchi R, Carta F, Tavoni AG, Migliorini P, Puxeddu R. J Immunol Res. 2018 Apr 1;2018:6936727. doi: 10.1155/2018/6936727. eCollection 2018. Review.
11. Salivary gland involvement disparities in clinical characteristics of IgG4-related disease: a retrospective study of 428 patients. Liu Y, Xue M, Wang Z, Zeng Q, Ren L, Zhang Y, Zhang S, Wang Y, Shen D, Xia C, Yu G, Li ZG. Rheumatology (Oxford). 2019 Aug 21. pii: kez280. doi: 10.1093/rheumatology/kez280. [Epub ahead of print]
12. Major salivary gland enlargement in IgG4-related disease is associated with multiorgan involvement and higher basal disease activity. Martín-Nares E, Ángeles-Ángeles A, Hernandez-Molina G. Mod Rheumatol. 2019 Jan 24:1-5
13. Mechanism of fibrogenesis in submandibular glands in patients with IgG4-RD. Yajima R, Takano K, Konno T, Kohno T, Kaneko Y, Kakuki T, Nomura K, Kakiuchi A, Himi T, Kojima T. J Mol Histol. 2018 Dec;49(6):577-587.
14. Neoplasia associated IgG4-related sclerosis: a new disease paradigm in the salivary gland and potential diagnostic pitfall. Toon CW, Parasyn A, Selinger C, Gupta R, Tomlinson J. Pathology. 2017 Dec;49(7):796-798.
15. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Allergy. 2014 Feb;69(2):269-272.

16. Lymphomas in IgG4-related disease: clinicopathologic features in a Western population. Bledsoe JR, Wallace ZS, Stone JH, Deshpande V, Ferry JA. Virchows Arch. 2018 May;472(5):839-852.
17. Rituximab for IgG4-related disease: a prospective, open-label trial. Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, Deshpande V, Smyrk TC, Chari S, Stone JH. Ann Rheum Dis. 2015 Jun;74(6):1171-7
18. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. Ann Rheum Dis. 2015 Jan;74(1):14-8.

AMR Seminar #76

Case – 10

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

Clinical History: 29-year-old male presented a lesion on side left forefoot IV-V toe.

Macroscopic Findings: The lesion measured 3 cm. It was greyish and showed necrosis area. The tumor infiltrated the tissue bone of the toe.

Histological Findings: The tumor was composed of a rather undifferentiated round-cell population featuring abundant geographical necrosis. The cells, arranged in nodules separated by fibrous septa, showed atypia and pleomorphism. Frequently the cells featured clear cytoplasm and eccentric nuclei and small nucleoli. Mitotic figures and apoptosis were present.

Immunohistochemical Findings: The neoplasm cells were focally positive for CD99, while were negative for LCA, TdT, Actin, Desmin, Calponin, p63, CK20, S100, Chromogranin, Synaptophysin, S100 and CD31. Cytoplasmic and nuclear immunoreactivity for WT1 (N-terminus), Cam5.2 were showed only by a very few cells.

Molecular Findings: Evaluated with RTqPCR and FISH, the case was negative for EWSR1 and FUS rearrangements while was positive for CIC-DUX 4 gene rearrangement **19q13.2** and **4q35.2** as tested by RTqPCR.

Diagnosis: Undifferentiated small cell round sarcoma CIC-DUX4.

Comments: CIC-DUX4 represents a well-described entity, with more than 100 cases having been reported in the literature. (1,2,3,4) CIC-DUX4 fusions seem to be the most frequent genetic abnormality in primitive small round cell sarcomas lacking EWSR1 rearrangements, comprising up to two thirds of EWSR1 rearrangement-negative undifferentiated round cell sarcomas of pediatric and young adult patients. One third comprise BCOR-CCNB3 fusion with an X chromosomal inversion, also CIC-FOXO4 fusions.

Undifferentiated small round cell sarcoma with CIC-DUX4 affects younger age group. Female sex is slightly more affected than the male one. Limbs are the most common body site affected by this neoplasia which metastasizes most commonly to lung, bone and brain. ES more frequently arises in the bone. Only one case was described in the bone.

Microscopically findings of undifferentiated small round cell sarcoma with CIC-DUX4 show solid proliferation of small to medium-sized of neoplastic cells, sometimes with nodular or vaguely nodular appearance. The cells are round to ovoid in morphology. The nuclear features display vesicular chromatin pattern, mild nuclear pleomorphism and geographic necrosis. Immunohistochemical stains show mild diffuse positivity for CD99, WT1 and in some cases, mild-focal positivity for citocheratin.

The diagnosis is suggested based on a combination of morphologic and immunophenotypic features but requires molecular testing for confirmation. In these tumors, CIC on 19q13.2 fuses with one of the DUX4 retrogenes on 4q35 or 10q26.3. Typically, these show t(4;19)(q35;q13.1) or t(10;19)(q26;q13.1), leading to CICDUX4 fusions.

The clinical, morphological, immunohistochemical and molecular evidence suggest that they should be considered a distinct entity from Ewing sarcoma.

The prognosis is very poor. Surgery and radiation therapy remain the main treatment for sarcomas.

References:

1) Graham C, Chilton-MacNeill S, Zielenska M, Somers GR (2012) The CIC-DUX4 fusion transcript is present in a subgroup of pediatric primitive round cell sarcomas. Hum Pathol 43(2):180–189

2) Sugita S, Arai Y, Tonooka A, Hama N, Totoki Y, Fujii T et al (2014) A novel CIC-FOXO4 gene fusion in undifferentiated small round cell sarcoma: a genetically distinct variant of Ewing-like sarcoma. Am J Surg Pathol 38(11):1571–1576

3) Gambarotti M, Benini S, Gamberi G, Cocchi S, Palmerini E, Sbaraglia M et al (2016) CIC-DUX4 fusion-positive round-cell sarcomas of soft tissue and bone: a single-institution morphological and molecular analysis of seven cases. Histopathology. 69(4): 624–634

4) Antonescu CR, Owosho AA, Zhang L, Chen S, Deniz K, Huryn JM et al (2017) SarcomasWith CIC-rearrangements Are a Distinct Pathologic EntityWith Aggressive Outcome: A Clinicopathologic and Molecular Study of 115 Cases. Am J Surg Pathol 41(7):941–949

AMR Seminar #76

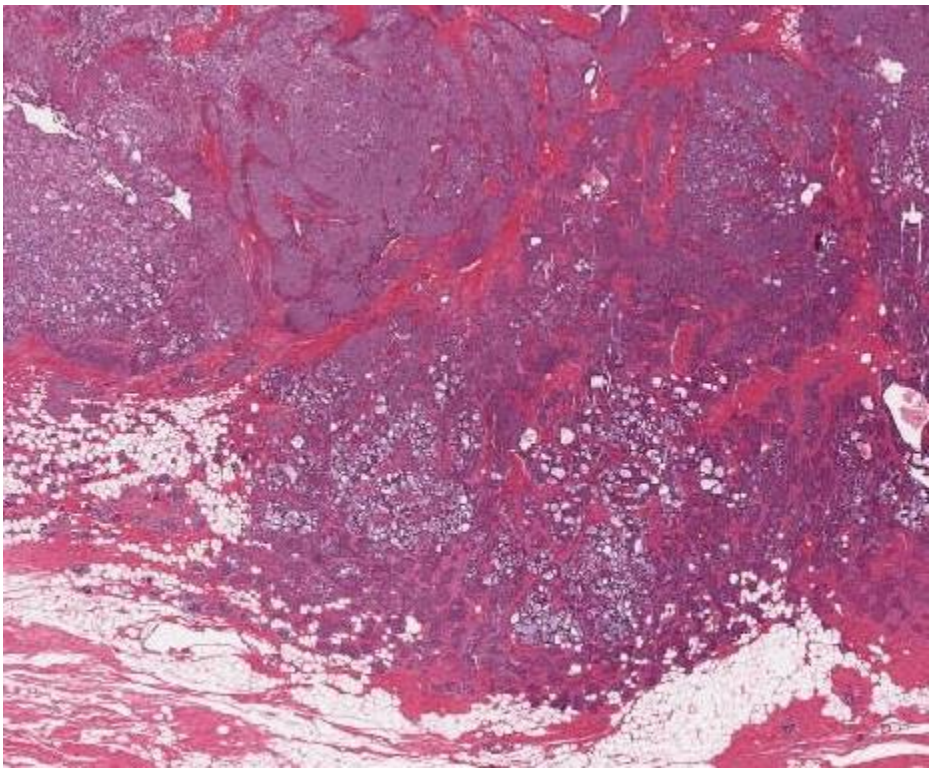
Case – 11

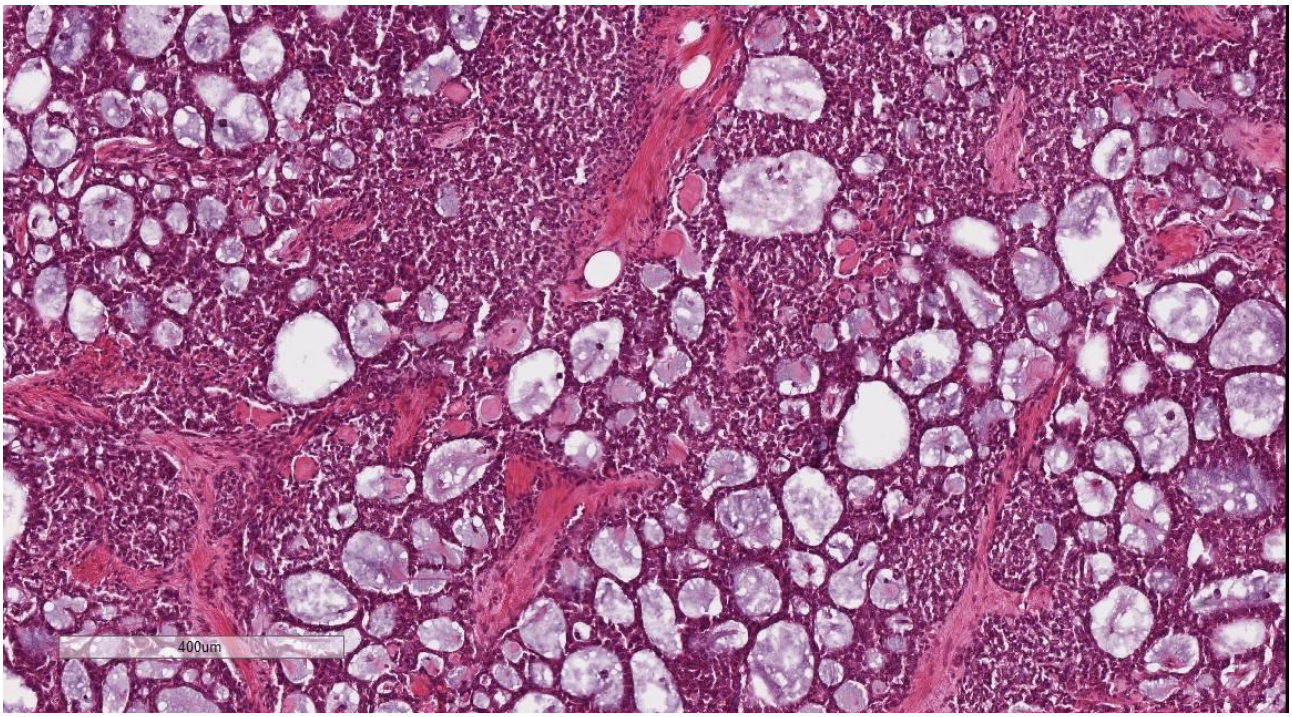
Contributed by: Maria Pia Foschini, M.D.

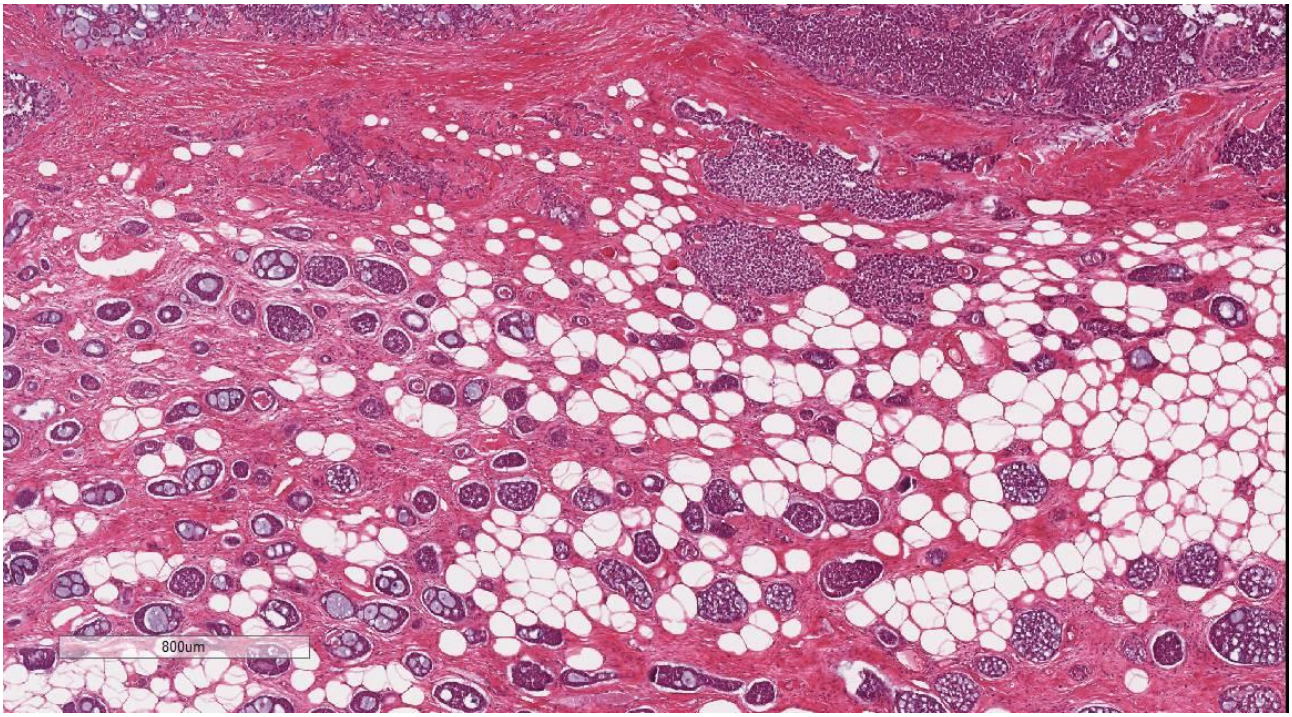
Clinical History: A woman, aged 84, presented with a 5.5 cm nodule of the left breast. After the diagnosis of adenoid cystic carcinoma (AdCC) of the breast, performed on core needle biopsy, quadrantectomy and axillary node dissection was performed. The nodule was completely removed, with clear margins; no metastases were present in the 27 axillary nodes. The patient was then followed up. She presented 11 years later, with a 4.5 cm mass, located in the left breast. The submitted specimen derives from the second surgery.

Histology: The first tumor was a breast AdCC classical type. It showed a predominant solid and cribriform pattern of growth with tubular areas at the periphery of the tumoral mass. No necrosis was seen. It was ER/PR/HER2 negative, Ki67 labelling index was low.

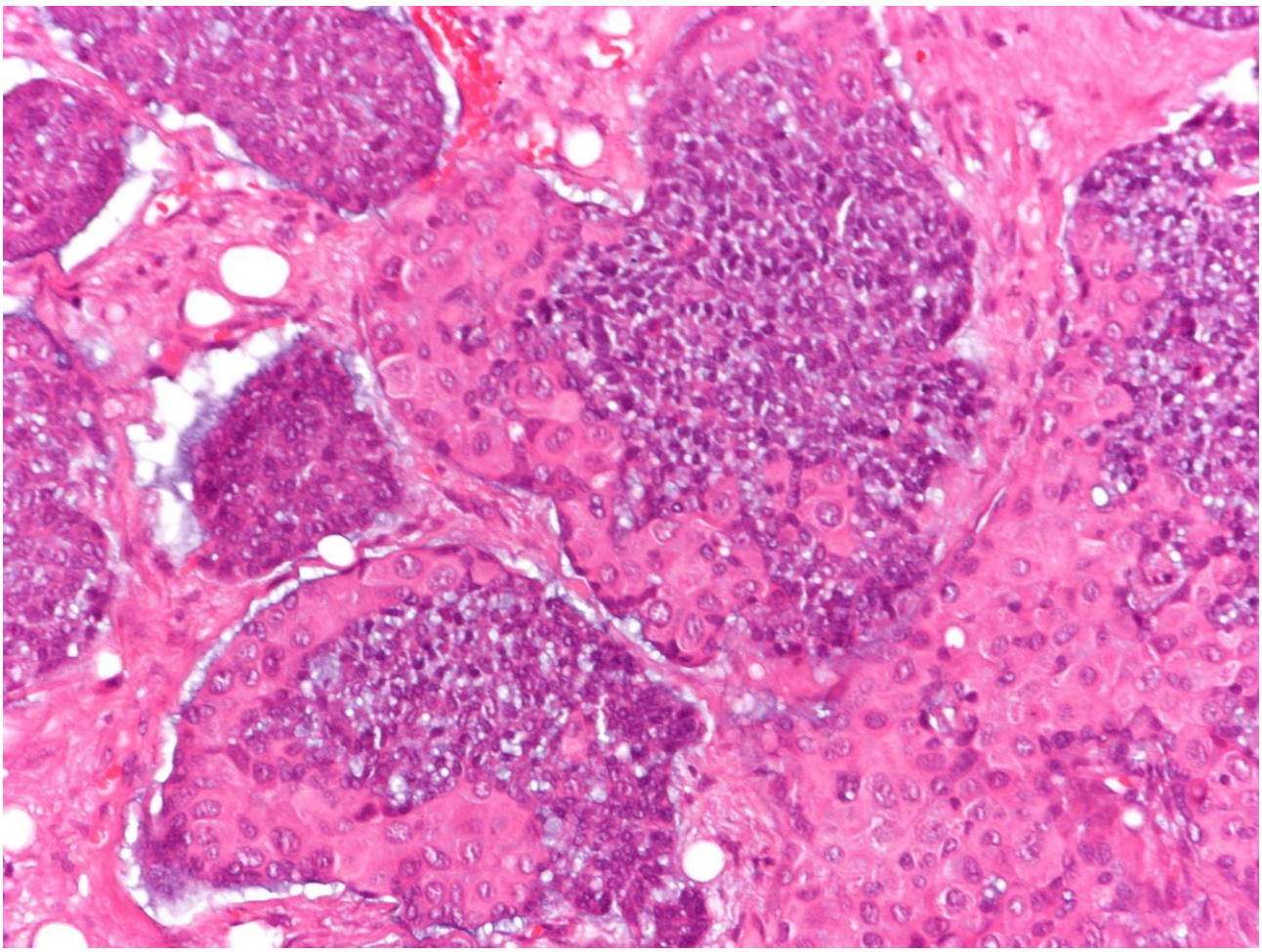
Images from the first tumor, showing the classical AdCC features.



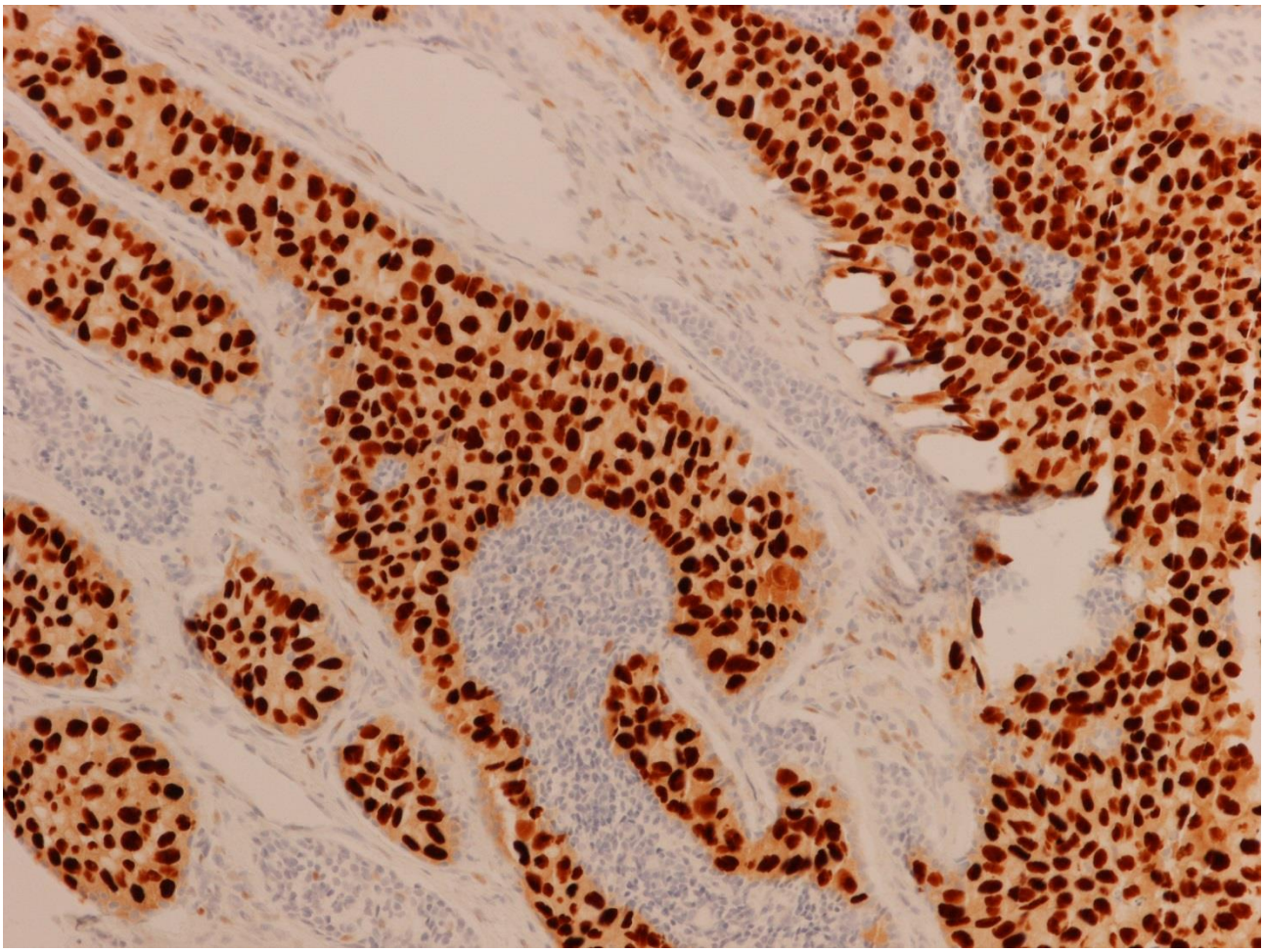

400um


800um

The recurrence was a highly invasive AdCC, with solid, cribriform and tubular areas. It showed diffuse features of neural invasion. The solid areas showed atypical mitoses. In addition to the AdCC features, a neoplastic proliferation of markedly atypical cells was present. These latter cells were strongly ER positive and focally PR positive.



The recurrent lesion with the highly aggressive neoplastic cells.



The high-grade component showed strong ER positivity.

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

Comments: High grade transformation in AdCC of the salivary glands has been recognized about 20 year ago and described as "dedifferentiation". In 2007 Seethala et al proposed the term of "high grade transformation". In spite of the name adopted, AdCC of the salivary glands can undergo to a transformation into an aggressive carcinoma. In those cases, the classical features of AdCC are associated to neoplastic areas of high-grade carcinoma. AdCC with high grade transformation is associated with accelerated clinical course.

AdCC of the breast is a very rare tumour, accounting for less than 1% of all breast carcinomas. Breast AdCC is well known to have a favorable long-term prognosis. It is considered a "triple negative tumor of low aggressive potential". Indeed, most of the reported cases followed a favorable course after complete surgical excision.

Shin and Rosen in 2002 described a variant of AdCC of the breast, characterized by solid-basaloid features (SB-AdCC). SB-AdCC is associated with more aggressive behavior, with higher metastasis and recurrence rates.

Also, AdCC of the breast can develop high grade transformation, characterized by highly aggressive features associated with classical AdCC features. These latter cases are associated with aggressive clinical course.

In most of the reported cases, the solid basaloid or the high-grade features appeared at presentation. On the contrary the present case showed a high-grade transformation in the recurrence. The feeling is that breast AdCC deserves a long term accurate follow up, even when completely excised.

References:

1. Cheuk W, Chan JK, Ngan RK. Dedifferentiation in adenoid cystic carcinoma of salivary gland: an uncommon complication associated with an accelerated clinical course. Am J Surg Pathol. 1999 Apr;23(4):465-72.
2. Chau Y, Hongyo T, Aozasa K, Chan JK. Dedifferentiation of adenoid cystic carcinoma: report of a case implicating p53 gene mutation. Hum Pathol. 2001 Dec;32(12):1403-7.
3. Nagao T, Gaffey TA, Serizawa H, Sugano I, Ishida Y, Yamazaki K, Tokashiki R, Yoshida T, Minato H, Kay PA, Lewis JE. Dedifferentiated adenoid cystic carcinoma: a clinicopathologic study of 6 cases. Mod Pathol. 2003 Dec;16(12):1265-72.
4. Seethala RR, Hunt JL, Baloch ZW, Livolsi VA, Leon Barnes E. Adenoid cystic carcinoma with high-grade transformation: a report of 11 cases and a review of the literature. Am J Surg Pathol. 2007 Nov;31(11):1683-94.
5. Foschini MP, Krausz T. Salivary gland-type tumors of the breast: a spectrum of benign and malignant tumors including "triple negative carcinomas" of low malignant potential. Semin Diagn Pathol. 2010 Feb;27(1):77-90.
6. Shin SJ, Rosen PP. Solid variant of mammary adenoid cystic carcinoma with basaloid features: a study of nine cases. Am J Surg Pathol. 2002 Apr;26(4):413-20.
7. Slodkowska E, Xu B, Kos Z, Bane A, Barnard M, Zubovits J, Iyengar P, Faragalla H, Turbin D, Williams P, Barnes PJ, Mulligan AM. Predictors of Outcome in Mammary Adenoid Cystic Carcinoma: A Multi-Institutional Study. Am J Surg Pathol. 2020 Feb;44(2):214-223.
8. Foschini MP, Rizzo A, De Leo A, Laurino L, Sironi M, Rucco V. Solid Variant of Adenoid Cystic Carcinoma of the Breast: A Case Series With Proposal of a New Grading System. Int J Surg Pathol. 2016 Apr;24(2):97-102

AMR Seminar #76

Case – 12

Contributed by: Masaharu Fukunaga, M.D.

Clinical History: A 29-year-old 0G0P female was admitted because of lower abdominal distention and menorrhagia. Her past history was uneventful. Image analyses indicated uterine myoma. A laparoscopic simple hysterectomy was performed. The patient is alive without evidence of disease four years after surgery.

Macroscopic Findings: Fragmented tissue measuring to 15cm was composed of the uterine cervix, body, multiple yellowish white or white nodules measuring up to 5cm and a lobulated 8.7x5.5x5.0cm tan yellow nodule.

Microscopic Findings: Multiple nodules except the largest nodule were conventional leiomyomas. The distributed slide was from the biggest nodule. The tumor was relatively well demarcated, but with infiltrative margins. This tumor had a variable histologic appearance and was characterize by trabecular, glandular, tubular, papillary, Sertoliform, retiform, alveolar proliferation of round cells. A fascicular or interlacing proliferation of spindle cell was also seen. The tumor cells have ovoid, round or spindle nuclei, small nucleoli and clear or amphophilic cytoplasm. Atypia was mild to moderate and no mitotic figures or necrosis was observed. Stroma was fibrous with prominent hyalinization. Vascular invasion was noted in the myometrium

Immunohistochemical Findings: The tumor was diffusely positive for D2-40, focally positive for WT1, calretinin, desmin, CD10, aSMA, HMB45 and negative for AE1/AE3, CAM5.2, inhibin, thyroglobulin, TTF1, HHF35, Melan A. Less than 1% of tumor cells were positive for Ki67

Diagnosis: Uterine tumor resembling ovarian sex cord tumor (UTROSCT).

Comments: The tumor is a mesenchymal tumor of uncertain malignant potential that resembles sex cord stromal tumor of the ovary. This type of tumor usually occurs in middle-aged women with an average age of 50 years. Histologic diagnosis is relatively straightforward. Histologically, a round or spindle tumor cell proliferation mimics Sertoli cell tumor or granulosa cell tumor. There was no element of endometrial stromal tumor. UTROSCT has a variable histologic appearance and polyphenotypic immunoprofiles.

Differential diagnoses are wide, including low grade endometrial stromal tumor with sex cord-like growth, adenosarcoma with extensive sex cord-like differentiation, epithelioid smooth muscle tumor and endometrioid carcinoma (grade 1) with sex cord-like growth. A variable histologic appearance including sex cord morphology, the absence of typical low grade endometrial stromal histology, along with a polyphenotypic immunoprofile, allow for diagnosis of UTROSCT to be favored.

Up to 23.5% of had extrauterine recurrence (1). Hysterectomy with or without bilateral salpingo-oophorectomy is considered standard treatment.

Fusions involving growth regulation by estrogen in breast cancer 1 (GREB1) and estrogen receptor 1 (ESR1) genes have recently been detected in UTROSCT (2-7).

References:

1. 1, Moore M, McCluggage WG. Uterine tumor resembling ovarian sex rod tumour: first report of a large series with follow-up. Histopathology, 2017;71:751-759.

2. Hurrell DP. McCluggare WG. Uterine tumour resembling ovarian sex cord tumour is an immunohistochemically polyphenotypic neoplasm which exhibits coexpression of epithelial, myxoid, and sex cord markers. J Clin Pathol 2007; 60:1148-1154.

3. Croce S, Lesluyes T, Delespaul L, et al. GREB1-CTNNB1 fusion transcript detected by RNA-sequencing in a uterine tumor resembling ovarian sex cord tumor (UTROSCT): a novel CTNNB1 rearrangement. Genes Chromosomes Cancer 2019; 58:155-163.

4. Dickson BC, Childs TJ, Colgan TJ et al. Uterine tumor resembling ovarian sex cord tumor: a distinct entity characterized by recurrent NCOA2/3 gene fusions. Am J Surg Pathol 2019:43:178-186.

5. Lee CH. Kao YC, Lee WR et al. Clinicopathologic characterization of GREB1-rearranged uterine sarcomas with variable sex-cord differentiation. Am J Surg Pathol 2019:43:928.

6. Moment-Boroujeni A, Chiang S. uterine mesenchymal tumours: recent advance. Histopathology 2020;76:64-75.

7. Goebel EA, Hernandez Bonilla S, Dong F, et al. Uterine tumor resembling ovarian sex cord tumor (UTROSCT): a morphologic and molecular study of 26 cases confirm recurrent NCOA1-3 Rearrangement. Am J Surg Pathol 2019.

AMR Seminar #76

Case – 13

Contributed by: Thomas Krausz M.D.

Clinical History: 22-year-old male who presented with abdominal pain and was found to have a large right paratesticular mass which was described by imaging as a heterogenously solid and cystic lesion. Right orchiectomy was performed.

Pathology: Grossly the right orchiectomy specimen showed a paratesticular, well-circumscribed, heterogenous, firm, tan mass (7.8 cm in maximum diameter) with fibrous septae and areas of hemorrhage as well as small areas of necrosis. The mass was grossly obliterating part of the spermatic cord but did not involve the testis and epididymis. Histologically it is composed of primitive small round to oval cells with scant amphophilic cytoplasm. There is no significant nuclear pleomorphism and the nuclei contain small nucleoli. Mitotic activity is brisk. The growth pattern varies from solid to microcystic/lacy with myxoid matrix. The tumor is richly vascular. The H&E differential diagnosis is within the broad category of small round blue cell tumors.

In order to characterize the neoplasm further, immunohistochemical study was performed. There is focal immunoreactivity for AE1/AE3, Cam 5.2, EMA, synaptophysin (rare cells), chromogranin (rare cells) desmin, SMA (rare cells). More diffuse staining for CD56 and TLE1 (nuclear). There is only weak patchy staining for CD99 and FLI1. Myogenin, ERG, CD45 are all negative. INI1 and BRG1 are retained. WT1 (N-terminus) shows focal perinuclear dot-like staining (antibody for C-terminus was not performed). The possibility of *CIC*-rearranged sarcoma and poorly differentiated synovial sarcoma were considered, and accordingly molecular studies were performed. Multiplex FISH studies gave NEGATIVE result for rearrangement of the *CIC* (19q13.2) locus and for rearrangement of the *SS18* (18q11.2) locus and POSITIVE for rearrangement of the *EWSR1* (22q12) locus.

As we know *EWSR1* rearrangement can occur not only in Ewing sarcomas but in many tumor types (1). In view of this result additional molecular studies with the aim of finding a possible fusion partner were performed. The result: POSITIVE for fusion of the *EWSR1* (22q12) and *WT1 (*11p13) loci.

Diagnosis: Paratesticular "desmoplastic" small round cell tumor (DSRCT).

Comments: DSRCT is an aggressive round cell sarcoma that arises in the abdominal cavity/pelvis of young males. The diagnosis of desmoplastic small round cell tumor with the typical morphology and IHC profile in the appropriate clinical context is relatively easy for a trained pathologist. However, in the submitted case, especially the lack of significant desmoplasia together with the paratesticular location did not originally prompt the diagnosis. The tumor was extensively sampled for histology and two out of the 10 blocks did show focal desmoplasia. Further imaging revealed retroperitoneal lymphadenopathy and abdominal as well as liver metastases.

Paratesticular DSRCT is rare with only 20 such cases reported (2). Paratesticular DSRCT can present with an isolated mass or with metastatic disease. Of the 20 reported cases, 12 had localized disease. Isolated paratesticular DSCRT have better outcome than the classic abdominal or pelvic location.

DSRCT have been reported a wide range of "atypical" anatomic locations like major salivary glands, intracranial, sinonasal, orbital, thoracic, braxial plexus, intraosseous, uterine corpus, ovary and paratesticular. They have also been described in older patients and with histology different than the classic type (3).

References:

1. Thway K, Fisher C. Mesenchymal tumors with *EWSR1* gene rearrangements. Surgical Pathology 2019; 12:165-190

2. Sedig L et al. Pediatr Blood Cancer 2017; 64:e26631

3. Al-Ibraheemi A et al. Desmoplastic small round cell tumors with atypical presentations: a report of 34 cases. Int J Surg Pathol 2019; 27:236-243

AMR Seminar #76

Case – 14

Contributed by: Brandon Larsen, M.D., Ph.D.

Clinical History: A 63-year-old man presented with increasing shortness of breath and respiratory failure, eventually requiring hospital admission. He was a previous cigarette smoker but quit in 2010. Imaging studies showed bilateral airway-centered ground glass opacities with focal consolidation, worse in the upper lobes. Radiologically, the possibility of hypersensitivity pneumonitis was raised, although infections and other acute lung injury processes were also in the radiologic differential dx. An extensive infectious disease workup was negative, and all of the cultures were negative. After repeated questioning, the patient remained highly evasive when asked about any personal history of "vaping" but behaved "in a very suspicious manner" according to the pulmonologist. The patient also admitted that many people at his work were vapers, and the pulmonologist strongly suspected vaping as the cause of his respiratory symptoms. Surgical wedge biopsies were obtained from multiple lobes.

Pathology: The sections show a nonspecific but exquisitely airway-centered micronodular pattern of organizing pneumonia with patchy residual intraalveolar fibrin (better seen on some slides than others), accompanied by chronic bronchiolitis, mild chronic inflammatory infiltrates, and accumulation of pigmented and finely vacuolated "foamy" macrophages in peribronchiolar airspaces. GMS and AFB stains were negative.

Diagnosis: Changes consistent with so-called "E-cigarette or Vaping product use-associated Acute Lung Injury" (the term coined by the CDC in the United States for this problem, often abbreviated in the literature as EVALI).

Comments: For many of the more tumor-oriented pathologists in the group, a non-neoplastic lung case may be less exciting, but I chose to include this in the current set of AMR cases to familiarize the group with an important public health problem that has received a lot of global attention in recent months. For those who sign out lung pathology, perhaps you'll find this more interesting…

EVALI is a recently recognized problem with a surge of cases occurring in the United States in the summer and fall of 2019, but also with scattered case reports from other countries. This problem has received significant attention, driven by the skyrocketing popularity of vaping, particularly among adolescents and young adults. To date, more than 2000 cases of EVALI have been reported in the United States with over 50 fatalities. Most cases have been associated with vaping of products containing THC, cannabidiol, or other cannabis derivatives and most cases have been reported in young men, but EVALI can occur across a wide age range and in women, too. The etiology of this problem remains elusive, but a growing body of evidence points to contamination of vape juices with vitamin E acetate in most cases.

Our group recently published a series of 17 cases of EVALI, detailing the pathologic features. This was followed shortly thereafter by a second series of cases reported by Sanjay Mukhopadhyay and colleagues at the Cleveland Clinic, who observed virtually identical findings in their cases. In general, the pathologic changes in EVALI are nonspecific and include various patterns of acute lung injury including diffuse alveolar damage, acute fibrinous pneumonitis / acute fibrinous and organizing pneumonia (AFOP) and organizing pneumonia. Not surprisingly, the majority of cases show injury that is accentuated around small airways and accompanied by bronchiolitis. A virtually universal finding is the presence of foamy macrophages and vacuolated pneumocytes, often but not always accompanied by lightly pigmented macrophages similar to those seen in cigarette smokers. Neutrophils can be prominent in up to half of cases, but eosinophils are uncommon. Granulomas have not been reported.

In early reports detailing the clinical and imaging findings in EVALI, much attention was given to the observation that oil red O-positive macrophages are almost universally present in BAL fluid in patients with EVALI, and it was hypothesized that EVALI could represent a form of "lipoid pneumonia" based on this indirect finding in BAL fluid. However, no histologic evidence of exogenous lipoid pneumonia has been identified in any cases of EVALI to date. Instead, the histopathologic changes seem to suggest an airway-centered chemical pneumonitis as the underlying mechanism of EVALI, rather than simple lipid accumulation, although inhaled vitamin E acetate, a toxic byproduct

from heating vitamin E acetate, or some other lipid compound could certainly be playing a role as a toxic chemical irritant. Surgical pathologists and cytopathologists have long known that lipid-laden macrophages in BAL fluid are nonspecific and can be seen in a variety of disorders causing acute lung injury. Despite initial enthusiasm for oil red O stains as a potential diagnostic test for EVALI, we and others believe these stains should not be relied upon to diagnose EVALI or to distinguish it from other causes of acute lung injury.

Ultimately, the pathologic changes in EVALI are nonspecific and the diagnosis requires clinicopathologic correlation after ruling out other causes of acute lung injury (e.g. infection, other drug reactions, and autoimmune disorders). However, there is still an important role for pathology in this diagnosis. The pathologist should consider the possibility of EVALI when an airway-centered acute lung injury process is seen with prominent foamy and/or pigmented macrophages. A former history of smoking can be an important clue in some cases (vaping is often used as a method for smoking cessation). Pathologists may be the first to suggest the possibility of EVALI, especially when the patient is reluctant to admit to a history of vaping, particularly when THC-containing products were used. We have seen several cases in our consultation practice where the patient only admitted to vaping after we suggested the possibility of EVALI to the clinician, based on the suggestive pathologic findings, and the clinician inquired again about vaping in a more directed manner once the pathology was known. It would be interesting to know if anyone else in the AMR group has had a similar experience…

References:

1. Butt YM, Smith ML, Tazelaar HD, Vaszar LT, Swanson KL, Cecchini MJ, Boland JM, Bois MC, Boyum JH, Froemming AT, Khoor A, Mira-Avendano I, Patel A, Larsen BT. Pathology of Vaping-Associated Lung Injury. N Engl J Med. 2019 Oct 31;381(18):1780-1781. PMID: 31577870.4.
2. Mukhopadhyay S, Mehrad M, Dammert P, Arrossi AV, Sarda R, Brenner DS, Maldonado F, Choi H, Ghobrial M. Lung Biopsy Findings in Severe Pulmonary Illness Associated With E-Cigarette Use (Vaping). Am J Clin Pathol. 2020 Jan 1;153(1):30-39.PMID: 31621873
3. Larsen BT, Butt YM, Smith ML. More on the Pathology of Vaping-Associated Lung Injury. Reply. N Engl J Med. 2019 Nov 20. [Epub ahead of print] PMID: 31747508.

AMR Seminar #76

Case – 15

Contributed by: Thomas Mentzel, M.D.

Clinical History: A 5-month-old baby boy presented with a large subcutaneous lesion arising at the right thigh, that was marginally excised.

Pathological Findings: Grossly, a 5.5 x 5.0 x 2.2 cm measuring specimen covered by epidermis with a 5.0 cm nodular tumour with yellow-white cut surfaces extending to the margins was described. Histologically, we found an irregular association of mature lipogenic cells with bland spindled tumour cells containing an ill-defined, pal eosinophilic cytoplasm and elongated, bland, spindled nuclei. Small islands of smaller lipogenic cells containing enlarged nuclei (pseudolipoblasts) were present. No increase number of mitoses and no areas of tumour necrosis were found. Immunohistochemically, spindle-shaped tumour cells strained positively for alpha-smooth muscle actin, whereas CD34, S-100 protein, Sox10, NTRK1, desmin and h-caldesmon were all negative.

Diagnosis: Lipo(myo)fibromatosis.

Comments: Lipofibromatosis represents a rare pediatric neoplasm more frequently seen in male patients, that arises often at the hands or feet, the extremities and the head and neck region. These neoplasms may reach a considerable size and have a high rate of local recurrences (in some cases, probably because of incomplete excision but have a no metastatic potential. The neoplasms contain abundant mature adipose tissue without nuclear atypia and an irregularly associated proliferation of bland spindled fibroblastic cells forming delicate trabeculae and fascicles. In newborn patient's immature fat lobules with a myxoid stroma may be present and usually small collections of pseudolipoblasts with enlarged and scalloped nuclei are seen. Rarely, pigmented melanocytic cells have been seen in the fibroblastic spindle-cell component. The spindled tumour cells show a variable expression of alpha-smooth muscle actin and CD34, whereas S-100 protein, Sox10, b-catenin, desmin and cytokeratins are usually negative. In addition to a three-way t(4;9;6) (q21;q22,q24) translocation in a 5-year-old boy a number of fusion genes encoding receptor tyrosine kinases with FN1-EGF being the most frequent one have been reported. Interestingly, the same fusion gene has been found in calcifying aponeurotic fibroma and hybrid-cases showing morphological features of liprofibromatosis-like component may suggest a relationship of these pediatric lesions as well. The differential diagnosis also includes fibroblastic connective tissue naevus (usually less cellular, usually more superficial, no pseudolipoblasts), lipofibromatosis-like neural tumour (homogeneous coexpression of S-100, CD34, NTRK1) and dermatofibrosarcoma protuberans (CD34 positive, characteristic genetic changes).

References:

1. Alyaa Al-Ibraheemi et al. Aberrant receptor tyrosine kinase signaling in lipofibromatosis: A clinicopathological and molecular analysis of 20 cases. Mod Pathol 2019 PMID: 30310176
2. Ayadi L et al. Pigmented lipofibromatosis in unusual location: case report and review of the literature. Virchows Arch 2008 PMID 18066591
3. Fetsch JF et al. A clinicopathologic study of 45 pediatric soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis. Am J Surg Pathol 2000 PMID: 11075850
4. Kenney B et al. Chromosomal rearrangements in lipofibromatosis. Cancer Genet Cytogenet 2007 PMID 18036401
5. Swiadkiewicz R et al. Congenital female fibrosarcoma associated with a lipofibromatosis-like component: one train may be hiding another. Am J Dermatopathol PMID 28525423
6. Thway K et al. B-catenin expression in pediatric fibroblastic and myofibroblastic lesions: a study of 120 cases. Pediatr Dev Pathol 2009 PMID 1893988

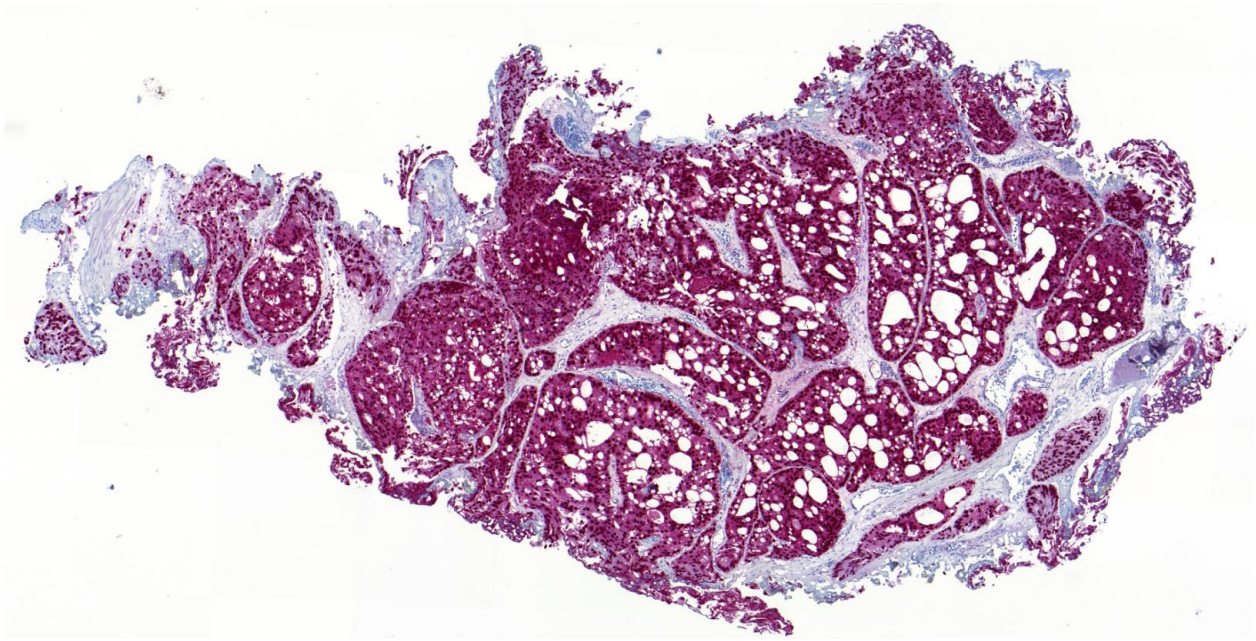
AMR Seminar #76

Case – 16

Contributed by: Michal Michal, M.D.

Clinical History: Female, 73-years-old, had a paraurethral tumor growing in a polypoid manner into urinary bladder. Immunohistochemically the tumor was Acid prostatic, PSA and NKX3.1 strongly positive.

PSA immunopositivity



On NGS (TruSight Tumor 170 Panel) we found clinically significant mutation in PTEN gene c.439_440delAA, p.(Lys147GlyfsTer32), and at the same time we found LOH in PTEN genu.

Diagnosis: Female adenocarcinoma from Skene glands (=female prostatic adenocarcinoma).

Comments: The female prostatic adenocarcinoma was defined and described by my late friend Dr. Zaviačič. Dr. Zaviačič was a Slovakian pathologist who dedicated his life to this "entity" (1,2). We lately saw prostatic differentiation on various sites of the female genital tract (3). He wrote a very nice book on Skene gland adenocarcinomas, which you can see, the pdf file of the book can be downloaded from our web page from the AMR seminar 76.

References:

1. M.Zaviačič, J.Šídlo, M.Borovský. Prostate specific antigen and prostate specific acid phosphatase in adenocarcinoma of Skenes paraurethral glands and ducts. Virchows Archive 1993;423:503-505
2. J.Sloboda, M.Zaviačič, J.Jakubovský, E.Hammar, J.Johnsen. Metastasizing adenocarcinoma of the female prostate (Skene's paraurethral glands). Pathology Research Practice 1998;194:129-136

3. D.V.Kazakov, C.J.R.Stewart, D.Kacerovská, R.Leake, B.Kreuzberg, Z.Chudáček, M.Hora, M.Michal. Prostatic-type tissue in the lower female genital tract: a morphologic spectrum, including vaginal tubulosquamous polyp, adenomyomatous hyperplasia of paraurethral skene glands (female prostate), and ectopic lesion in the vulva. America Journal of Surgical Pathology 2010;10:950-955

AMR Seminar #76

Case – 17

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

Clinical History: A 60-year-old male with history of fast-growing prostate tumor treated with radical prostatectomy and apparently no other treatments. The case was sent to our hospital for a second opinion.

Pathology Findings: We received 13 slides and paraffin blocks. The neoplasm shows a heterogenous surface. We can recognize acinar component with cribiform pattern with transition to solid areas with epithelioid cells, atypical mitosis and focal necrosis. Other areas showed fusiform atypical cells in transition to chondroid areas with atypia and areas with rhabdoid cells. Immunostains were positive to PSA in acinar component, epithelioid areas were negative to PSA and focally positive to CK18, fusiform and chondroid areas were negative to PSA and CK18.

Diagnosis: Prostate carcinosarcoma.

Comments: This case is not difficult to diagnose, but is unusual, that is the reason why I want share with you. Approximately 2/3 of cases have history of radiotherapy or hormonal treatment; many of the patients have normal or elevated PSA serum levels and obstructive urinary symptoms.

There are 3 different categories for these tumors: Carcinoma admixed with sarcomatoid spindle cell component (which is the most common), carcinoma admixed with sarcomatous component with heterologous elements (as our case) and monophasic spindle cell tumor with ancillary evidence of epithelial differentiation (By immunohistochemistry or electron microscopy).

While high grade acinar carcinoma is the most frequent epithelial component, other carcinomas as ductal, adenosquamous, small cell, basaloid and urothelial carcinoma as well as polygonal cells component in transition to spindle cells have been described.

The most frequent mesenchymal component is a hypercellular fusiform component without specific lineage of differentiation, however, a myxoid, giant cell and pleomorphic areas have been described. Heterologous elements as osteosarcoma, chondrosarcoma, leiomyosarcoma, rhabdomyosarcoma and angiosarcoma have been described in relation to spindle cell component. Immunostains reactions are positive depending on the component, so we have, that acinar component is positive for acinar markers (KKX3.1 etc). Sarcomatoid spindle cell component is focally positive for epithelial markers and heterologous component are negative for epithelial markers and positive to actin, desmin etc.

Recently, Salvi el al found a distinct molecular pattern between prostate adenocarcinoma and carcinosarcoma, which was characterized by high AR copy number variation gain; positive expression of PD-L1, AR, and phosphorylated AR; low expression of GSTP1 in the epithelial component. The sarcomatoid component had a lower gain of the AR gene, and no expression of PD-L1, AR, phosphorylated AR, or GSTP1. Both components had a gain of c-MYC copy number variation; suggesting that carcinosarcoma has specific molecular characteristics that could be indicative for early diagnosis and treatment selection.

References:

Hansel DE, Epstein JI. Sarcomatoid carcinoma of the prostate: a study of 42 cases. Am J Surg Pathol. 2006;30:1316-21.

Salvi S et al. Carcinosarcoma of the prostate: case report with molecular and histological characterization. Int J Biol Markers. 2018;33:540-544.

Amin MB, Tickoo SK. Prostate gland and seminal Vesicle. Diagnostic Pathology Genitourinary. Second edition. 2016 Elseviere Inc.

AMR Seminar #76

Case – 18

Contributed by: Cesar Moran, M.D.

Clinical History: 12-year-old child presented with symptoms of cough and dyspnea. Diagnostic Imaging was performed and interpreted as a possible "pulmonary sequestration."

Diagnosis: Low Grade Mucoepidermoid Carcinoma (MEC).

Comments: MEC is not an unusual tumor in the pediatric age group.

AMR Seminar #76

Case – 19

Contributed by: Brian Rubin, M.D.

Clinical History: 38-year-old man with a left distal mainstem endobronchial mass clinically concerning for a malignant neoplasm or carcinoid.

Gross Pathology: The gross specimen consisted of a 2.1 cm in greatest dimension gray-yellow, gelatinous-appearing nodule. On cross section the lesion had a gray-yellow, gelatinous cut surface with a peripheral, firm yellow area.

Histology: The lesion is surrounded by unremarkable endobronchial mucosa and there is entrapment of bronchial glands. The lesion is composed of an admixture of well-differentiated adipose tissue and low-grade appearing spindle cells with prominent myxoid stroma and fine capillary-type blood vessels. Some of the adipocytic cells are similar to the univacuolated and bivacuoloated adipocytic cells associated with myxoid liposarcoma. The spindle cells have enlarged nuclei and one or more cytoplasmic processes. I did not see any mitotic activity. There are numerous admixed mast cells.

Immunohistochemistry: For what it's worth, lesional spindle cells were uniformly positive for CD34.

Molecular Diagnostics: HMGA2-LPP gene fusion demonstrated by next generation sequencing/modified Archer gene fusion panel.

Diagnosis: Endobronchial lipoma mimicking myxoid liposarcoma.

Comments: I've never seen a lipomatous lesion of the endobronchial region before and I found this case to be very difficult. I originally had a differential diagnosis of pulmonary hamartoma and lipomatous neoplasm, but I thought pulmonary hamartoma was very unlikely based on the lack of a cartilaginous component and the presence of fat. Once I narrowed it down to lipomatous neoplasm I was concerned that it could be an unusual myxoid liposarcoma, presenting as a primary pulmonary lesion or a metastasis from an occult primary. I've seen myxoid liposarcoma present as a metastasis of an occult primary before and myxoid liposarcoma likes to metastasize to unusual sites, especially skin, soft tissue, and bone, so I am always cautious when I seem something that is reminiscent of myxoid liposarcoma in an unusual site. Because of the possibility of the differential diagnosis of mxyoid liposarcoma versus other lipomatous neoplasm, I examined the lesion genetically using an expanded Archer Dx next-generation sequencing-based gene fusion assay, which revealed a *HMGA2-LPP* gene fusion, which excluded the diagnosis of myxoid liposarcoma (typically has a *FUS-DDIT3* gene fusion) and supported the classification as lipoma.

Lipomatous neoplasms of the bronchial tree are unbelievably rare. A brief jaunt through the literature revealed mostly case reports. However, I did find one study by distinguished alumni of the AMR slide club which discussed the clinicopathologic findings in 12 cases (1). The cases arose mostly in older men (91%). Most patients (80%) had a heavy smoking history which seems like a possible confounder since the smoking population is most likely to get a chest x-ray. In fact, three patients had concurrent pulmonary squamous cell carcinoma and one had a history of multiple lung cancers. Most lesions were small (< 2.5 cm) and discovered incidentally. A subset of the tumors showed atypical histological features such as spindle cells and myxoid stroma. The case illustrated in Fig. 3 looks very similar to the case that I submitted for this seminar. All cases tested did not possess gene amplification of the *MDM2* gene region (as detected by a probe to *CPM*), which argues against a diagnosis of atypical lipomatous tumor/well-differentiated liposarcoma. Seven cases were tested for *HMGA1* and *HMGA2* gene region rearrangements. Four possessed *HMGA2* gene region rearrangements and one possessed a *HMGA1* gene region rearrangement, supportive of a diagnosis of lipoma. All cases with cytologic atypia behaved in a benign manner.

With regard to the genetics of the current case, *HMGA2* gene region rearrangements are very common in lipomas (2). *HMGA2-LPP* gene fusions results from a t(3;12) (q27-28:q14-15) translocation. In one study by Kubo et al. which

is based on RT-PCR, they found evidence that suggested that 19 of 98 lipomas (19%) harbored *HMGA2-LPP* gene fusions.

Follow-up: Very recent consult case.

Summary: Lipomatous tumors of the endobronchial region are extremely rare. The case reviewed here had a deceptively atypical appearance suggesting a possibly malignant lipomatous neoplasm such as myxoid liposarcoma. Fusion identification through a next generation sequencing-based platform identified an *HMGA2* gene fusion, typical of benign lipoma, clarifying the diagnosis in this very unusual case.

References:

1. Boland JM, Fritchie KJ, Erickson-Johnson MR, Oliveira AM, Colby TV, Folpe AL. Endobronchial lipomatous tumors. Clinicopathologic analysis of 12 cases with molecular cytogenetic evidence supporting classification as "lipoma". Am J Surg Pathol 2013;37:1715-1721.

2. Kubo T, Matsui Y, Naka N, Arak N, et al. Expression of *HMGA2-LPP* and *LPP-HMGA2* fusion genes in lipoma: identification of a novel type of *LPP-HMGA2* transcript in four cases. Anticancer research 2009;29:2357-2360.

AMR Seminar #76

Case – 20

Contributed by: Niels Rupp, M.D.

Clinical History: 38-years old female with chronic cough. Diagnostic workup revealed a large tumor in the right inferior lobe of the lung. Initial biopsy diagnosis was squamous cell carcinoma and lobectomy was performed.

Gross: The lobectomy specimen showed a partially endobronchial tumor of 6 cm size.

Pathological Findings: On histology, the neoplastic cells showed a rather monomorphic, basaloid aspect with extensive mature keratinization, keratin pearls and abundant keratin debris. Some slides may show very focal non-keratinizing squamous islands. Growth patterns encompassed solid and prominent cystic growth with comedonecrosis. Focal endobronchial extension could be observed, as well as venous invasion. No lymph node metastases were evident. Immunohistochemical staining revealed positivity for p40, whereas TTF-1 was negative. p16 showed a chessboard-like expression without convincing block-type positivity. NUT immunohistochemistry showed only partial, weak but distinctive speckled-type nuclear expression. Synaptophysin, chromogranin and CD34 were negative. Molecular testing was performed and revealed a *NSD3-NUT* fusion.

Diagnosis: NUT carcinoma with *NSD3-NUT* fusion.

Comments: This is the most unusual case of a NUT carcinoma I have seen so far. This tumor seems to be quite mature for this entity and the abundant mature keratin debris is rather uncommon, mimicking a basaloid squamous cell carcinoma. Furthermore, in the present case no metastases were present, an observation I have not encountered in this entity, yet. 18 months after resection, there is still no evidence for dissemination (!). The endobronchial growth could be one reason, leading to early symptoms and rapid diagnosis. Any previous NUT case I have seen in my practice so far was metastasized on primary diagnosis. Another interesting thing is, that the presentation with a partially endobronchial growth is similar to a previously described case harboring a similar *NSD3-NUT* fusion [1]. An additional case report communicated a *NSD3-NUT* fusion positive lung carcinoma, however with more classical morphology, metastases and progressive disease [2]. A larger case series found two *NSD3-NUT* rearranged cases out of 24 NUT-rearranged neoplasia, again with similar classical morphology and reported metastases in one case [3]. NSD3 is a histone methyltransferase, which has been shown to interact with bromodomain-containing protein 4 (BRD4) [4]. The *NSD3-NUT* fusion was comprehensively studied by French et al. and has been shown to support the development and maintenance of NUT carcinomas [5]. Interestingly, a binding of the NSD3-NUT fusion product to BRD4 (the typical NUT-fusion partner in "more common" NUT variants) could be demonstrated. This is important, as there is a rationale to potentially include patients with this less common *NSD3-NUT* fusion positive tumors into ongoing bromodomain inhibitor studies (e.g. NCT02516553). At least in my personal observation, classical NUT carcinoma is extraordinarily resistant against conventional chemotherapy. I can only speculate on the present case, but maybe there are other genomic or epigenetic changes leading to this more mature phenotype and apparently less aggressive biological behavior.

References:

1. Harms A, Herpel E, Pfarr N, et al (2015) NUT carcinoma of the thorax: Case report and review of the literature. Lung Cancer 90:484–491. https://doi.org/10.1016/j.lungcan.2015.10.001

2. Suzuki S, Kurabe N, Ohnishi I, et al (2015) NSD3-NUT-expressing midline carcinoma of the lung: First characterization of primary cancer tissue. Pathology - Research and Practice 211:404–408. https://doi.org/10.1016/j.prp.2014.10.013

3. Stevens TM, Morlote D, Xiu J, et al (2019) NUTM1-rearranged neoplasia: a multi-institution experience yields novel fusion partners and expands the histologic spectrum. Mod Pathol 32:764–773. https://doi.org/10.1038/s41379-019-0206-z

4. Rahman S, Sowa ME, Ottinger M, et al (2011) The Brd4 Extraterminal Domain Confers Transcription Activation Independent of pTEFb by Recruiting Multiple Proteins, Including NSD3. Molecular and Cellular Biology 31:2641–2652. https://doi.org/10.1128/MCB.01341-10

5. French CA, Rahman S, Walsh EM, et al (2014) NSD3-NUT Fusion Oncoprotein in NUT Midline Carcinoma: Implications for a Novel Oncogenic Mechanism. Cancer Discovery 4:928–941. https://doi.org/10.1158/2159-8290.CD-14-0014

AMR Seminar #76

Case – 21

Contributed by: **Paul E. Wakely, Jr.**

Clinical History: A 62-year-old man presented with a lytic lesion in his left tibia. Plain X-ray showed a well-defined lucency in the anterior aspect of the proximal tibia measuring approximately 1.4 x 2.6 cm. No pathologic fracture or other osseous lesions were identified. He underwent curettage and bone grafting and has had no recurrence on follow-up more than 10 years later.

Pathologic Findings: Multiple tan-pink fragments measuring 2.8 x 1.8 x 0.8 cm. in aggregate were submitted for microscopic examination. Low power exam shows irregularly contoured lobulated foci having a slightly chondroid, but more myxoid appearing matrix dispersed in hypercellular mesenchymal tissue. Uniformly-sized cells are primarily tapered and stellate or slightly spindled. Nuclear borders are slightly irregular, rounded, or ovoid with evenly dispersed chromatin, and lacking enlarged nucleoli. Nuclear anaplasia and background necrosis are absent; few mitoses are apparent. Only S-100 staining was performed, and it was weakly positive.

Diagnosis: Chondromyxoid fibroma [CMF], tibia.

Comments: Since I don't believe the club has had a case of CMF, I thought to submit this pretty straightforward example. CMF accounts for <1% of bone tumors, generally presenting in the metaphysis of long bones, particularly on both sides of the knee. At age 62 years, this patient is at the end of the bell curve, since most cases arise in the 2nd to 3rd decades of life. CMF can affect multiple bony sites including the head and neck and pelvis. It exhibits a combination of chondroid, myxoid, and fibrous components organized in a pseudolobulated fashion. It may contain atypical cells suggesting malignancy, and giant cells particularly at the periphery of these lobules. In some cases, anaplastic cells with enlarged hyperchromic nuclei are also present raising the possibility of a sarcoma. However, it has never been reported to transform into a high-grade tumor or to metastasize. Radiographically, they appear benign with well-defined borders on plain X-ray. This case had no anaplasia, and also did not contain any giant cells.

Unlike conventional chondrosarcoma, CMF lacks well-formed hyaline cartilage type matrix, and lacunae formation is absent. Chondroblastoma is another potential consideration in the differential diagnosis of CMF, but those tumors typically possess rounded, not stellate cells with visible cell borders; delicate lace-like calcification is sometimes present. Also, the H3F3 K36M mutant monoclonal antibody is highly specific for chondroblastoma. Unlike giant cell tumor of bone, chondroblastoma lacks H3G34W expression, but the mutation-specific H3K36M antibody shows nuclear expression in 96% of chondroblastomas by immunohistochemistry.

CMF can show weak positivity for S-100 as was seen in this case. However, immunohistochemistry, like electron microscopy, plays little to no role in the diagnostic recognition of this neoplasm which is largely an H&E/radiologic correlation diagnosis. A study of 25 head and neck CMFs by Meredith et al. showed all tumors to be negative for keratin and GFAP (0/24), positive for SMA (7/7) and only occasional staining for EMA (5/24) and S-100 (2/24).

Previous reports show chromosomal rearrangement of 6q24, where glutamate receptor gene *GRM1* is located. Whole genome mate-pair sequencing and RNA sequencing has demonstrated that the recombination of the *GRM1* gene with several partner genes representing strong promoters, is responsible for the high expression of GRM1 in 90% of cases. An antibody to this is not available for diagnostic purposes.

References:

• Romeo S, Aigner T, Bridge JA. Chondromyxoid fibroma. In: Fletcher CDM, Bridge JA, Hogendoorn PC, eds. WHO Classification of Tumours of Soft Tissue and Bone. Lyon, France: IARC Press; 2013:255-256.

• Romeo S, Duim RA, Bridge JA, et al. Heterogeneous and complex rearrangements of chromosome arm 6q in chondromyxoid fibroma: delineation of breakpoints and analysis of candidate target genes. Am J Pathol. 2010;177(3):1365-1376.

• Nord KH, Lilljebjorn H, Vezzi F, et al. GRM1 is upregulated through gene fusion and promoter swapping in chondromyxoid fibroma. Nat Genet. 2014;46(5):474-477.

• Meredith DM, Fletcher CDM, Jo VY. Chondromyxoid fibroma arising in craniofacial sites: a clinicopathologic Analysis of 25 Cases. Am J Surg Pathol. 2018;42:392-400.

• Baumhoer D, Amary F, Flanagan AM.An update of molecular pathology of bone tumors. Lessons learned from investigating samples by next generation sequencing. Genes Chromosomes Cancer. 2019;58:88-99.

• Amary MF, Berisha F, Mozela R, et al. The H3F3 K36M mutant antibody is a sensitive and specific marker for the diagnosis of chondroblastoma. Histopathology. 2016;69:121-127.