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**Case Number 1 (Adam Beattie, MD): Myxoinflammatory Fibroblastic Sarcoma (MIFS)**

**Histology:** At low magnification, an infiltrative, lobulated, vaguely multinodular lesion is centered in deep dermal and subcutaneous tissue. The process is composed of fibrosclerotic stroma interrupted by pools of mucin, and a patchy inflammatory infiltrate. At higher magnification, the tumor cells vary from plump spindled to more epithelioid cells with enlarged, vesicular nuclei. Some of the larger cells have a ganglion-like appearance owing to the presence of voluminous deeply eosinophilic ameboid cytoplasm while others possess inclusion body-/ Reed-Sternberg-like nucleoli. Within the myxoid areas, tumor cells with cytoplasm distended by mucin-filled vacuoles (pseudolipoblasts) are occasionally identified. Rare giant cells demonstrating emperipolesis are also encountered. Mitotic activity is present but low. Tumor cells show variable expression of D2-40 and CD34.

**Differential Diagnosis:**

1. **Nodular Sclerosis Classical Hodgkin Lymphoma**: Most commonly affects a younger aged population and is typically lymph node based. On cut surface, the lymph nodes demonstrate a vaguely nodular architecture with bands of collagen traversing the process and partitioning nodules of tumor. Tumor nodules are composed of a variable number of Reed-Sternberg cells within a background of small lymphocytes and other inflammatory cells. Although the inflammatory infiltrate and Reed-Sternberg cells and overlap with the inflammatory mileau and hallmark cells of MIFS, the latter possesses a significant population of ganglion-like cells, myxoid areas with pseudolipoblasts, and foci of hyalinized (as opposed to strickly birefringent) collagen in a more haphazard distribution. Unlike MIFS, the immunoprofile of Reed-Sternberg cells includes expression of CD15, CD30, and dim expression of PAX5.
2. **Pleomorphic Hyalinizing Angiectatic Tumor of Soft Parts (PHAT)**: Similar to the tumor under discussion, the PHAT is a slow-growing, fairly well-circumscribed subcutaneous mass usually affecting the distal extremities of females. Microscopically, the tumor contains congeries of ectatic, thin-walled vessels filled with thrombotic material and fibrin. Surrounding these vessels and often admixed with fibrin are tumor cells arranged in sheets and vague fascicles. The key lesional element is a pleomorphic cell with a bizarre-appearing hyperchromatic nucleus and frequent presence of an intranuclear cytoplasmic inclusion. The mitotic activity is low. A mixed inflammatory infiltrate is often present. In contrast to MIFS, PHAT lacks the bizarre cells with inclusion body-like nucleoli, mucin pools with pseudolipoblasts, and its cells more diffusely express CD34. Notably, ectatic vessels with fibrin are infrequently observed in conventional MIFS .
3. **Hemosiderotic FIbrolipomatous Tumor (HFLT):** Similar to PHAT and MIFS, the HFLT is a **w**ell-circumscribed, subcutaneous mass that predominately occurs primarily in superficial soft tissue of the dorsal aspect of the foot and ankle region of middle-aged females. Microscopically, the process consists of bland spindled and occasionally epithelioid cells within the interlobular fibrous septa of subcutaneous fat. Hemosiderin pigment is present with the cytoplasm of the spindle cells as well as in macrophages. An inflammatory infiltrate is common. The spindle cells immunoexpress CD34 and calponin. The subcutaneous component of MIFS and the periphery of PHAT often times show features of HFLT. Additionally, the fact that both HFLT and MIFS share a t(1;10) which maps to TGFBR3 and MGEA5 and reported cases exhibiting hybrid features of HFLT and MIFS exist indicate the these tumors probably represent a morphological spectrum.
4. **Myxofibrosarcoma:**  This common sarcoma typically presents in adults as a slow-growing lesion either in the dermis or skeletal muscle of the lower limbs. Macroscopically, the tumor is variably myxoid with a multinodular cut surface. Microscopically, the highly myxoid nodules of this tumor are populated by atypical spindled and stellate cells characteristically apposed to curvilinear, thick-walled vessels. In contrast to MIFS, myxofibrosarcoma occurs in more proximal soft tissue, and exhibits more uniform cytological atypia, a greater concentration of curvilinear and branching vessels, a greater amount of myxoid stroma, higher mitotic activity (in high grade examples), and less inflammation.
5. **Superficial CD34-positive superficial fibroblastic tumor:** A recently described low-grade sarcoma that occurs in adults and predilects superficial soft tissue of the lower extremity and hip girdle. Cellular fascicles and sheets of atypical spindled cells and highly pleomorphic cells resembling the Reed-Sternberg-like cells of MIFS, low mitotic activity, and an arborizing vascular element typify this process. Tumor cells show diffuse expression of CD34 and focally express keratin. In contrast, MIFS features myxoid areas with pseudolipoblasts and hyalininzed areas, a more prominent inflammatory component, absence of diffuse pleomorphism, and only focal CD34 expression. Despite seemingly overlapping histological features, no t(1;10) was identified in the few cases of CD34-positive superficial fibroblastic tumor tested.

**Summary:**

MIFS was originally described in 1998 by three independent groups. The tumor affects middle-aged patients and shows a slight female bias. The process occurs primarily in dorsal superficial distal upper and lower extremity soft tissue as a small (median, 2.5 cm.) lobulated or nodular mass. Histologically, the tumor is composed of fibrosclerotic stroma, foci of mucin, and a variable inflammatory infiltrate. The tumor cells vary from plump spindled to more epithelioid with enlarged, vesicular nuclei, some of which demonstrate inclusion body-like nucleolus. Within the myxoid areas, bizarre appearing pseudolipoblast are frequently encountered. Mitotic activity is typically low (less than 5 mitoses per 50 high-powered fields). Immunohistochemically, the tumor cells are typically positive for vimentin, and focally positive for D2-40 (over 80% of cases), CD34 (50%), and pan-cytokeratin (33%). Recent molecular studies have shown that MIFS (and HFLT) harbor t(1;10) which maps to TGFBR3 and MGEA5 and results in upregulation of FGF8 which is important for limb development. Prognostically, these tumors are regarded as low-grade sarcoma with a significant potential for local recurrence (mean recurrence rate of 30%). Only a handful of reports claiming metastatic spread of tumor exist in the literature. A recent comprehensive study of over 100 examples of the tumor found that (1.) small areas of hypercellularity or complex sarcoma-like vasculature, or increased mitotic activity do not significantly impact recurrence rates and (2.) the only statistically significant parameter correlating with reduced recurrence rate was the adequacy of excision (initial margin-negative excision or re-excision shortly after initial biopsy/excision).

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**Case Number 2 (Heidi Rahn, MD): Extranodal NK/T Cell Lymphoma, Nasal Type, of the Testicle.**

**Histology and immunohistochemical profile:**

Representative sections show a hypercellular lesion composed of mostly large, individually dispersed cells with open, dispersed chromatin and visible nucleoli as well as smaller-sized lesional cells. The infiltrate is mainly located in interstitial stroma of the testis, surrounding atrophic tubules, but effacing the entire normal architecture of the organ. Focally, aggregates of apoptotic bodies and foci of necrosis are identified. Immunohistochemically, the tumor cells immunoexpress CD2, CD3ε (cytoplasmic instead of membranous expression of CD3), TIA-1, CD56, and EBER, but do not express T-cell markers, CD5, CD7, BetaF1; B-cell markers, PAX5 and CD20; immature hematopoietic precursor cell markers,CD34, TDT, CD117; or OCT4 or PLAP (seminoma-related immunomarkers)

**Differential Diagnosis:**

**1. Seminoma-** When lesional tissue is inadequately fixed, the cells appear dyscohesive and mimic lymphoma cells. Even in this situation, a vague sense of compartmentalization of the process with nests of cytologically uniform tumor cells juxtaposed to fibrovascular septa with chronic inflammatory cells assist in the diagnosis. Unlike lymphoma cells, seminoma cells display thin (pencil-like) cytooplasmic borders, similar-sized nuclei with angled contours, and abundant glycogen-rich cytoplasm. Immunoprofiling the cells greatly assists in the differential diagnosis of seminoma from lymphoma.

**2. Infectious (viral) orchitis-** This process, most often caused by mumps virus, results in a reactive appearing lymphohistiocytic infiltrate within and around seminiferous tubules and in a perivascular distribution. Unlike lymphoma, the cells are cytologically bland (with enlarged immunomodulated lymphocytes requiring distinction from lymphoma cells), most are intratubular in location as opposed to stromal, and necrosis and apoptosis are rare. Most of the lymphocytes are T-cells, which show membranous (and not cytoplasmic) expression of CD3. Accompanying histiocytes are highlighted with CD68 or CD163.

**3. Lymphoblastic Leukemia/Lymphoma (AL/L)**- Aggressive, predominantly T-cell neoplasm affecting young-aged individuals. The process rapidly progresses from a lymphomatous (nodal/extranodal/thymic) phase to a leukemic (bone marrow) phase. In contrast to extranodal NK/T cell lymphoma where most of the lesional cells are large with prominent nucleoli, the cells of AL/L are small to intermediate in size with a greater degree of uniformity and possess rounded, non-nucleolated nuclei exhibiting brisk mitotic activity. A “starry-sky” pattern of histiocyte infiltration is commonly encountered. Cells immunoexpress CD99, CD3, CD7, Tdt, and only occasionally CD56 and CD57, but not EBER.

**4.Non-Hodgkin Lymphoma-** Diffuse, large B-cell lymphoma is most common primary lymphoma of the testis in patients over 50 years of age (70% of testicular lymphomas). These tumors express B-cell immunomarkers and typically do not express CD56, TIA, or EBER (most cases composed of non-germinal center cells lacking CD10 and/or bcl-6 expression). Other CD56-positive hematopoietic malignancies that may enter the differential diagnosis are not associated with EBV infection or exhibit EBER-expression.

**Summary:**

Extranodal NK/T cell lymphoma (nasal type) rarely involves the testicle as either a primary or secondary lymphoma. As this neoplasm most commonly arises in the nasal cavity and less often in extranasal sites, a complete evaluation of the patient must be performed before considering the lesion primary to the testicle. Importantly, the contralateral testis is the most commonly affected organ in dissemination of the disease or in relapse. At least for conventional nasal NK/T cell lymphoma, combined chemoradiotherapy is the mainstay of treatment. In addition, L-asparaginase-containing chemotherapeutic agents (with or without stem cell transplant) have been used successfully in patients with relapse of disease.

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**Case Number 3 (Natasha Lewis, MD): Plexiform fibromyxoma of the stomach**

**Gross, histologic and immunohistochemical findings:** Distal gastrectomy revealed a 5.5 cm submucosal mass with overlying mucosal erosion . Cut surface showed a soft, ill-defined, yellow-tan, multilobulated mass involving the entire thickness of the stomach wall with frond-like projections extending from the serosa. Representative sections revealed an infiltrative lesion with a plexiform, multinodular growth pattern arising within the muscularis propria with nodules protruding from the serosal surface. Higher-power of tumor lobules shows an abundant myxoid matrix, an accentuated non-branching capillary network, and a low to moderately cellular proliferation of short spindle cells with scant eosinophilic cytoplasm and cytologically bland nuclei with evenly dispersed chromatin and inconspicuous nucleoli. Very rare mitoses were observed. Immunohistochemically, the spindled lesional cells were diffusely positive for smooth muscle actin (SMA), focally positive for CD10 and negative for CD117, DOG-1, CD34, S-100, D2-40, β catenin, and keratin AE1/AE3.

**Differential diagnoses:**

1. **Myxoid variant of gastrointestinal stromal tumor (GIST):** GISTs are the most common mesenchymal gastric tumors. They typically form solitary masses without plexiform intramural growth. GISTs with loss of expression of succinate dehydrogenase are an exception, however, as they commonly display a plexiform growth pattern. However, these lesions are typically very cellular, predominantly epithelioid cell neoplasms. Myxoid GISTs are composed of epithelioid and/or spindled cells arranged in vague, loose fascicles within a predominantly myxoid stroma. Similar to their non-myxoid counterparts, they are commonly positive for CD117, CD34 and DOG-1 by immunohistochemistry and often possess mutations in the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes (85%-90%).
2. **Inflammatory fibroid polyp (of Vanek):** A benign polypoid lesion most commonly occurring in the stomach antrum. The process typically arises in the submucosa but can extend into the muscularis propria. In contrast to fibromyxoma, the inflammatory fibroid polyp is composed of bland epithelioid to spindled cells and a mixed inflammatory cell infiltrate including eosinophils within a loose fibromyxoid background. A distinct plexiform growth pattern does not typically occur. In addition, the tumor cells have a tendency to encircle vessels with open lumina and perivascular collagen deposition. The lesional cells are immunoreactive for vimentin and CD34 and commonly have activating PDGFRA mutations.
3. **Plexiform neurofibroma:** A benign peripheral nerve sheath tumor with an obvious gross and microscopic plexiform growth pattern. In the gastrointestinal tract, the process typically arises as a polypoid lesion in the colon but can occur in the stomach, and can involve any layer of the GI tract wall. Unlike the growth pattern of fibromyxoma, plexiform neurofibroma demonstrates enlarged nerve bundles composed of spindle cells with wavy nuclei apposed to wavy bundles of collagen within a myxoid matrix. This variant in particular is closely associated with neurofibromatosis type 1. As with other forms of neurofibroma, immunoexpression of S100 protein and CD34 is characteristic.
4. **Gastrointestinal schwannoma:** A benign peripheral nerve sheath tumor that occurs primarily in the stomach. The tumor is typically unencapsulated and can appear infiltrative, but does not usually show plexiform growth. Lymphoid aggregates are characteristically present along the periphery and scattered intralesional lymphocytes and plasma cells are present. The lesional cells are arranged in vague fascicular or microtrabecular patterns in a variable fibromyxoid stroma (and lacking the nuclear palisading and the vascular changes of conventional schwannoma). Compared with the round to oval nuclei of fibromyxoma, the spindled cells of GI tract schwannoma feature hyperchromatic nuclei with irregular contours. Additionally, the cells of GI tract schwannoma are strongly and diffusely positive for S100 protein and also express GFAP. Unlike conventional schwannoma, the GI tract schwannoma lacks monosomy of chromosome 22 or mutations in the *NF2* gene.
5. **Myxoid leiomyoma:** A benign mesenchymal neoplasm of smooth muscle cell origin. It is a hypocellular lesion that may have a plexiform architecture, however, typically does not display the discontinuous multinodularity characteristic of plexiform fibromyxoma. It is composed of microtrabecular fascicles of bland spindled cells in a myxoid background. Unlike the cells of fibromyxoma, leiomyoma cells have central nuclei with blunted ends and bright, fibrillary eosinophilic cytoplasm and immunoexpress not only smooth muscle actin, but also desmin and caldesmon.
6. **Intra-abdominal fibromatosis:** Locally aggressive myofibroblastic proliferation that most commonly arises from the pelvis, small bowel mesentery or retroperitoneum and can secondarily involve the stomach wall thereby mimicking fibromyxoma. It characteristically has an infiltrative pattern within muscle and fat, but does not typically show true plexiform growth. The cells of fibromatosis are arrayed in elongated, infiltrating fascicles with a collagenous and focally myxoid stromal matrix. Compared with the small spindled cells of fibromyxoma, the main lesional element of fibromatosis is a plumper spindle cell with somewhat fibrillary cytoplasm and an elongated nucleus with a small, but conspicuous, nucleolus. In contrast to the straight-lined capillaries of fibromyxoma, fibromatosis demonstrates elongated, somewhat curvilinear, and open, stellate-shaped vessels. The spindled cells show positive nuclear immunoexpression of β-catenin. This process is associated with Gardner’s syndrome.

**Summary:**

Plexiform fibromyxoma is a rare type of gastric myxoid mesenchymal neoplasm, initially described by Miettinen, et al. in 2009. These myxoid tumors of the stomach have previously been reported as “myxoma” or “fibromyxoma”, and for those with multinodular architecture, “plexiform angiomyxoid myofibroblastic tumor of the stomach”. The plexiform fibromyxoma arises exclusively within the antrum of the stomach, but often extends focally into the pyloric region and duodenal bulb. The process arises in the muscularis propria and extends into the serosal and extragastric soft tissue in polypoid, frond-like projections. However, tumor nodules have not been identified in the omentum or distant peritoneal sites. Histologically, the tumor is characterized by a distinct plexiform intramural growth pattern with multiple myxoid or myxocollagenous micronodules. A prominent simple capillary network composed of small, thin-walled vessels is also characteristic. The tumor cells are bland, oval to spindled with indistinct cell borders and inconspicuous nucleoli. Mitoses are rare (up to 4/50 high-power fields). Although ulceration, mucosal and vascular invasion have been reported, they have not been found to adversely affect the favorable outcome. The tumor cells are characteristically immunopositive for smooth muscle actin and variably for CD10, vimentin, desmin, caldesmon and muscle specific actin. They are consistently negative for CD117 (c-KIT), DOG-1, CD34, S100, EMA, and keratin AE1/AE3. Our case was negative for beta-catenin (a result not previously reported). KIT and PDGFRA gene mutations have not been identified. These lesions are considered benign as no recurrences or metastases have been reported to date. Complete surgical resection is considered curative.

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**Case Number 4 (Kimberly Golden, MD): Columnar Cell Variant of Papillary Thyroid Carcinoma**

**Gross, histologic and immunohistochemical findings:** The thyroidectomy specimen demonstrated a 4 cm. well-circumscribed, encapsulated, fleshy-tan, multinodular mass. Representative sections revealed an encapsulated lesion with complex tubulopapillary architecture. Lesional cells are columnar with lightly eosinophilic cytoplasm and overlapping columnar nuclei. High-power revealed nuclear crowding and pseudostratification; however, no nuclear chromatin “clearing”, longitudinal nuclear grooves or intranuclear cytoplasmic inclusions are present. The tumor cells were diffusely immunopositive for thyroglobulin, TTF-1 and CDX2, focally positive for CD56 and p63, and negative for calcitonin, synaptophysin, chromogranin, HMB4E-1, CEA and p63.

**Differential diagnoses:**

1. **Hyalinizing trabecular adenoma**: Encapsulated follicular lesion composed of elongated cells arranged around blood vessels with an associated hyalinized stroma. Tumor predilects women from the third to eighth decades of life and presents as an asymptomatic neck mass. These lesions are characterized by a trabecular, organoid growth pattern with fibrovascular hyalinized stroma. Similar to the cells of columnar variant, the lesional cells of hyalinizing trabecular adenoma are large, elongated and sharply outlined with round, oval or elongated nuclei. However, these nuclei frequently possess grooves and eosinophilic intranuclear inclusions (mimicking conventional papillary thyroid carcinoma but not columnar variant), and perinucleolar “haloes”. The tumor cells immunoexpress thyroglobulin, TTF-1, cytokeratin and vimentin, *PTC/RET* translocations (as encountered in a minority of conventional papillary thyroid carcinomas) and wild-type *B-raf* characterize the molecular profile of this tumor. .
2. **Follicular adenoma with trabecular growth (embryonal adenoma):** Benign encapsulated tumor with evidence of follicular cell differentiation. This subtype of follicular adenoma affects women more often than men and peaks in the fifth and sixth decades of life. The lesion usually presents as a solitary encapsulated mass. This adenoma is cellular with a solid trabecular growth pattern of typical follicular cells and lacks cells with columnar orientation and elongated nuclei. Tumor cells immunoexpress thyroglobulin, TTF-1 and cytokeratins and negative for calcitonin, chromogranin and synaptophysin.
3. **Medullary thyroid carcinoma:** Malignant neuroendocrine tumor showing C-cell differentiation that occurs in familiar and sporadic forms. The tumor usually presents as a palpable thyroid mass. Patient may have elevated basal serum levels of calcitonin. Tumors may be encapsulated, but some show an infiltrative growth pattern. Histologically, growth patterns may include papillary (mimicking columnar variant of papillary carcinoma), organoid, trabecular, solid or sheet-like patterns. In contrast to the elongated, pseudostratified nuclei of the columnar variant, the nuclei of medullary carcinoma are round to oval with finely granular chromatin and showing varying degrees of pleomorphism including the presence of coarse chromatin and multinucleation. The cytoplasm is ill-defined and most often eosinophilic to amphophilic and granular. Stromal amyloid can be seen in 25% of more of cases. Tumor cells are immunoreactive for calcitonin, synaptophysin and chromogranin . TTF-1 reactivity is variably present.
4. **Tall cell variant of papillary thyroid carcinoma:** Aggressive variant of papillary thyroid carcinoma where the height of the tumor cells are 3x their widths and the cytoplasm is distinctly eosinophilic. By definition, at least 50% of the tumor should be composed of tall cells in order to make the diagnosis. This variant is uncommon and occurs mostly in women. Similar to the columnar cell variant, this subtype generally affects an older aged population with a peak incidence in the sixth decade of life, and tends to be large (>5 cm in greatest dimension) with extrathyroidal extension. Histologically, the tumors tend to be unencapsulated and infiltrative. A prominent papillary growth pattern is present and marked fibrosis is usually observed. Nuclei are basally located and, unlike the columnar cell variant, show features of conventional papillary carcinoma including an “optically clear” chromatin pattern, nuclear grooves and eosinophilic cytoplasmic intranuclear inclusions. Tumor cells are positive for thyroglobulin, cytokeratin, Leu-M1, EMA and negative for calcitonin, chromogranin and synaptophysin.

**Summary**

Columnar cell variant of papillary thyroid carcinoma is characterized by columnar-shaped cells exhibiting stratification of their elongated nuclei (at least 50% of the cells composed of columnar cells). This papillary carcinoma subtype is rare and occurs more in men than women. The tumor clinically appears as a “cold nodule” on thyroid scan. Fine needle aspiration reveals a moderately cellular aspirate with sheets, papillary clusters, and micro follicular arrays of cells with oval nuclei and finely granular chromatin. Cells are frequently demonstrate pseudostratified nuclei that lack intranuclear cytoplasmic inclusions or grooves. Grossly, the tumors appear as either large masses (measuring > 5 cm.) with an invasive growth pattern or as smaller (< 5cm), encapsulated lesions. Histologically, there is a prominent papillary growth pattern. However other growth patterns such as follicular, cribriform and solid can be observed. The cells are twice as tall as they are wide and show prominent nuclear stratification. The nuclei tend to be elongated and hyperchromatic. Cytoplasmic changes may vary from a nondescript eosinophilic appearance to a clear or vacuolated appearance with subnuclear vacuolization similar to that seen in secretory-type endometrium. Squamoid morules are occasional identified. High mitotic activity is sometimes encountered, but necrosis is generally not found. The tumor cells immunoexpress thyroglobulin, TTF-1, cytokeratins, vimentin and, notably, CDX2.

Treatment should include complete excision and postoperative radioiodine therapy for more aggressive lesions. These tumors occasionally metastasize to cervical lymph nodes or to distant sites including lung and bone. The columnar cell variant has been associated with high mortality rates and death that typically occurs within 4 years of diagnosis. The aggressive behavior of the columnar cell variant of papillary thyroid carcinoma correlates with advanced patient age, tumor size (>5cm) and presence of extrathyroidal extension.

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**Case Number 5 (Todd DeJulio, MD): Penile lymphangioma-like Kaposi Sarcoma (KS) in an HIV-negative male**

**Histology and immunohistochemistry:**

Representative sections show a portion of skin with a largely unremarkable epidermal surface. In the dermis, there is a diffusely infiltrative vascular process composed of dilated (under the epidermis) and anatamosing vascular channels that dissect the dermal collagen. An attenuated lining of relatively small endothelial cells with little cytoplasm exhibiting focal mild atypia is observed. A focal and inconspicuous perivascular lymphoplasmacytic infiltrate is present. No accompanying spindle cell component with extravasated red cells or intra-/extracellular hyaline globules are identified. Lesional cells immunoexpress CD31, D2-40, and LANA (LNA-1) in a stippled nuclear pattern (the most specific marker for KS).

**Lesions in the differential diagnosis of pure lymphangioma-like KS:**

1. **Lymphangioendothelioma (acquired progressive lymphangioma):**

* + Typically a unifocal macula/plaque in immunocompetent young patients; associated with radiation exposure in some patients.
  + Lesion shows a striking morphologic similarity to the pure lymphangioma-like KS variant but lacks appreciable endothelial atypia in contrast to focal mild atypia noted in latter.
  + Lacks WT-1 (indicating that this lesion, like “hobnail” hemangioma, is a lymphatic malformation and not a neoplasm)
  + Lacks LNA-1 (HHV8)

2. **Low-grade cutaneous angiosarcoma**

* + May be associated with radiation, chronic lymphedema, or actinic damage (former two clinical subtypes are associated with c-myc immunoexpression).
  + Often displays a greater degree of endothelial atypia than lymphangioma-like variant of KS including intraluminal papillary structures, and multilayered endothelium.
  + LNA-1 (HHV8) negative in the vast majority of cases. Most cases do not express lymphatic-endothelial related markers, VEGFR-3 and PROX-1.

3. **“Hobnail” hemangioma (targetoid hemosiderotic hemangioma)**

* + Red to blue papule sometimes with a “targetoid” appearance occurring in young to middle aged immunocompetent individuals
  + Similar morphology to lymphangioma-like KS with ectatic lymphatic channels under the epidermis and a “pseudosarcomatous” lymphatic channel proliferation in deeper dermis, and hemosiderin deposition.
  + Unlike lymphangioma-like KS, this process is characterized by a prominent cuboidal epithelioid (“hobnailing”) endothelial cells that lack nuclear atypia.
  + WT-1 negative (see above)
  + LNA-1 (HHV8) negative

4. **Endovascular papillary angioendothelioma (intralymphatic angioendothelioma)**

* + The “Dabska tumor” is a low-grade tumor showing lymphatic differentiation and mostly affecting children and teenagers. Process arises principally in dermis and subcutaneous tissues.
  + In contrast to lymphangioma-like KS, this lesion features lymphatic spaces lined by cuboidal epithelioid (“hobnailing”) endothelial cells and tufted papillary projections protruding into the vascular space.
  + LNA-1 (HHV8) negative

5. **Retiform hemangioendothelioma**

* + Very low-grade lymphatic tumor presenting as a red to blue dermal nodule or plaque in young adults.
  + Elongated, arborizing lymphatic spaces typically lined by more epithelioid (“hobnail”) endothelial cells than lymphangioma-like KS; only rare presence of the endothelial-lined intraluminal hyaline cores that typify intralymphatic angioendothelioma)
  + Typically associated with a spindle cell component and chronic inflammation.
  + LNA-1 (HHV8) negative

**Summary:**

Kaposi sarcoma (KS) is a low-grade vascular tumor that is seen in four different epidemiologic-clinical settings: Classic, African (endemic), AIDS-associated (epidemic) and iatrogenic (immunosuppessive). The AIDS-associated and the lymphadenopathic form of Africa KS are the most aggressive clinical subtypes. KS typically progresses through three distinct clinical and histopathological stages: early (patch) stage, plaque stage and nodular (tumor) stage. Histologically, classical Kaposi sarcoma is characterized by a variably cellular and mildly atypical spindle cell proliferation accompanied by slit-like vascular spaces lined by mildly atypical endothelial cells. The former component becomes more prominent with advanced stages of the disease. Extravasated red blood cells are characteristically observed within the spindled cell component, and hemosiderin deposition is common. Protrusion of native adnexal or vascular structures into neoplastic vessels (the “promontory” sign) is observed in early Kaposi’s sarcoma (as well as in other lymphatic tumors). A lymphoplasmacytic infiltrate is commonly noted within lesional tissue.

A number of histologic variants have been reported in the literature, including lymphangiectatic, lymphangioma-like (under discussion), anaplastic, pyogenic granuloma-like, intravascular, bullous, keloidal, micronodular, verrucous, and telangiectatic types. These lesions are rarely seen in their pure form and most commonly occur in association with classic-appearing KS. In our case, typical Kaposi sarcoma morphology was not identified in the tissue analyzed resulting in a broad differential diagnosis. As the pure form of the tumor mimics other lymphangiomatous processes, including low-grade angiossarcoma, clinical correlation is recommended as the other lesions in the differential are not associated with immunosuppression. Importantly, LNA-1 is the most specific immunomarker available for diagnosing KS. However, it should be noted that immunoexpression of this protein has been reported in rare examples of angiosarcoma, hemangioma, and dermatofibroma. As Kaposi sarcoma is one of the more common AIDS-defining malignancies, it is necessary for the pathologist to be aware of the various morphologic expressions of the disease, especially in the absence of traditional-appearing KS.

The lymphangioma-like variant generally coexists with conventional Kaposi sarcoma but rarely may present in a pure form (like the case under discussion). Similar to other subtypes of KS, the tumor cells immunoexpress LNA-1 (most specific immunomarker for KS), CD31, Fli-1, ERG, CD34; lymphatic endothelial-related markers, D2-40, VEGFR3 and PROX-1, and variably expresses WT-1. Ki-67 index is low. The pathogenesis of this cytologically bland and clinically indolent KS variant is an enigma and fuels speculation. Research has shown that HHV-8 viral infection alone is insufficient for the development of KS and therefore absence of promoting factors may result in this attenuated form of KS. Alternatively the virus, or the LANA protein that binds various regions of the circular episomal viral complex and facilitates histone modification and gene transcription may be defective and not able to elicit the same degree of endothelial proliferation or inflammatory response as in classical KS.

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**Case Number 6 (Alexandra Larson, MD): Pregnancy- associated breast carcinoma (PABC)**

**Clinical:** A 41-year-old G4P4 woman recently weaned her 15-month-old son. She presents with a 1.9cm palpable mass in the right breast at 11:00, 6cm from the nipple.

**Histology**

Representative sections show a lobulated mass composed of solid nests and sheets of epithelial tumor cells. The tumor exhibits high-grade morphological features including absence of gland formation, marked cellular pleomorphism, and high mitotic activity (up to 20 or more per 10 high-power fields). Lymphatic spread of the tumor is evident. The surrounding breast parenchyma shows prominent lactational changes. Tumor cells showed high immunoexpression of Ki-67 (90%), but no expression of estrogen receptor or progesterone receptor proteins or HER-2 (“triple negative”). P53 was also not expressed in the tumor.

**Differential Diagnosis**

-Breast carcinoma: pregnancy-associated breast cancer

-Metastatic carcinoma

-Melanoma

**Summary and brief discussion:**

Pregnancy-associated breast cancer (PABC) is breast cancer diagnosed in a pregnant woman or a post-partum woman up to 1 year following delivery. Though PABC can present as any histologic subtype (ductal, lobular, medullary), PABCs are usually high-grade, poorly differentiated carcinomas as commonly observed in young women with breast carcinoma. Relative to other cancers diagnosed in pregnancy, breast cancer is about as common as melanoma or Hodgkin lymphoma—though relatively less common than cervical cancer diagnosed during pregnancy. Of the 6 million pregnancies annually in the US, up to 1 in 3000 of them will be complicated by maternal breast cancer. Put another way, 0.2-3.8% of all breast cancer diagnoses are PABC, which is 25-30% of all breast cancers diagnosed in pre-menopausal women. Pregnancy-associated breast cancer confers a poorer prognosis (overall survival and disease free survival) in comparison to age and stage-matched non-PABCs. Additionally, women diagnosed with PABC in the 2-5 year post-partum period have higher rates of metastatic disease. Though pregnancy is a risk for breast cancer in the 5-10 years post-partum, there is a dual effect of pregnancy on breast cancer incidence, with a decline in incidence in parous women (compared to nulliparous women) over the 20-30 year period post-partum. There are many hypotheses for the mechanisms of both the promotive and protective effects of pregnancy. Although there is no unifying histology for PABC, emerging data suggest a common theme regarding the tumor’s biology: **increased expression of hormone-regulated cell cycling genes.**

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