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CASE 1 (Dr. Timothy Tan, D.O.): Microcystic Adnexal Carcinoma

Clinical History:
The patient is a 28-year-old man with a history of occasional marijuana use presenting with left breast pain and swelling for six years. He has a family history of breast cancer. On initial evaluation, he was referred for an ultrasound and FNA, which was consistent with gynecomastia. However over the last year, his breast and nipple have become more swollen and tender. Mammogram revealed an irregular spiculated mass and subsequent left breast ultrasound revealed a 1.5 x 0.7 x 1.2 cm hypoechoic irregular mass that involved the nipple areolar complex. Patient underwent biopsy and later resection of the mass.

Histologic findings:
Representative sections show a deeply infiltrative process involving the dermis and subcutaneous soft tissue. Low power examination shows haphazardly arranged nests of cells displaying solid, cystic, and focal cribriform architecture, some with comma-like extensions, in a dense fibrotic stroma. Extensive perineural invasion is present. High power examination shows small-to-medium sized cells with scant cytoplasm, monomorphic nuclei with inconspicuous nuclei, with a low mitotic rate. Intracytoplasmic lumina are identified and well as focal sebaceous differentiation. Estrogen receptor (ER) is negative in the tumor cells. P63 shows strong and diffuse staining of the basal cells. CK 5/6 shows strong and diffuse cytoplasmic staining in the tumor cells.

Differential Diagnosis:
- Nipple adenoma with adenosis pattern
- Syringomatous adenoma
- Tubular carcinoma
- Invasive cribriform carcinoma
- Low grade adenosquamous carcinoma
- Morpheaform basal cell carcinoma
- Squamous cell carcinoma
- Syringoma of skin
- Microcystic adnexal carcinoma
- Desmoplastic trichoepithelioma

Summary:
Primary skin tumors should always be considered in the differential diagnosis of a superficial lesions of the breast. This can be diagnostically challenging as often the specimen is a small punch or needle core biopsy and there can be morphologic overlap between breast and skin tumors. However, this distinction is critically important as the treatment is different for a primary breast cancer (excision with sentinel lymph node

biopsy, often followed by radiation therapy, hormonal therapy and chemotherapy) versus a primary non-melanocytic skin cancer (often excision alone).

Microcystic adnexal carcinoma (MAC) is a locally aggressive malignant adnexal tumor displaying sweat duct and follicular differentiation. Overall, MAC affects both sexes equally and presents in a wide age range (6-90 years, median age of 68 years). MAC presents as a slow-growing, yellow or erythematous, firm plaque or nodule that typically involves the face (particularly the nasolabial and periorbital regions), though lesions involving the trunk, axilla, breast, toe, and vulva have been reported. Patients sometimes experience pain, burning, or paresthesia due to perineural infiltration.

Histologically, MAC is poorly circumscribed and usually deeply infiltrating, often extending into the subcutaneous fat or skeletal muscle. Superficially, cysts with epithelial or pilar keratinization are present. More deeply, epithelial cords and strands with ductal differentiation and intracytoplasmic lumina predominate. Perineural invasion is a major diagnostic feature. Cytoplasmic clear cell change is not uncommon and sebaceous and apocrine differentiation is rarely seen. The stroma is densely sclerotic. There is mild cytologic atypia and minimal mitotic activity. Generally, H&E sections are sufficient for the diagnosis, especially if the lesion is extensively sampled; however, immunohistochemical staining may support the diagnosis. Cytokeratin AE1/AE3 is expressed in the tumor cells. EMA and CEA highlight ductal differentiation. Hard keratins (AE13 and AE14) highlight follicular differentiation. LeuM1, CK15, and Ber-EP4 have also been observed.

In our case, our patient presented with a highly suspicious subareolar mass on mammogram and with a strong family history of breast cancer, thus primary breast lesions were also considered. While especially difficult to exclude on the initial small biopsy specimen, a nipple adenoma and syringomatous adenoma of the nipple were excluded at the time of excision on the basis of extensive perineural invasion and infiltration into the deep soft tissue. In any breast mass composed of infiltrative tubules with low grade nuclear atypia, a tubular carcinoma must be ruled out. In our case, the tubules were ER negative and a p63 highlighted an intact peripheral layer of myoepithelial cells, definitely excluding a tubular carcinoma. The tubular component of a low grade adenosquamous carcinoma would be ER negative, p63 positive, and CK 5/6 positive, similar to our case, and this diagnosis was considered at the time of biopsy. However, no squamous component was identified in the excision, making that diagnosis less likely.

MAC must also be distinguished from other primary skin lesions such as desmoplastic trichoepithelioma (DTE), syringoma, morpheaform basal cell carcinoma (mBCC), and desmoplastic squamous cell carcinoma (dSCC). MAC differs from DTE and syringoma by its deep infiltrative growth pattern, perineural invasion, and presense of ductal differentiation. mBCC and dSCC are excluded on the basis of ductal differentiation and intracytoplasmic lumina.

The mainstay of treatment is surgical excision. However, because the tumor often is more extensively involved than clinically apparent, recurrence is common even after surgical excision, with recurrence rates up to 30 to 40 percent. Radiation therapy may be considered in cases where complete surgical excision is difficult (i.e., periorbital area). Lymph node and distant metastasis are rare events but have been reported. Recurrence of MAC may occur after many years, thus long-term routine follow-up is necessary.

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Case 2 (Dr. Janice Aportela, MD): **Endometrial Stromal Sarcoma with Sex Cord-like Elements**

Clinical History: 69-year-old non-smoker female with no significant past medical history presenting with an upper GI bleed requiring endoscopic intervention and blood transfusion.
Chest x-ray during that admission identified a left lung nodule that was further characterized on CT to be a 3x2 cm pleural mass superficial to the left upper lobe. The patient reports no cough, chest wall pain, or recent weight loss.

Histology: The tumor is composed of plump spindle cells exhibiting mild cytologic atypia and low mitotic activity (<4 mitoses/10 high power fields). A cord-like growth pattern of cells (sex cord-like elements) is also focally identified within the tumor. Tumor cells show strong expression of CD10 and strong expression of estrogen receptor, supporting diagnosis of an endometrial stromal tumor. The infiltrative pattern of invasion supports diagnosis as a stromal sarcoma. Tumor cells demonstrate variable nuclear expression of beta-catenin, but only rare cells expresses Bcl-1 (cyclin D1). This combined with the low-grade morphology is consistent with a low-grade rather than a high-grade endometrial stromal sarcoma. Tumor cells do not express Bcl-2, TTF-1, or progesterone receptor. The sex cord-like elements show strong and diffuse expression of cytokeratins 7, AE1/AE3, and CAM5.2; strong nuclear expression of WT1 in the sex cord-like elements with patchy expression in the spindled component; and weak and focal expression of calretinin and inhibin, but no expression of EMA. This immunoprofile supports the diagnosis of endometrial stromal sarcoma with sex cord-like elements. Origin of this tumor includes metastasis from an endometrial or, less likely, an ovarian primary, or from deposits of endometriosis.

Differential Diagnosis:

- Solitary fibrous tumor (SFT): Bland-appearing spindle cell proliferation with prominent vascular pattern (often hemangiopericytoma-like vessels) and variable degrees of stromal sclerosis. IHC: Cells are positive for vimentin, CD34, Bcl-2, and CD99
  - Our tumor: Focal staghorn vessels are present, but the tumor is negative for CD34 and Bcl-2.
- Low-grade fibrosarcoma: Fibroblastic tumor characterized by atypical spindle cells with enlarged, hyperchromatic nuclei. IHC: Cells are positive for vimentin, CD34, Bcl-2, and CD99 in well-differentiated areas.
  - Our tumor: The cells are fibroblastic and there are areas of hyalinization, but our tumor is negative for CD34 and Bcl-2.
- Mesothelioma: Pleural-based tumor characterized by epithelioid cells forming tubules or papillae, or by spindled cells (sarcomatoid variant) arranged in short fascicles with fibrous stroma. The spindled cells are usually cytologically malignant, although cytologically bland tumors may also be seen. IHC: Cells are positive for mesothelial markers such as calretinin and WT1.
  - Our tumor: This is a spindle cell tumor with WT1-positivity. However, calretinin is negative in the spindled component, and diffuse WT1 positivitiy is seen in the sex cord-like elements, with patchy positivity in the spindled component.
- Synovial sarcoma: May be biphasic or monophasic. Biphasic tumors are composed of corded and glandular structures with intraluminal eosinophilic proteinaceous material, admixed with a population of atypical spindle cells. IHC: Cells are strongly positive for Bcl-2 and CD99. Keratin is positive in the epithelial component and often demonstrates some positivity in monophasic tumors as well.
  - Our tumor: Like synovial sarcoma, this is a spindle cell proliferation within the pleura, and the sex-cord-like elements may lead to consideration of a biphasic neoplasm. However, our tumor is Bcl-2 negative, and keratin is positive in the sex-cord-like elements only.
- Sarcomatoid carcinoma: Sarcomatoid carcinomas in the lung frequently represent poorly differentiated squamous cell carcinomas with sarcomatoid differentiation. These tumors demonstrate significant cytologic atypia and mitotic activity. IHC:. Cells are strongly positive for EMA and keratin.

- Our tumor: This is also a spindle cell proliferation, and the sex-cord-like elements may lead to consideration of focal residual epithelioid elements in a sarcomatoid carcinoma, However, keratins are positive in the sex-cord-like elements only, EMA is negative, and there is minimal cytologic atypia and mitotic activity.

Discussion:
Clement and Scully reported a series of uterine mesenchymal tumors resembling ovarian sex cord tumors in 1976, and divided these into two different categories. Type I tumors are endometrial stromal tumors with sex-cord like elements (ESTSCLE), and type II tumors are uterine tumors resembling ovarian sex cord tumors (UTROSCT). ESTSCLE consists of an endometrial stromal neoplasm containing only a minor portion of sex cord-like cells, while in UTROSCT the sex cord-like elements constitute the predominant or exclusive component. These tumors are believed to arise from pluripotent mesenchymal cells of the uterus. There is a high frequency of *JAZF1-JJAZ1* gene fusion in ESTSCLE, while this translocation is not present in UTROSCT. As wild-type JAZF1 is expressed in normal endometrium, it is postulated that the *JAZF1-JJAZ1* gene fusion creates a chimeric protein that disrupts transcription in a lineage-specific manner. The behavior is ESTSCLE is dependent on the type of stromal neoplasm present. Those with circumscribed borders (endometrial stromal nodule) behave in a benign fashion, while tumors with infiltrative borders, as in this case, behave like low-grade endometrial stromal sarcomas and may be aggressive or recur.

Take Home Points:
- Uterine tumors with sex cord elements are divided into two groups: endometrial stromal tumors with sex cord-like elements and uterine tumors resembling ovarian sex cord tumors. The behavior of the former is based on the type of stromal neoplasm present, regardless of the presence of sex cord-like elements.
- Mesenchymal tumors of gynecologic type or origin may be encountered in non-gynecologic sites, either as a metastasis or arising from Mullerianosis, and should be considered in the case of unusual lung or pleural tumors.

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Case Number 3 (Andres G. Madrigal, MD, PhD): Psammomatous melonotic schwannoma.

Gross and histologic findings:
Abdominal wall fistula excision revealed a pink, brown-tan, soft tissue fragment measuring 3.9 x 3.5 x 2.0 cm. The specimen was serially sectioned to reveal a tubular structure with adjacent areas of purulence and necrosis. Histologic sections reveal a well circumscribed lesion in a background of fibromuscular tissue and abscess formation. The lesion reveals architectural heterogeneity, including an area with round and elongated clusters of large eosinophilic cells with ovoid nuclei and nucleoli. Lesional cells contain a variable degree of vacuolization. Nuclear pleomorphism and mitosis are not identified. The clusters of tumor cells lie in a background of pink fibrilar stroma containing scattered brown pigmented cells and pseumomatous calcification. The architecture transitions to sheets of tumor cells with some forming fascicles. There are increased number of cells with granular brown pigment in the cytoplasm and scattered histiocytes. Lympho-vascular invasion and necrosis was not identified.

Immunohistochemical stains:

S-100:	Positive
Vimentin:	Positive
HMB45:	Positive.
AE1/AE3	Negative
CK7:	Negative
CK20:	Negative
Desmin:	Negative
D2-40:	Negative
p63:	Negative
CD31:	Negative
CD68:	Negative
ki-67	labeling index is very low (<1%).

Differential Diagnosis:

Inflammatory myofibroblastic tumor: also called inflammatory pseudotumor, inflammatory fibrosarcoma and plasma cell granuloma. A polymorphic infiltrate of proliferative plump oval to spindle cells arranged in a vaguely fasicular pattern with inflammatory elements, including plasma cells and lymphocytes. Immunohistochemical stains are positive for vimentin, alpha SMA, muscle specific actin, calponin, and ALK-1 (80%); one third of cases are positive for keratin and desmin. Immunohistochemical stains are negative for S100, CD117/c-kit, HHV8, CD34, and h-caldesmon. Immunohistochemical staining precludes diagnosis.

Mesenteric panniculitis: Also called isolated lipodystrophy of the mesnery, retractile mesenteritis and sclerosing mesenertitis). A rare condition of idiopathic primary inflammatory and fibrotic process that can affect the mesentery. Microscopically, there is infiltration of inflammatory cells, myofibroblasts and foamy macrophages. SMA positive, CD117/c-kit negative, beta-catenin negative.

Schwannoma: Morphologically, the conventional schwannoma is composed of spindle-shaped neoplastic Schwann cells with a biphasic pattern of cellular Antoni A and hypcelluar Antoni B areas. The cellular variant reveals hypecellularity, fascicular grown to cell and occasional hyperchromasia and atypia. The morphological the melanin pigmentation and psammoma bodies distinguish precludes these diagnosis.

Pigmented neurofibroma: A rare variant of neurofibroma of scattered melanin-containing cells and benign neural crest cells. The tumor is not encapsulated and contains classic features of neurofibroma composed of all the elements of a peripheral nerve: neoplastic Schwann cells, perineurial-like cells and fibroblasts in a matrix of collagen fibers and mucosubstances. Cell nuclei are characteristically ovoid to spindle, often curved, and smaller than those of schwannomas. Mitotic activity is low. In contrasts to schwannomas, Verocay bodies, palisading of nuclei and hyaline thickening of the vessel wall are absent in neurofibromas. Immunohistochemical staining of the tumor cells are positive for S100, Melan-A and CD34, but negative for HMA-45.

Pigmented epitheliod melanocytoma: a rare variant of melanoma. The tumor often arises on the extremities. It is composed of sheets and nodules of heavily pigmented epitheliod of spindled melanocyes in the the deep dermis. Variable cytologic atypia, rare to absent mitosis. Immunohistochemical stains are positive for S100, MiTF, NKI/C3, p53 and CD68. Negative stains include HMB45, Mart-1 and R1alpha. The location and immunohistochemical profile of this entity precludes diagnosis.

Metastatic melanoma: may present in any anatomic location with variability of cytological architecture, spindle to epitheliod cells, and variability in dysplasia. Metastasis are occasionally S100 negative, but can still be identified as melanoma due to a) a negative work up for carcinoma, lymphoma and sarcoma, b) HMB45+, MART1+, c) clinical history of melanoma. Immunohistochemical staining precludes diagnosis.

Summary:

Psammomatous melonotic schwannoma is a rare melanin producing peripheral nerve tumor of neoplastic Schwann cells, originating from the neuroectoderm. Melonotic schwanommas frequently involve the dorsal spinal roots. Cranial nerves may be affected. Additional anatomic locations of involvement include the gastrointesintal tract, skin, soft tissues and bone. Macroscopically, the tumor is often circumscribed and markedly pigmented. Histologic features include relatively bland eosinophilic spindle cells, melanophages, psammoma bodies and fat. The presence of psammoma bodies distinguishes the lesion from psammomatous melonotic schwanomma from nonpsammomatous melonotic schwanomas. Ultrastructural features by electron microscopy include elongated cytoplasmic processes with interdigitations, continuous pericellular external lamin and mesaxons. Immunohistochemical staining profiles include positive staining for S-100, HMB45, MART-1, and vimentin. Approximately half of cases of psammomatous melonotic schwanomas are sporadic and the other half are components of Carney complex, a clinical disorder characterized by increased risk of developing pigmented skin lesions, myxomas and endocrine tumors. Mutations in the *PRKAR1A* gene cause most cases of Carney complex. The gene encodes a subunit of protein kinase A (PKA) that regulates PKA activity of cell proliferation. Mutations in *PRKAR1A* that are involved with Carney complex results in abnormal subunit protein stability and degradation, resulting in unregulated cell growth. Carney complex is inherited in an autosomal dominant pattern in the majority of cases. Psammomatous melonotic schwanomas have historically been considered benign with ~10% cases with potential for malignancy. However, increasing cases suggests the rate of malignant transformation of psammomatous melonotic schwanomas may be greater than previously thought.

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Case #4 (Dr. Audrey Deeken-Draisey, MD): **Autoimmune enteritis with FOXP3 mutation, consistent with IPEX syndrome**

Clinical History: The patient is an 18 year old male with a life-long history of diarrhea and malnutrition. At age 7, he underwent sub-total colectomy and ileostomy. The patient has one maternal uncle who died as an infant with chronic diarrhea and failure to thrive, and a second maternal uncle with chronic diarrhea requiring Infliximab treatment. The patient also has a documented FOXP3 mutation.

Histology: Representative sections of duodenum reveal overall villous blunting with increased lymphoplasmacytic infiltrate throughout the lamina propria. There is mild glandular architectural distortion and crypt hyperplasia. Goblet cells and Paneth cells are notably absent throughout. There are focal crypt abscesses and cryptitis. There is no increase in intraepithelial lymphocytes.

Differential Diagnosis:

- Celiac sprue: Biopsy shows significantly increased intraepithelial lymphocytes and severe villous blunting with retained goblet cells, clinical response to removal of gluten from diet.
- Crohn disease: Bimodal presentation (20s and 50s) with multifocal inflammation throughout GI tract and skip lesions, biopsy showing acute and chronic inflammation with increased intraepithelial lymphocytes and retained goblet and Paneth cells, can identify granulomas.
- Small bowel bacterial overgrowth: Presents in older patients, due to underlying medical conditions or acid-lowering medications, biopsy with acute and/or chronic inflammation with retained goblet and Paneth cells.
- Common variable immune deficiency: Decreased levels of immunoglobulins with notable absence of plasma cells in GI biopsies.

Special Stains:

FOXP3:	Positive and focally increased within lamina propria lymphocytes.
CD3:	Increased lymphocytes within lamina propria.
CD8:	Increased lymphocytes within lamina propria.
CD4:	Mild increased lymphocytes within lamina propria.
CD20:	Scattered positive cells within lamina propria and lymphoid aggregates.

Discussion:

Autoimmune enteritis is a rare condition characterized by small intestinal villous atrophy that is unresponsive to dietary restriction. This condition presents with unrelenting diarrhea and patients have a predisposition to autoimmune disorders. It

predominantly presents in newborns and infants, with rare cases presenting up to age 20.

IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is a major cause of autoimmune enteritis. It is an often fatal condition presenting in newborns with diarrhea, endocrinopathy, and eczematous dermatitis. It is caused by mutations in FOXP3 gene, which is important for differentiation and function of T regulatory cells. Tregs exhibit potent immune suppressive effects, and when mutated result in autoimmune and allergic inflammation.

Mutations in FOXP3 gene can result in qualitative or quantitative defects in expression. Quantitative defects are most common, resulting in markedly decreased or absent levels of Tregs and FOXP3 expression by immunohistochemistry. Multiple documented cases have shown qualitative defects that produce non-function Tregs and retain FOXP3 positivity in IHC. These rare cases are associated with milder clinical phenotype.

Treatment of IPEX includes intensive immune suppression and dietary modification and supplementation. Stem cell transplants offer potential for cure.

Take Home Points:

- Autoimmune enteritis is an important consideration in GI biopsies for chronic diarrhea from infancy.
- Variable histologic presentation with increased lymphoplasmacytic infiltrate, absent intraepithelial lymphocytes, variable acute inflammation, and occasional absence of goblet cells and Paneth cells.
- IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) is associated with mutations in FOXP3 gene.

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Case Number 5 (Dr. Kate Poropatich, M.D.); Dedifferentiated liposarcoma with epithelioid and rhabdoid histology.

Clinical history: The patient is a 49-year-old male with a clinical history of rheumatoid arthritis who presents to his physician with night sweats. An outside CT scan revealed a mass lesion between the renal artery and vein that appeared to surround the right kidney and extend upwards between the vena cava and liver.

Gross and histologic findings and immunohistochemical profile: The specimen consists of a radical nephrectomy (1764 gm) with a kidney measuring 15 x 6 x 5 cm and an intact, compressed adrenal gland. There are two distinct, yellow-tan masses, the first that extends into the kidney hilum, measuring 15 x 12.5 x 11 cm, and the second that is cystic and hemorrhagic and located at the superior pole of the kidney and measures 6 x 5.5 x 3.3 cm. Representative sections of the intrarenal mass show sheets of epithelioid cells with vesicular chromatin, enlarged nuclei and centrally-placed nucleoli. Additionally, there are tumor cells with the characteristic 'rhabdoid' appearance consisting of an enlarged cellular size with an eccentrically-placed nucleus and abundant eosinophilic cytoplasm. Mitoses are frequent (>5 mitoses per 10 high power fields). Lesional cells coexpress by immunohistochemistry: vimentin, CD56, MDM2 and p16 and are negative for S100, HMB45, desmin, SMA, AE1/AE3, Cam5.2, WT1, CD99, NSE, C-kit, MART1.

Differential Diagnosis:

1. **Renal Cell Carcinoma—Rhabdoid Variant:** As a primary renal cell neoplasm, this is a rare variant of RCC that consists of a population of neoplastic cells that morphologically resemble rhabdomyoblasts. It represents a poor prognostic variant, comprising around 4-7% of all RCC's, most often of which co-occur with the clear cell type. Rhabdoid cells may be in sheets or clusters and are epitheliod with vesicular nuclei, prominent nucleoli and large eosinophilic intractyoplasmic inclusions. Immunohistochemistry: Positive for vimentin, EMA, pan-cytokeratins, PAX2, PAX8, CD10, NSE.
2. **Adult Wilms Tumor:** Large and nodular tumors (mean size of 12 cm) affecting adults with a mean age of 32 (range: 21 – 67). Primary renal neoplasm with primitive blastematous spindle cell or round cell component admixed with varying amounts of epithelial and stromal component. Immunohistochemistry: positive for Cytokeratin and CD56
3. **Atypical Angiomyolipoma:** Atypical features in an otherwise often benign neoplasm consisting of thick-walled vascular component with smooth muscle and adipose tissue with spindle cell and epithelioid cells. <1% of intrarenal tumors;

may also occur outside the kidney. Associated with LOH for TSC2.
Immunohistochemistry: Positive for HMB45.

Summary:
Dedifferentiated liposarcoma (DDLPS) account for most pleomorphic sarcomas in the retroperitoneum and have a better prognosis than other high grade pleomorphic sarcomas. 10% of DDLPS cases are recurrences. The risk of dedifferentiation is higher in deep-seated (i.e. retroperitoneal) sarcomas. The retroperitoneum is the most common location; also found in the head & neck, trunk, extremities and spermatic cord and they are rarely present in the superficial, subcutaneous tissue.

Histologically, DDLPS is a high-grade sarcoma with an abrupt transition from atypical lipomatous tumor/well-differentiated liposarcoma to dedifferentiated non-lipogenic sarcoma with 5+ mitotic figures/10 HPF. Grossly, the solid fleshy areas with hemorrhage correlates with the high-grade liposarcomatous component. This high-grade component may have lipoblastic differentiation as isolated cells or as diffuse sheets; 'homologous lipoblastic differentiation.' The dedifferentiaed area resembles undifferentiated pleomorphic sarcoma or intermediate- to high-grade liposarcoma. It is made up of short fascicles of fibroblastic spindle cells with mild-to-severe nuclear atypia, intermediate-to-increased cellularity. In these dedifferentiated areas, heterologous differentiation may be present in 5-10% of cases, consisting of myogenic, osteo- and chondrosarcomatous, neural or angiosarcomatous elements.

A genetic hallmark of DDLPS is their diffuse expression of MDM2 and/or CDK4, as well as HMGA2 and p16. Overamplification of MDM2 (12q15) with/without CDK4 amplification often occurs by supernumerary ring formation. 12q13-21 is also found amplified in some atypical liposarcoma/well-differentiated liposarcomas. Coamplifications can occur with 1p32 and 6q23, which include JUN and its activating kinase ASK1.

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CASE 6 (Dr. Amanda Meindl, M.D.): Primary Cutaneous Mammary Analogue Secretory Carcinoma

Clinical History: An otherwise healthy 40 year-old female presents with a long-standing mass on her arm. Patient first noted the lesion on her left proximal forearm 8 years ago following trauma to the area. Upon excision the mass measured 2.2 x 1.9 x 1.5cm.

Histology: The lesion is sharply demarcated, well-circumscribed and intradermal, far from the margins of resection. The epithelium is unremarkable over the lesion. It is a relatively homogenous lesion composed of large epithelial cells arranged in a trabecular pattern with formation of gland-like spaces filled with eosinophilic and mucinous secretions. Cystic spaces with abundant eosinophilic secretions rimmed by large epithelial cells, with abundant eosinophilic cytoplasm, oval to round nuclei and prominent nucleoli and rare mitoses noted. IHC was positive for S100, mammaglobin, vimentin, CK7, CK8/18 and AE1/AE3. Negative stains include calponin, p63, ER/PR, HER2/neu, EMA and SMA.

Molecular Studies: RT-PCR identified the ETV6-NTRK3 fusion gene transcript.

Differential Diagnosis:

- **Cutaneous Adenoid Cystic Carcinoma:** These tumors have slow growth, and are locally aggressive. They are often located on the scalp and chest. They are composed of monomorphic basaloid cells arranged in tubules, elongated nests and cords and ductal lumina may be present. The cells have compact nuclei, and scant eosinophilic cytoplasm and the ductal lumina have mucoid matrix with a basophilic hue. There is often deposition of brightly eosinophilic basement membrane material in intercellular spaces. Cells are EMA, CK7, CD117 positive. Our case was lacking a mucoid matrix with a basophilic hue as well as a dense basement membrane matrix deposition.

- **Cutaneous Ductal Apocrine Carcinoma:** There are several different types of apocrine carcinoma, and specifically the ductal type was on our differential. It is composed of randomly oriented ducts arranged in tubular, cribriform and papillary forms, lined by cells with eosinophilic cytoplasm and apocrine snouts. The cytoplasm of the cells stains positive for PASD and there can be cytologic atypia, increased mitoses and necrosis. On IHC our case did not show PASD positivity in the cytoplasm of the cells.

- **Secretory Carcinoma of the Breast (Metastatic):** This tumor can occur at any age however, there is a higher incidence in children and young adults. It is composed of cystic spaces filled with abundant pale-pink secretions that are PASD(+). These cystic spaces are lined by ductal cells with small, bland nuclei with rare mitotic activity and abundant pale, eosinophilic, granular, and vacuolated cytoplasm. Of note the cells themselves are PASD (-). These tumors are generally EMA+, S100+, ER/PR and HER2/neu(-) and many (~90%) have been associated with the ETV6-NTRK3 fusion gene. Our case appeared histologically similar to this lesion and thus remained on our differential.

- **Acinic Cell Carcinoma of the Salivary Gland (Metatstatic):** This entity often presents with a mass that can involve the facial nerve, and can be bilateral. There are solid, microcystic, papillary-cystic, and follicular patterns composed of multiple cell types, including acinar, intercalated ductal, vacuolated, clear, and glandular. It is not uncommon for a given tumor to exhibit a mixture of cell types and architectural patterns, whereas our lesion was relatively homogenous. This lesion can have eosinophilic luminal secretions, particularly in the follicular type. The cells have small, round, bland nuclei, but mild atypia or pleomorphism can be seen. It is important to note that PASD is positive within the acinar cells as well as within the secretions.

- **Mammary Analogue Secretory Carcinoma of the Salivary Gland (Metastatic):** Last on our differential was a metastatic mammary analogue secretory carcinoma. It resembles a secretory carcinoma of the breast based on IHC, molecular findings, and histology. It is architecturally homogenous, forming tubular, microcystic, and solid patterns and is composed of uniform cells, with bland, vesicular nuclei, eosinophilic vacuolated cytoplasm and PASD+ luminal secretions. Again as in secretory carcinoma of the breast, the cells are negative. Compared to acinic cell carcinoma, there is complete lack of acinar cells in MASC. Cells stain positive for S100, mammaglobin, vimentin and CK. Most reported cases have found the same ETV6-NTRK3 fusion gene as described in secretory carcinoma of the breast. Our case wass also similar to this entity and therefore it remained on our differential.

Summary: There have only been two previously reported cases of primary cutaneous mammary analogue secretory carcinoma in the literature. The first case was reported in the AJSP in 2009 and was a case of a 13 year-old girl with a cutaneous nodule in her axilla. The second was a case of a 40 year-old man with a cutaneous nodule on his right flank. Both showed similar morphologic findings to secretory carcinoma of the breast. Both stained positive for S100. Neither one of the lesions showed the ETV6-NTRK3 fusion gene transcript, however. Clinical workup for any other primary tumors was negative. Excision with negative margins was found to still be effective therapy several months later. To conclude, the final diagnosis for this case was a primary cutaneous mammary analogue secretory carcinoma based on IHC and morphology as well as molecular studies showing the ETV6-NTRK3 gene fusion transcript. The ETV6-NTRK3 fusion transcript has been identified in large proportion of secretory carcinoma of breast as well as MASC, congenital fibrosarcoma, congenital mesoblastic nephroma and Acute Myeloid Leukemia. It is a balanced chromosomal translocation t(12;15)(p13;q25) that creates a fusion gene between ETV6, a transcription regulator on chromosome 12 and NTRK3, a membrane receptor kinase on chromosome 15. This gene fusion promotes cell proliferation and survival. In order to render the diagnosis of primary cutaneous MASC there has to be no evidence of another primary tumor.

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