Granulosa cell tumors (GCT) are more common in adults than children, with only 5% of GCTs presenting in the prepubertal age group. Juvenile granulosa cell tumor (JGCT) accounts for 10% of ovarian neoplasms in children and is the most common of the sex-cord-stromal tumors in children, representing approximately one-third to one-half of sex-cord-stromal tumors in the pediatric population. In children, the average age at diagnosis of JGCT is 8-9 years. It is rare in infancy, accounting for only 6% of cases in one large series of JGCT (Young, 1984). Congenital cases have been reported. Clinical presentation in young children is typically characterized by signs of isosexual precocious puberty (pubic hair growth, clitoral enlargement, vaginal bleeding, breast development, advanced bone age), whereas adolescents are more likely to have menstrual irregularity, abdominal pain and swelling, or rarely virilization. Rupture occurs in approximately 10% of cases. Granulosa cell tumors are bilateral in only 3% of patients. Serum markers of JGCT include estradiol, inhibin, and anti-Mullerian hormone, although approximately 30% of JGCT do not produce steroid hormones and can not be followed in this way. Due to increased inhibin secretion, serum FSH, LH, and GnRH may be very low. If elevated, CA-125 may also serve as a tumor marker. JGCT has been reported in association with Ollier disease (enchondromatosis), Maffucci syndrome (enchondromas and hemangiomas), and other sporadic tumors of soft tissue and bone. JGCT has also been identified in children with abnormal karyotypes and ambiguous genitalia. Grossly, these tumors are typically solid, often with a cystic component. Tumor size ranges from 3 cm to 30 cm in greatest dimension, with an average size of 12 cm. The ovarian capsule is typically intact and smooth. Approximately 80% of granulosa cell tumors in children have morphology of the juvenile type (JGCT) and 20% are of adult type (AGCT). Microscopically, juvenile granulosa cell tumors have a multinodular growth pattern with diffuse cellular nodules and macrofolicles, surrounded by loose stroma. The cyst walls of the macrofolicles are lined by stratified granulosa cells and often contain mucoid fluid. Some granulosa cells may be leuteinized. Reticulin stains highlight clusters of granulosa cells surrounded by reticulin fibers. In contrast to AGCT, JGCT tumor cells have hyperchromatic oval nuclei with only rare nuclear grooves. Microfolicles (Call-Exner bodies) are rare or absent. Nuclear atypia and frequent mitotic activity is more typical of JGCT than AGCT. Tumor size, degree of nuclear atypia, and mitotic rate correlate with poor prognosis of JGCT when all stages are considered, but do not predict prognosis for Stage Ia and Stage Ib tumors. JGCT are typically located to the ovary and show benign behavior. Unlike pediatric germ cell tumors, granulosa cell tumors typically prompt surgical staging, including biopsy of the contralateral ovary, peritoneal cytology, and/or peritoneal biopsy. Treatment for JGCT confined to the ovary (Stage I) is surgical excision only, and outcome is excellent (83-98% survival for Stage Ia tumors). Advanced stage
granulosa cell tumors, particularly those with disease outside of the ovaries and uterus, are more difficult to treat, and have a significant associated mortality, with only 50% durable remission after chemotherapy. Although there is limited data on treatment and outcome of advanced stage JGCT, these tumors have been treated with combination chemotherapy using a cisplatin-based regimen, similar to AGCT. Recurrence of JGCT is infrequent relative to AGCT, but tends to occur earlier. The most important prognostic factor for JGCT is tumor stage, and no histologic parameters have been proven to be independently predictive of aggressive course.

References:

DX: Sertoli Leydig Cell Tumor of Ovary - 77% of respondents

Other Diagnosis: Sex Cord / Sclerosing Stromal Tumor 16%; Juvenile Granulosa Cell Tumor 6%; Gonadal Stromal Tumor 1%

Q1: (D) 90% (C) 6% (E) 3% (B) 1%
Q2: (D) 96% (B) 4%
Q3: (C) 94% (D) 5% (E) 1%

The left ovarian tumor was comprised of a proliferation of round to oval cells with variable cytoplasm and hyperchromatic nuclei, growing in sheets and lining cyst walls. Some cells show monomorphous round nuclei with prominent nucleoli, indicating Sertoli cells. Other admixed small cells with granular eosinophilic cytoplasm showed morphology of Leydig cells. No nuclear grooves were identified. Mitotic figures were rare and there was no evidence of tumor necrosis or cytologic atypia. Reticulin stain shows reticulin fibrosis surrounding small nests of cells and perivascular regions. CD99 and inhibin stains were both positive in the tumor cells. The absence of well-formed tubules makes diagnosis difficult in this case, however the presence of scattered Leydig cells is a clue to the correct diagnosis of Sertoli-Leydig cell tumor.

Sertoli-Leydig cell tumor (SLCT), also called arrhenoblastoma, is a rare ovarian tumor which accounts for 0.5% of all ovarian tumors and approximately 5-20% of sex-cord stromal tumors, a group that also includes juvenile granulosa cell tumor (JGCT), pure Sertoli cell tumor, and sex cord tumor with annular tubules. SLCT is approximately one-fifth as common as granulosa cell tumors. Average age at presentation is 25 years, and approximately half (52%) of SLCTs are diagnosed in patients under the age of 20. Most patients present either with androgenic effects (virilization) or abdominal swelling or pain with no hormonal effects. Laboratory testing may show elevated testosterone metabolites, and in some cases elevated alphafetoprotein levels. Peutz-Jeghers syndrome is associated with sex cord-stromal tumors, including the distinctive sex cord tumor with annular tubules (SCTAT), Sertoli cell tumor, and SLCT.

Pathologically, Sertoli cell tumors are typically solid, yellow, and range from 4-12 cm in diameter. A predominantly cystic component, as in this case, is uncommon (5%). The growth pattern may be diffuse or nodular, most often with a tubular histologic pattern. A number of other patterns have been described, including cords and trabeculae, diffuse, pseudopapillary, retiform, islands/alveolar, and spindled forms. Children more often show poorly differentiated or retiform patterns, and the retiform pattern has been associated with malignant behavior in 25% of cases. There is typically abundant stroma, which shows sclerosis and/or calcification in some cases. A minority of cases (10%) are “lipid-rich” with abundant cells showing clear foamy cytoplasm. More than rare Leydig cells admixed with the Sertoli cell component warrant the designation of SLCT, as in this case. Heterologous elements may also be seen in SLCT, including gastrointestinal epithelium, carcinoid, cartilage, and skeletal muscle. Immunohistochemistry is typically positive for pan-cytokeratin or Cam 5.2 (65%), inhibin (82%), CD99 (86%), and vimentin (94%). Calretinin and neuron specific enolase are each positive in approximately half of cases, and S100 and smooth muscle actin are positive in a minority of cases (10% and 22%, respectively). Epithelial membrane antigen and chromogranin are negative. Inhibin is a marker of the sex-cord stromal tumors and is typically negative in the epithelial tumors.

Histologic patterns other than tubular morphology may result in diagnostic difficulty and need for immunohistochemical stains to delineate the correct diagnosis. In adults, the most common differential diagnoses of SLCT include endometrioid carcinoma and carcinoïd tumor, and an immunohistochemical panel for inhibin, EMA, and chromogranin aids in diagnosis in such cases. In children, the primary differential diagnosis is with other sex-cord stromal tumors, principally juvenile granulosa cell tumor.

Most SLCT are unilateral and stage I (80%) with bland cytology and clinically benign behavior. If confined to the ovary, treatment requires surgery alone, and prognosis is generally excellent. Advanced stage disease requires surgical resection followed by a platinum-based chemotherapy regimen. Unlike pediatric ovarian germ cell tumors which require staging only for gross disease, patients with sex-cord stromal tumors often undergo more extensive intraoperative staging, including peritoneal washings, peritoneal biopsies, wedge biopsy of suspicious lesions of the contralateral ovary, bilateral retroperitoneal lymph node sampling, and omentectomy. Histologic features which may portend recurrence and a worse prognosis in Stage I tumors include moderate to severe cytologic atypia, necrosis, and a high proliferative rate (> = 20 mitoses/10 high power fields).

It should be noted that the pathogenetic relationship between the SLCT and pineoblastoma in this patient remains unclear, as this specific association has not been documented in the medical literature.
References:

The explanted liver weighed 1331 grams and showed a vaguely nodular firm yellow-brown cut surface. Microscopically, the liver shows features of primary sclerosing cholangitis. The bile ducts are large, irregular, and dilated, surrounded by loose mesenchyme and moderate to severe chronic inflammation, including plasma cells and lymphoid aggregates. The hepatocytes show eosinophilic cytoplasm. PAS stains show no evidence of PAS-positive diastase-resistant globules, as in alpha-1-antitrypsin deficiency. Thick collarettes of fibrosis and concentric fibroplasia surround stenotic bile duct profiles. Trichrome stain highlight areas of mild bridging fibrosis extending from some portal tracts, but there was no evidence of cirrhosis. This is accompanied by neutrophilic inflammation in the portal tracts and infiltrating the ductal epithelium (acute pericholangitis). Electron microscopy showed normal rosettes of glycogen and no abnormalities of mitochondria or peroxisomes.

Non-specific parenchymal changes associated with cholestasis include feathery degeneration of hepatocytes, canicular bile, and Kupffer cell bile phagocytosis. In contrast to non-obstructive forms of cholestasis, obstructive cholestasis is further characterized by bile ductular proliferation, bile stasis in ducts, portal tract edema, neutrophilic inflammation, and cholestasis in periportal hepatocytes. Longstanding obstruction also results in portal fibrosis. Potential etiologies for obstructive cholestasis in neonates and young children include primarily extrahepatic biliary atresia, common bile duct obstruction (biliary sludge, gallstones, choledochal cyst), and inspissated bile (cystic fibrosis). In older children and adolescents, the differential diagnosis includes common bile duct obstruction (gallstones, stricture), primary biliary cirrhosis, and primary sclerosing cholangitis, as well as graft versus host disease and liver transplant rejection in susceptible populations.

Primary sclerosing cholangitis (PSC) is a disease of uncertain etiology characterized by inflammation and obliterative fibrosis of extrahepatic and intrahepatic medium and large bile ducts, accompanied by dilation of preserved ducts. Clinically, childhood PSC most often is diagnosed in older children and adolescents, and occurs with equal frequency in boys and girls. Clinical symptoms are non-specific, typically fatigue, anorexia, and pruritus. Splenomegaly due to portal hypertension is another mode of presentation. Unlike adults, most children (80%) do not present with jaundice. PSC is associated with inflammatory bowel disease (IBD) in only approximately 50% of pediatric cases, less commonly than in adults. Furthermore, hepatic disease often predates recognition of IBD in the pediatric population. Childhood PSC often mimics autoimmune hepatitis clinically, and associated serologic markers may include anti-nuclear antibodies (ANA), anti-smooth muscle actin antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), and occasionally anti-liver kidney microsomal antibodies (LKM). Cholangiography is essential for diagnosis, showing a characteristic “beaded” pattern caused by alternating strictures and dilated segments of the extrahepatic biliary tree.

Histologically, PSC causes progressive concentric periductal fibrosis (“onion skin fibrosis”) resulting in atrophy of the ductal epithelium and obliteration of the lumen by fibrous scars. The intervening dilated ducts develop periductal edema with neutrophil infiltrates (pericholangitis). End-stage disease manifests with a pattern of biliary cirrhosis. Some cases have overlapping features of AIH, with portal plasma cell infiltrates and piecemeal necrosis. However, the additional features indicating a chronic cholangiopathy (bile duct epithelial damage, bile ductular proliferation, and circumferential interlobular bile duct fibrosis) support a diagnosis of PSC. It should be noted that the periductal fibrosis characteristic of PSC may be difficult to detect in needle biopsies, due to the preferential involvement of large ducts in this disease.

Treatment of PSC may include corticosteroids, particularly in cases with features of AIH, as well as ursodeoxycholic acid for cholestasis, although the most effective therapies have not been determined. The natural history of PSC is typically slow progression to end-stage disease, with a median survival of approximately 10 years, although patients with severe extrahepatic duct stenosis at presentation have a more rapid course, typically requiring transplantation within 5 years of diagnosis.

The differential diagnosis of PSC in children includes secondary forms of sclerosing cholangitis, including Langerhans cell histiocytosis, Hodgkin lymphoma, immunodeficiencies associated with cryptosporidiosis or CMV infection, and cystic fibrosis. In contrast to PSC, PBC is an autoimmune liver disease of adults, most commonly women, which is characterized by elevated anti-mitochondrial antibodies and progressive small duct lymphocytic inflammation and destruction. PBC does not involve extrahepatic bile ducts.
References:

SPP 08-09

DX: Gastric Smooth Muscle Tumor of uncertain biologic potential - 68% of respondents

Other Diagnosis: Inflammatory Myofibroblastic Tumor 22%; GIST 9%; other 1%

Q1: (A) 68% (B) 19% (C) 9% (D) 4%
Q2: (D) 77% (C) 20% (B) 3% (A) 7%
Q3: (D) 63%* (B) 21% (C) 9% (A) 7%

- Includes diagnoses of Leiomyoma, Leiomyosarcoma, GSMT or GSMT of uncertain biology
  - Correlation between Diagnosis and “option selected” to Q3:
    - Leiomyoma + "B" Benign Neoplasm = 10%
    - Leiomyoma + "D" Uncertain biology = 20%
    - Leiomyosarcoma + "C" High-grade = 9%
    - Leiomyosarcoma + "D" Uncertain = 11%
    - GIST + "D" Uncertain biology = 9%

The partial gastrectomy specimen weighed 261 grams and included a protruding, ulcerated, antral transmural tumor with fistulous tract into the omentum. The tumor measured 6.5 x 6 x 5.5 cm., the cut surface appears fasciculated, firm and was of fleshy consistency, softening related to area of fistula and abscess formation.

Microscopic sections show an infiltrative spindle cell tumor with smooth muscle morphology, extensive deep ulceration creating a fistulous tract deep into the wall of the stomach. There is extensive inflammation and necrosis within the ulcer and immediately adjacent mass. Tumor cells are organized as bundles and fascicles intersect, invading lamina propria and muscularis propria of the stomach, as well as the perigastric omental soft tissue. There is variable associated fibrosis and inflammation. Individual cells show ovoid elongated nuclei and sarcoplasm with longitudinal filaments; no epithelioid features noted, mild to moderate pleomorphism noted, no anaplasia.

Ultrastructure includes features of subplasmalemmal and sarcoplasmic filaments with dense condensations and micropinocytotic vesicles. Mitotic activity averages 1-2/50 HPF’s. No atypical mitosis seen. The proliferative index by Ki-67 averages 3%. Several regional lymph nodes were uninvolved.

Tumor cells are diffusely and strongly positive for desmin, muscle specific actin (image) and smooth muscle actin. Pertinent negative markers included CD117, CD34, S100, keratin, EMA, ALK1 and EBER, which help to exclude many alternative diagnoses including synovial sarcoma, nerve sheath tumor, inflammatory myofibroblastic tumor with / without ALK rearrangement, and specifically GIST. No EBV encoded RNA documented. The immunophenotype, morphology and infiltrative borders support a diagnosis of Gastric Smooth Muscle Tumor of uncertain biologic potential or Leiomyosarcoma - uncertain biologic behavior. The absence of high mitotic activity (>10/10 HPFs) and pleomorphism are arguments against an overt high-grade leiomyosarcoma.

Gastric tumors in childhood and adolescence are rare, the vast majority represented by mature (biologically benign) teratomas, inflammatory myofibroblastic tumors, GIST’s lymphomas and rare adenocarcinomas associated with underlying disorders.

Since the identification and reliable diagnosis of GIST among mesenchymal gastric neoplasms, most GI leiomyomas / leiomyosarcomas became re-classified as Stromal Tumors. One large series describes up to 94% of “smooth muscle tumors” re-classified as GIST. Only those extremely rare neoplasms such as this patient’s lesion, are considered “true” smooth muscle neoplasms, either leiomyomas, smooth muscle tumors of uncertain biology or leiomyosarcomas. A recent review gastric mesenchymal tumors in children and young adults from the AFIP, reports that from 1877 tumors, 55 occurred in young age group, 44 GISTs were identified and 11 tumors reclassified as IMT, desmoids, desmoplastic small round cell tumor, 3 mesenchymal tumors NOS and 2 unclassified sarcomas. No true leiomyomas or leiomyosarcomas were identified.
Smooth muscle tumors that are EBV-derived tend to be small and often multifocal, many times clinically silent. In the gastrointestinal tract they become manifest by bleeding or obstructive symptomatology. They arise from the muscularis mucosa or emanate from the walls of arterioles. Rarely it may involve the stomach. This tumor did not reveal any EBV encoded RNA, but the rarity of visceral and soft tissue smooth muscle tumors in children warrant exclusion of an underlying immunodeficiency disorder. In the setting of post-organ or stem cell transplant, these tumors are more common. While recent advances in classification and stratification of risk for GIST has been defined, no such parameters exist for smooth muscle tumors since their extreme rarity precludes large clinicopathologic studies. The older literature of gastric mesenchymal neoplasms certainly consists of series of GISTs and not smooth muscle neoplasia.

A few clinical and morphologic correlative criteria do exist for smooth muscle tumors arising from the GI tract. These tend to occur in distinctive sites. The colorectal region gives rise to small tumors, usually emanating form the muscularis mucosae and is usually benign. Leiomyomas arising in the distal esophagus and esophagogastric junction form another distinct clinical group, which appear to also behave in a benign fashion regardless of size; they usually show low to moderate degree of cellularity and low index of mitoses. Leiomyosarcomas of the GI tract tend to be morphologically recognized readily as malignant by their morphology or at least significant mitotic activity. In some cases they become a diagnosis of exclusion.

Immunohistochemistry, in-situ hybridization and ultrastructure contribute greatly to the recognition, diagnosis and classification of mesenchymal tumors of the gastrointestinal tract.

References:


Miettinen M, Sarlomo-Rikala M, Sobin LH. Mesenchymal tumors of muscularis mucosae of colon and rectum are benign leiomyomas that should be separated from gastrointestinal stromal tumors-a clinicopathologic and immunohistochemical study of eighty-eight cases. Mod Pathol. 2001;14:950-956.


Rosai-Dorfman disease (RDD) is one of the several idiopathic non-LCH histiocytoses that is considered to be a generally benign histiocytic inflammatory process; it may present either in lymph nodes, most frequently the cervical chain, where it is designated SHML, or extranodally, where it tends to pursue a slightly more aggressive course. RDD typically involves adolescents and young adults, with a mean age of 20 years at initial presentation; however, it has been described in infants and young children (as in the present case) as well as in middle-aged to older adults. African Americans are affected to a greater degree than whites and there is a slight male predilection in cases of cervical lymph node involvement, although males and females are equally affected in cases of extranodal disease. Extranodal sites include Waldeyer's ring, the upper respiratory tract, skin, subcutaneous tissues of the trunk and proximal extremities, orbit, bone (including the skull), meninges (dura mater), and breast. RDD is almost always a sporadic condition, as only rare familial clusters have been reported in the literature. Characteristically, patients with nodal disease present with painless lymphadenopathy, while those with extranodal involvement present with a space-occupying mass. Occasionally, however, systemic or constitutional symptoms may be present, in the form of fever, night sweats, and weight loss, which may be accompanied by polyclonal hypergammaglobulinemia and occasionally autoantibodies may appear in the serum. The constellation of constitutional and inflammatory findings is most probably related to the phenomenon of macrophage overactivation and hypercytokinemia attributable to immune dysregulation.

Grossly, the lesion most often appears as moderately to markedly ("massively") enlarged lymph nodes or a mass with capsular thickening by fibrosis. Microscopically, the nodal lesion may appear on low power to be regressing RDD lesions may resemble an inflammatory pseudotumor.

The differential diagnosis for RDD consists predominantly of other nodal sinus histiocytosis proliferations, namely, sinus histiocytosis (but macrophages are considerably smaller than RDD histiocytes), lymph nodes draining prosthetic implants or other foreign bodies, LCH, and a "RD-like" reaction within lymph nodes involved by Hodgkin lymphoma, LCH, or autoimmune lymphoproliferative syndrome (ALPS). Late or regressing RDD lesions may resemble an inflammatory pseudotumor.
The prognosis of RDD is generally favorable, as RDD usually follows an indolent clinical course with a slow but spontaneous regression of the inflammatory process. It may also regress rapidly and occasionally, it may recur. Extramedullary disease, particularly at anatomically "vulnerable" sites, is most strongly linked to poor outcome and mortality; such sites include the central nervous system, dura and leptomeninges, and upper respiratory tract. Associated immune derangements (i.e., hypergammaglobulinemia) worsen the clinical outcome. Corticosteroids and surgery have been used for progressive disease, while chemotherapy has been employed for refractory or life-threatening lesions.

The pathogenesis of RDD is truly enigmatic. Although infectious etiologies have been proposed, namely Epstein-Barr virus (EBV) and human herpesvirus-6 (HHV-6), none have been substantiated. The generally accepted theory is that RDD represents an exaggerated hematopoietic response to an unidentified immunologic stimulus. Its previously mentioned association with ALPS may offer some insight into its mechanisms. ALPS is a genetic disorder of programmed lymphocyte death initiated by mutations in genes that prevent apoptosis in lymphocyte subsets; the immunologic signature in classical ALPS is a mutation in either Fas or the Fas ligand, resulting in defective Fas/FasL signaling and leading to impaired apoptosis. Intriguingly, recent studies have demonstrated Fas mutations in patients with RDD that is not associated with ALPS, suggesting that RDD may somehow be related to deregulation of apoptotic signaling pathways, ultimately resulting in histiocyte proliferation and hyperfunction. RDD may also be related to familial hemophagocytic lymphohistiocytosis by virtue of defective lymphocyte-mediated cytotoxicity. In summary, RDD perhaps may be best conceptualized as a "disorder of immune homeostasis".

The relationship between RDD and LCH is perhaps even more enigmatic. Interestingly, although the coexistence of RDD and LCH within the same organ is rare, it has been described previously in the literature on two occasions. RDD may represent a reaction pattern to the LCH; alternatively, LCH within a predominant pattern of RDD may be a response to the nodal microenvironment created by the LCH. Jaffe, in his schematic representation of the histiocyte developmental pathway, emphasizes that histiocytes, being derived from CD34+ myeloid bone marrow precursors, give rise to a CD14+ monocyte pool of circulating intermediates that then possess the capability to differentiate into either macrophages or antigen-presenting dendritic cells. Furthermore, there is inherent plasticity in this histiocytic ontogenetic paradigm by virtue of the fact that both macrophages and dendritic cells can be driven in the direction of each other by various stimuli, especially cytokines (i.e., dendritic cells in the presence of interleukin-10 [IL-10] or monocyte colony-stimulating factor [M-CSF] can acquire a macrophage phenotype), referred to in a recent case report of coexistent RDD and LCH as a "phenotypic switch". The somber truth is that the precise relationship of the two disorders is not clear; but it is important to acknowledge that the biologic process may not necessarily reflect the relative proportions of the different histiocyte populations.

REFERENCES


