

Rush University Medical Center
Department of Pathology



Illinois Registry of Anatomic Pathology
November 18, 2013

Case # 1

Presenter: Lin Cheng, M.D. Ph.D.

Attending: Shriram Jakate, M.D.

Diagnosis: Adenoid Cystic Carcinoma Metastatic to Colon

Differential Diagnosis:

- Carcinoid tumor of colon

Key Features of Adenoid Cystic Carcinoma:

- Clinical features:
 - Indolent tumor with slow growth
 - Local recurrence
 - Late distant metastasis: involving lung, liver, bone, and soft tissue
- Morphological features:
 - Epithelial-myoeplithelial dual lineage
 - Cribriform, tubular, or solid growth pattern
 - Minimal cytological atypia
 - Rare mitotic figures
- Immunophenotypic features:
 - Epithelial cells: positive for CK AE1/AE3, CD117, and CEAp
 - Myoeplithelial cells: positive for SMA and P63
- Genetics:
 - Cytogenetics:
 - Aneuploidy correlates with worse prognosis
 - Deletion of 1p32-36
 - Translocation t(6;9) results in MYB-NFIB fusion protein
 - Molecular studies:
 - C-kit overexpression/mutations
 - EGFR/VEGFR overexpression
 - SOX4 transcription factor overexpression

Discussion:

Primary adenoid cystic carcinoma can be seen in salivary glands, lung, breast, and cervix. The tumor has epithelial-myoeplithelial dual lineages with distinct immunophenotypes, and a lengthy clinical course with slow growth and late distant metastasis. Here we present a case of such tumor metastatic to colon 19 years after resection of the primary tumor. Metastasis to colon has not been previously reported in English literature.

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Case # 2

Presenter: Lauren Rosen, MD

Attending: Pincas Bitterman, MD

Diagnosis: Mesonephric Adenocarcinoma

Important Differential Diagnosis of Mesonephric Adenocarcinoma:

- Mesonephric Hyperplasia
- Adenoid Basal Carcinoma
- Adenoid Cystic Carcinoma
- Minimal Deviation Adenocarcinoma

Key Morphological, Clinical and Histological Features:

Mesonephric adenocarcinoma is a rare cervical neoplasm derived from mesonephric rests, with fewer than 40 cases reported in the literature. Patients range in age from 34-78 years with a mean age of 52 years at diagnosis. The majority (70%) of patients present with abnormal uterine bleeding. On gross examination, the cervix shows either an endophytic lesion involving the lateral wall or an exophytic mass. Clement et al in 1995 described five morphologic patterns of mesonephric adenocarcinoma including tubular, ductal, retiform, solid, and sex cord like. Most tumors show an admixture of patterns with tubular and ductal being the most common. Carcinomas with tubular, ductal and solid patterns are associated with dense eosinophilic intraluminal secretions. Histologically, mesonephric adenocarcinoma is characterized by an infiltrative growth pattern with an inconspicuous stromal response, necrosis, prominent perineural invasion, and adjacent mesonephric hyperplasia. The tumor cells are hyperchromatic with coarse nuclear chromatin and occasional small solitary nucleoli with an elevated mitotic index. Due to the rare nature of this tumor, the immunohistochemical profile has yet to be established. The majority of mesonephric adenocarcinomas are positive for cytokeratin AE1/AE3, CAM 5.2, EMA, CK7, CA125, PAX8, vimentin; and negative for monoclonal CEA, ER, PR, CK20, and WT-1. Mesonephric adenocarcinomas are treated with total abdominal hysterectomy and salpingo-oophorectomy with or without pelvic lymph node dissection. Patients with extracervical extension or metastases are often treated with chemotherapy and/or radiation. The majority of patients are diagnosed with low stage disease, which behaves more indolently than conventional low stage endocervical adenocarcinomas. High stage tumors carry an increased risk of recurrence and metastases.

Discussion:

Gross examination of the total hysterectomy specimen revealed a tan-white firm mass replacing the cervix and involving the lower uterine segment. The maximum thickness of the cervix measured 2.2 cm. Histologically, the lesion showed a varied morphology composed of infiltrative tubules and admixed small and large nests of cells with an inconspicuous stromal response. The tubules were composed of bland cuboidal cells. The small nests of cells showed glandular differentiation and were composed of cells with a high N:C ratio, open to vesicular chromatin, small nucleoli, and mild pleomorphism. The large nests of cells were composed of similar cells arranged in cords and clusters separated by eosinophilic hyaline material. Mitotic figures were easily identified. The large nests of cells show focal glandular differentiation, with intraluminal eosinophilic secretions. In other areas, the lesion showed prominent necrosis. Perineural invasion was marked. Immunohistochemically, the tumor was positive for HMWK, cytokeratin AE1/AE3, CD10, P16, P63; focally positive for CD117, SMA, and S100 and showed luminal positivity for vimentin. The intraluminal material was positive with PAS and PAS-D.

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The tumor was negative for synaptophysin, chromogranin, CK7, CK20, calretinin, monoclonal CEA, ER, and PR.

Our differential diagnosis for this lesion included mesonephric hyperplasia, adenoid basal carcinoma, adenoid cystic carcinoma, and minimal deviation adenocarcinoma. Mesonephric hyperplasia is typically an incidental finding. It is characterized by a localized or diffuse increase in the number of mesonephric tubules or increase in lobular size, and involves the deep lateral cervical wall. The tubules are lined by cuboidal cells and contain eosinophilic secretions. In contrast to mesonephric adenocarcinoma, mesonephric hyperplasia shows a simple tubular architecture, lacks cytologic atypia, has <1/10 mitosis per hpf, and displays no lymph-vascular invasion or necrosis.

Adenoid basal carcinoma is a rare cervical neoplasm that occurs predominately in elderly African American females. Patients are often asymptomatic and the cervix is grossly unremarkable. Microscopically, the tumor is composed of nests and cords of small uniform basaloid cells with peripheral palisading. The nests may show glandular differentiation, but characteristically lack eosinophilic secretions. The prognosis is favorable as the majority of tumors are benign and cured with hysterectomy. Unlike adenoid basal carcinoma, mesonephric adenocarcinoma shows cytologic atypia, has a varied architecture with a predominant tubular pattern and shows glandular differentiation with intraluminal eosinophilic material. Additionally, mesonephric adenocarcinoma is commonly associated with adjacent mesonephric hyperplasia and patients are generally symptomatic with abnormal uterine bleeding.

Adenoid cystic carcinoma is a rare cervical neoplasm that occurs predominately in elderly African American females. Microscopically, adenoid cystic carcinoma is characterized by nests of basaloid cells with a cribriform appearance due to punched out spaces filled with basement membrane material. Mitoses and necrosis are common. Unlike adenoid cystic carcinomas of other sites, those involving the cervix lack myoepithelial cells and are typically cytokeratin positive, focally CEA and EMA positive, and are negative for SMA and S100. The prognosis is poor due to late visceral metastases. In contrast to adenoid cystic carcinoma, mesonephric adenocarcinoma shows a varied architecture with a predominant tubular pattern. Tubules and solid nests of cells show true glandular differentiation with intraluminal eosinophilic material, and adjacent mesonephric hyperplasia is commonly present. Additionally, mesonephric adenocarcinoma is negative for mCEA.

Minimal deviation adenocarcinoma is a rare well-differentiated cervical neoplasm, occurring in women between the ages of 25-72 with a mean age at diagnosis of 42. Microscopically, minimal deviation adenocarcinoma is composed of cytologically bland to dysplastic glands with irregular contours and a haphazard pattern of infiltration that are positioned deeper in the myometrium than the lower level of normal endocervical glands. The tumor is typically positive for CEA and negative for ER, PR and P16. Unlike minimal deviation adenocarcinoma, mesonephric adenocarcinoma shows a varied morphology with predominant tubules and ducts and adjacent mesonephric hyperplasia. Additionally, mesonephric adenocarcinoma is typically negative for CEA, ER, PR and variably positive for P16.

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Case # 3

Presenter: Matthew Fox, MD

Attending: Larry Kluskens, MD, PhD

Diagnosis: Aortic Aneurysm, Loeys Dietz Syndrome

Important Differential Diagnosis of Aortic Dissection:

- Idiopathic aortic aneurysm
- Marfan's Syndrome
- Ehlers Danlos Syndrome
- Familial Thoracic Aortic Aneurysm and Dissection, and variants

Key Features:

Mutations in the TGF- β receptor pathway are associated with connective tissue disorders, leading to sequela including aortic aneurysms.

Discussion: Environmental and genetic conditions contribute to the development of aortic aneurysms. Environmental conditions risk factors include hypertension, smoking, severe exercise (power lifting), pregnancy, cocaine, trauma, oral contraceptives (under investigation / controversial), infectious diseases (under investigation / controversial).

Genetic conditions are classified as syndromic or non-syndromic.

Syndromes include:

- Marfan's syndrome
- Ehlers Danlos (vascular type) syndrome
- Loeys Dietz syndrome

Non-syndromic:

- Familial thoracic aneurysms and dissections and their variants

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Case #4

Presenter: Jamie Macagba Slade, M.D.

Attending: David Cimbaluk, M.D.

Diagnosis: LECT2 Amyloidosis

Important Differential Diagnoses of LECT2 Amyloidosis:

By light microscopy, the differential diagnosis includes any process that results in an accumulation of eosinophilic material in the interstitium, glomeruli, and/or vessels.

Accumulations of collagenous matrix, as in diabetic glomerulosclerosis or sclerosis secondary to glomerulonephritis, can be distinguished from amyloid by the Congo red stain. In addition, massive glomerular deposits of immune complex glomerular diseases, fibrillary glomerulonephritis, immunotactoid glomerulopathy, fibronectin glomerulopathy, and collagenofibrotic glomerulopathy also may mimic amyloidosis on H&E stained sections, but special stains, fluorescence microscopy, and electron microscopy demonstrate the distinctive features of each of these diseases. Of course, Congo red staining is always an option to confirm a diagnosis of amyloidosis.

Key Features of LECT2 Amyloidosis:

- Clinical features:
 - Ethnic predominance in Hispanic population
 - Presents in slightly older age compared to other amyloid subtypes
 - Variable degrees of impaired kidney function and proteinuria
 - Localizes to the kidney, but may be systemic

- Pathologic features:
 - Prominent congophilia
 - Characterized by a predominantly interstitial deposition with or without mesangial and vascular involvement
 - Greater degree of tubular atrophy and interstitial fibrosis than other subtypes

Discussion:

LECT2 Amyloidosis is a newly described and distinctive clinicopathologic subtype of amyloidosis first reported in 2008. LECT2 amyloidosis is derived from LECT2 (leukocyte chemotactic factor 2), a multifunctional factor involved in chemotaxis, inflammation, immunomodulation, and the damage/repair process. Recent case studies show that LECT2 amyloidosis is the third most common type of renal amyloidosis. There is an ethnic predominance in the Hispanic population. Patients present at a slightly older age (mean age = 68) compared to other amyloid subtypes (mean age = 63). This new subtype of amyloidosis is usually unsuspected clinically, due to the lack of paraproteinemia, lack of family history of amyloidosis, rarity of extrarenal involvement, and variable degree of proteinuria. It seemingly targets the kidney, however not enough is known yet about LECT2 amyloidosis to determine systemic involvement. The distribution of LECT2 within the kidney is characterized by strong congophilic deposits with a predominantly interstitial deposition with or without mesangial infiltration and vascular involvement. No mutations in the LECT2 gene have been identified but most patients with LECT2 amyloidosis have been found to be homozygous for the G allele. The pathogenesis and prognosis of LECT2 amyloidosis remain to be determined.

References:

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Case #5

Presenter: Sahr Syed, MBBS

Attending: Ritu Ghai, MD

Diagnosis: Mammary Analog Secretory Carcinoma (MASC)

Important Differential Diagnosis:

- Acinic cell carcinoma
- Low grade cribriform cystadenocarcinoma
- Low grade mucoepidermoid carcinoma
- Adenocarcinoma (NOS)

Key Morphological, Clinical and Histological Features:

Mammary analog secretory carcinoma (MASC) was first described by Skálová et al in 2010. This rare salivary gland neoplasm recapitulates the morphological, immunohistochemical and genetic features of secretory carcinoma of the breast, a rare malignancy that occurs mainly in young women. Furthermore, it also exhibits the same characteristic ETV6 gene rearrangement. Since its original description, more cases are being reported and a recent study by Sethi et al reviewed 92 cases of MASC described in the literature. This tumor presents over a wide age range with a peak incidence in the 40s and a slight male preponderance. The most common site of presentation is in the parotid gland however, lesions have also been described in the submandibular gland, soft palate, buccal mucosa, base of tongue and lips. It usually presents as a slow growing painless mass. Most cases are indolent however, there was a case described in the literature in which there was rapid growth of a tumor with regional and distant metastases which progressed and led to the patient's death. There have also been recent reports of lesions that underwent de-differentiation. Microscopically MASC is composed of microcystic/solid and tubular structures with abundant eosinophilic homogenous or bubbly secretory material. Less commonly, the tumors are dominated by one large cyst, with multi-layered lining, which can

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display tubular, follicular, macro- and microcystic or papillary architecture, with occasional solid areas. The cells display minimal pleomorphism, have abundant eosinophilic cytoplasm with round to oval vesicular nuclei with finely granular chromatin and distinctive central nucleoli. Mitotic figures are rare. The cells demonstrate strong positivity for CK 8/18, CKAE1/AE3, CAM 5.2, CK7, CK19, EMA, S100, vimentin, mammoglobin, STAT-5a and GCDFP (particularly in the secretions). The secretions are PAS positive-diastase resistant and mucicarmine positive. Myoepithelial markers are usually negative. The defining cytogenetic abnormality is the presence of the t(12;15)(p13;q25) ETV6-NTRK3 translocation. Although this translocation has been described in other tumors such as congenital fibrosarcoma, congenital mesoblastic nephroma and acute myeloid leukemia, it has not been described in other salivary gland neoplasms as yet.

Discussion:

On histological examination, there was a well-circumscribed mass with a dense fibrous capsule present in the parotid gland. There were a few foci of infiltration by the tumor cells into the capsule however there was no parenchymal invasion. The tumor was composed mainly of solid sheets of cells with few cystic areas. The solid areas of the tumor were composed of a homogenous population of cells with abundant eosinophilic vacuolated cytoplasm forming tubules and solid sheets with abundant intraluminal eosinophilic colloid like secretions. The cells themselves were low-grade with bland round to oval nuclei with vesicular fine chromatin. Mitoses were rare and no areas of necrosis are identified. However, there was perineural and intraneural invasion by tumor cells. The tumor cells were strongly positive for cytokeratin 8/18, S100, vimentin and mammoglobin. The tumor cells were negative for CD117 and SMMS while p63 was positive in rare cells. The luminal secretions were strongly positive for PAS and were diastase resistant and were also positive for mucicarmine.

Our differential diagnosis included Acinic cell carcinoma, Low grade cribriform cystadenocarcinoma, Low grade mucoepidermoid carcinoma and Adenocarcinoma (NOS). Acinic cell carcinoma is a malignant epithelial neoplasm of salivary glands in which at least some of the neoplastic cells demonstrate serous acinar cell differentiation with prominent PAS positive diastase resistant intracellular zymogen granules. The most common site affected is the parotid gland and there is a slight female preponderance with a wide age range described in affected patients (2-7th decade). Architectural patterns that have been described include solid/lobular, microcystic, papillary-cystic, and follicular growth patterns and the cytology includes clear cells, vacuolated cells, serous cells and intercalated duct cells. Morphologically our tumor cells were similar to intercalated duct cells however our tumor did not display the varied architectural patterns described for acinic cell carcinoma and there was a distinct lack of PAS positive/diastase resistant zymogen granules within the cytoplasm. A zymogen granule poor acinic cell carcinoma has been described in the literature however a recent report by Chiosea et al reclassified 4 of 5 such cases into MASC based on the presence of the ETV6-NTRK3 translocation.

Mucoepidermoid carcinoma is a malignant glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with columnar, clear cell and oncocytoid features.

They are usually multicystic with a solid component and the cystic spaces are lined by mucous cells with basaloid or cuboidal intermediate cells interspersed, and to a lesser degree, epidermoid cells. Mucous cells constitute less than 10% of the tumour and sialomucin content can be demonstrated by mucicarmine. More than 50% of MEC are characterized by a t(11;19) translocation which codes a CRTC1-MAML2 fusion protein. Although the intra-luminal secretions in our case were positive for mucicarmine and the tumor cells were positive for cytokeratin 8/18 similar to MEC, the lack of cytoplasmic mucin and distinct squamous and mucus cells and the p63 negativity excluded this from our differential. Also the strong S100 positivity seen in our case would have been distinctly unusual in MEC.

Low grade cribriform cystadenocarcinoma is usually unencapsulated, consisting of single or multiple cysts, accompanied by intra-ductal proliferation with cribriform, micropapillary and solid areas. The histologic appearance resembles atypical ductal hyperplasia or low grade intra-ductal carcinoma of the breast. These tumors demonstrate strong diffuse S100 positivity similar to our case but in LGCC myoepithelial markers highlight cells rimming the cystic spaces which was absent in our case.

Adenocarcinoma (NOS) is a malignant salivary gland tumor that exhibits ductal differentiation but lacks any of the histomorphologic features that characterize other salivary gland tumors. There is considerable variability in the architectural structure with small confluent nests or cords of tumor cells, or large discrete islands with intervening trabeculae of fibrous connective tissue, or even solid densely cellular sheets of cells. However Adenocarcinoma (NOS) is a diagnosis of exclusion and the distinct formation of tubules with abundant eosinophilic secretions, the characteristic immunoprofile and the presence of an ETV6-NTRK3 translocation helped to exclude this from our differential diagnosis.

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Case # 6

Presenter: Jon Gates, MD

Attending: Ira Miller, MD, PhD

Diagnosis: Low-Grade Central Osteosarcoma

Important Differential Diagnosis:

- Fibrous dysplasia
- Osteofibrous dysplasia
- Desmoplastic fibroma
- Parosteal osteosarcoma

Key Clinical Features:

- Peak incidence in 4th decade, 1 decade older than conventional osteosarcoma
- Pan with minimal if any palpable mass
- Usually at least focal destruction of the cortex on imaging

Key Histological Features: Medullary-based, bone forming tumor that infiltrates and expands the cortex. The tumor shows variable woven bone formation with some areas with extensive bone formation with long, parallel seams of branching trabeculae and other areas showing less densely packed trabeculae resembling Chinese characters. The lesion has low to moderate cellularity with ovoid cells with minimal atypia. Some of the woven bone trabeculae are lined by osteoblasts.

Key Genetic Features: CDK4 and MDM2 amplification by FISH.

Discussion:

Low-grade central osteosarcoma is a low grade osteosarcoma that arises in the medullary cavity of bone. It is a rare tumor, accounting for 1-2% of all osteosarcomas. It can be confused radiologically with many entities, including fibrous dysplasia, desmoplastic fibroma, and conventional osteosarcoma. It is characterized by subtle cytologic atypia and variable patterns of bone production, making it difficult to diagnose on small biopsies. MDM2 and CDK4 amplifications are frequent in LGCO, but complex chromosomal abnormalities and TP53 mutations are not seen.

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Case # 7

Presenter: Rohit Singh MD

Attending: Jerome Loew MD

Diagnosis: Ectopic Hamartomatous Thymoma (Branchial Anlage Tumor)

Important Differential Diagnosis:

- Ectopic Thymoma
- Ectopic salivary gland mixed tumor
- Biphasic synovial sarcoma

Key Morphologic Features:

- Epithelial cells admixed with spindle cell areas and adipose tissue
- Well circumscribed lesion
- Epithelial areas reveal follicular and adnexal (apocrine, sebaceous) differentiation.
- Mitotic figures rare, necrosis absent
- Lymphocytes scarce.
- Spindle cells have a myoepithelial cell phenotype (positive for keratins CK5/6, CK8/18, CD10, SMA but negative for desmin)

Discussion:

- Rare neoplasm.
- Rosai et al (1984) introduced the term “ectopic hamartomatous thymoma” to reflect their belief that the process is derived from the third branchial arch and composed of abnormal thymic tissue.
- Peak incidence in the 4th and 5th decades. Mean age 42.4 years. Male to female::10:1
- Presents as a slow growing, well marginated mass in the lower neck, sternoclavicular, and presternal region

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- In addition to epithelial cells, it has plump spindle cells that have been shown to have a myoepithelial cell phenotype
- Pursues a benign course; local excision is usually curative
- Local recurrence is uncommon
- No compelling evidence of thymic derivation.
- Presumed origin from remnants of cervical sinus of His
- Epithelial and myoepithelial cell population
- Scarce lymphocytes, negative for CD1a and CD99
- New designation: Branchial **Anlage Mixed Tumor has been proposed by Fetsch et al (2004)**

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