SPP 07-11

DX: **Alveolar Soft-Part Sarcoma** = 93% of respondents
Other Diagnoses: Granular Cell Tumor = 5% / Melanoma of Soft Parts = 2%

Question answers:
- Q1: (D) 95% (B) = 5%
- Q2: (D) 93% (B) = 5% (A&E) = 2%
- Q3: (A) 93% (B) = 6% (C) = 1%

The cut surface shows a lobulated, fleshy mass infiltrating regional soft tissues of the orbit. Histologic sections demonstrate a large-cell neoplasm growing in nests, lobular and solid and pseudoalveolar formations, infiltrating skeletal muscle and regional vasculature. There is a conspicuous vascular network creating an organoid appearance to the tumor. The tumor cells are variably polygonal with abundant eosinophilic and coarsely granular cytoplasm, many with elongated densities apparent on H&E, accentuated by the PAS stain as evidence of crystalline structures. The nuclei of the tumor cells appear relatively uniform with variable but usually conspicuous central nucleoli. Mitotic activity and necrosis are not conspicuous. By ultrastructure, these tumor cells have distinctive and characteristic membrane-bound, rhomboid crystalline inclusions, showing a 10nm periodicity as confirmatory evidence of Alveolar Soft Part Sarcoma (ASPS). While there is no consistent immunohistochemical reagent or panel that confirms this diagnosis, nuclear expression of TFE-3 for the carboxy-terminal portion is consistently expressed in the majority of ASPS's.

The diagnostic term and its distinctive features were initially characterized by Christopherson, Foote and Stewart in 1952. The report included 12 well-documented cases, establishing a distinction from granular cell tumors / myoblastomas and various other diagnostic terms. Since then, numerous case reports and reviews have expanded the clinical spectrum of this rare but morphologically and clinically distinctive neoplasm. Alveolar Soft-Part Sarcoma is a slow growing tumor with a marked propensity for metastatic dissemination. It arises usually in soft tissues of extremities, but has been described in multiple sites, including rare sites such as the trunk, abdominal wall and retroperitoneum and genitourinary tract. In the head and neck regions, the soft tissues of the orbit and tongue are particularly frequent sites of involvement, particularly in younger patients. The largest series of orbital ASPS describes most patients presenting with proptosis, mass, and as seen in this patient, there may be dilated conjunctival vessels. Duration of symptomatology varied from weeks to years. The two patients that died at 14 and 21 years after diagnosis. Primary presentation in bone is rare. The reported age range is between 11 months to 75 years of age. Metastatic ASPS at presentation is not a rare event, particularly in children and adolescents. At presentation or during dissemination, the favored sites of metastases are the lungs, brain, skeleton, lymph nodes and liver. In the initial report of this tumor, Christopherson noted a late (18-year) post resection recurrence in the lung, liver and diaphragm of a "golf ball-sized" buttock mass. The differential diagnosis of ASPS varies with the site of presentation, but may include malignant granular cell tumor, paraganglioma, melanoma, and metastatic adrenocortical, renal and hepatocellular carcinoma. The largest clinico-pathologic series document relatively consistent adverse prognostic factors which include: tumor size >5cm, advanced local stage, bone involvement and metastatic dissemination.

Cytogenetic studies of ASPS has repeatedly demonstrated shown various abnormalities involving chromosome 17 q25 region resulting form a rearrangement between Xp11 and 17q creating a derivative chromosome 17 der(17) t(X;17)(p11.2;q25). This alteration fuses the TFE3 transcription factor gene to ASPL gene at 17q25. Of interest is the presence of this gene fusion in primary renal epithelial neoplasms with distinctive morphologic characteristics, unique among the translocation associated RCC spectrum. These renal tumors in some areas of their morphologic spectrum are indistinguishable from ASPS, including the presence of crystalline rhomboid structures. Nuclear expression of TFE3 as detected by immunohistochemistry for the
C-terminal portion is helpful in the appropriate context, since other tumors in the differential diagnosis may rarely show nuclear expression.

Prompt recognition and adequate tumoral resection with clear margins remain the best therapeutic option for these patients. The distinctive morphology of ASPS, readily apparent PAS resistant crystalline structures, ultrastructural features and exclusion of pertinent entities by immunohistochemistry allow an accurate and rapid diagnosis. Confirmation with a nuclear TFE3 expression and documentation of molecular gene fusion aid in the completion of the diagnostic workup. Close and long-term follow-up is warranted in these patients.

References:

DX: Gastrointestinal Stromal Tumor = 99% of respondents
Other Diagnoses: Epithelioid Leiomyoma = 1%

Question answers:
Q1: (B) 48% (C)= 43% (E)= 6% (A)= 3%
Q2: (B) 86% (D)= 10% (A)= 2% (C)= 2%
Q3: (D) 66% (B)= 28% (E)= 4% (A&C)= 2%

CT imaging showed multiple stomach nodules protruding into the gastric lumen. Grossly, the partial gastrectomy specimen showed multifocal submucosal and intramural tan-red masses, ranging in size from 1.2 cm to 9 cm in greatest dimension each, with the largest lesion associated with overlying mucosal ulceration. Microscopically, the masses were composed of a monotonous proliferation of spindled and epithelioid cells with a vaguely fascicular pattern. The cells showed bland ovoid nuclei with no cytologic atypia and only rare mitotic figures. Ki67 (Mib1) showed a proliferative index of 10-15%. Occasional infiltrating inflammatory cells were also noted. Immunohistochemistry showed the tumor to be positive for CD34 and CD117 (ckit), confirming the diagnosis of gastrointestinal stromal tumor (GIST).

Gastrointestinal tumors are mesenchymal tumors of the intestinal tract thought to arise from the peristalsis-regulating cells of the gut, the interstitial cells of Cajal (ICC). GISTs encompass lesions previously reported as gastrointestinal autonomic nerve tumor, leiomyoma, leiomyosarcoma, and leiomyoblastoma, and may have smooth muscle, neural, or mixed differentiation. The most common sites of involvement are the stomach (50%) and small intestine (25%) with the remainder involving esophagus, colon, rectum, mesentery, and retroperitoneum. By immunohistochemistry, GISTs typically express CD117 (95%) and CD34 (60-70%), with variable expression of SMA (30-40%) and S100 (5%). The differential diagnosis of CD117-negative mesenchymal tumors in the gastrointestinal tract includes a true smooth muscle tumor or nerve sheath tumor, fibromatosis, solitary fibrous tumor, and inflammatory myofibroblastic tumor.

Most cases (90%) are diagnosed in adults over 40 years of age, and only rarely (<1%) in children. Common features of GIST in children include predominantly female gender, gastric primary and predominantly epithelioid morphology. Multicentricity and tendency for lymph node involvement have also been reported in children. While over 80% of GISTs in adults have activating mutations in one of two receptor tyrosine kinase genes (KIT or PDGFRA), GISTs in children typically lack these mutations.

Most GISTs in pediatric patients are sporadic (non-syndromic), however some occur in the setting neurofibromatosis type 1 (NF1) and Carney triad (GIST, pulmonary chondroma, paraganglioma). NF1-associated GISTs tend to be multiple, involve the small and large intestine, have spindle cell morphology and skeinoid fibers, and are associated with ICC hyperplasia. Familial GIST syndrome resulting from autosomal dominant germline mutations in KIT, or rarely PDGFRA, may result in multicentric tumors in young adults, but appears to be uncommon in the pediatric population. GIST has also been reported in association with multiple endocrine neoplasia syndrome type I, familial paraganglioma, mastocytosis/urticaria pigmentosa, melanocytic abnormalities, and dysphagia/achalasia.

The biologic behavior of GISTs is difficult to predict based on histologic features alone, and are not defined as “benign” or “malignant” on this basis. Instead, GISTs are classified into clinical risk categories based on tumor size and mitotic activity. Tumors less than 5 cm in diameter and with less than 5 mitoses in 50 high power fields have low risk of metastasis, while tumors greater than 10 cm or with greater than 10 mitoses in 50 high power fields have the highest risk of malignant behavior. Gastric tumors also have a more favorable prognosis than intestinal tumors, independent of size and mitotic activity. While the clinical behavior of pediatric GIST has been suggested to be more indolent than in adults, others have found unpredictable
behavior with metastasis despite otherwise favorable characteristics (small tumor size with low mitotic activity). Aggressive GISTs most often metastasize to the liver, abdomen, or lungs.

Treatment of GIST is primarily complete surgical resection. Advanced or unresectable GIST is treated with the tyrosine kinase inhibitors Imatinib or Sunitinib as first-line and second-line therapy, respectively. These agents are also used in children, despite frequent absence of KIT or PDGFRA mutations and generally poor clinical response. Intensity of KIT expression by immunohistochemistry does not predict response to therapy, as KIT-negative tumors may also respond to the tyrosine kinase inhibitors. The effectiveness of Imatinib as adjuvant or neoadjuvant therapy is currently being studied.

References

Although no abnormalities were seen at 20 weeks gestation, prenatal ultrasound at 30 weeks gestation during follow-up examination for gestational diabetes showed a hyperechoic left lung lesion. Subsequent fetal MR imaging at 33 weeks gestation showed an 8mm simple fluid-filled cyst in the left chest at the hilum, as well as abnormally increased signal throughout a slightly enlarged left upper lobe, raising a differential diagnosis of bronchogenic cyst versus congenital pulmonary airway malformation.

Gross examination of the left upper lobe removed at 9 weeks of age showed a distended upper lobe with an accessory pseudofissure, partially delimiting the lingula from the remainder of the left upper lobe. Superior to the hilum was a firm portion of cartilage with an underlying cystic lesion filled with mucus (mucocele). Serial parasagittal sections showed abnormally developed microcystic lung tissue peripheral to this lesion, involving approximately 60-70% of the left upper lobe and demonstrating a distribution roughly corresponding to the anterior and apicoposterior segments of the lung. The superior and inferior segments of the lingula were spared.

Microscopically, the lesion shows a pattern of “microcystic maldevelopment”, identical to the pattern described as Stocker type II Congenital Pulmonary Airway Malformation (CPAM) (previously called congenital cystic adenomatoid malformation (CCAM). The lung shows distended cystic spaces forming bronchiolar-like structures predominantly lined by respiratory epithelium. Other intervening areas show enlarged and simplified airspaces lined by alveolar-type epithelium. Some of the cysts and larger central airways show mucus and scattered muciphages in the lumen, indicative of bronchial obstruction. The gross features, presence of mucus stasis, and evidence of microcystic maldevelopment of the lung in a segmental distribution is diagnostic of Bronchial Atresia.

The differential diagnosis of cystic lesions of the lung include developmental lesions (bronchogenic cyst, bronchial atresia, CPAM, intralobar pulmonary sequestration), postnatally-acquired lesions (congenital lobar overinflation, pneumatocele, abscess, persistent pulmonary interstitial emphysema), and neoplasia (low-grade Cystic Pleuropulmonary Blastoma, type I). Pleuropulmonary Blastoma is excluded by the presence of numerous cysts lined by respiratory-type epithelium and absence of hypercellular foci of hyperchromatic spindled cells. Prenatal detection in this case excludes the acquired lesions. Congenital lobar overinflation may clinically resemble bronchial atresia, but is characterized by normally developed lung with the usual distribution of airways surrounded by alveolated parenchyma. The alveoli are markedly distended due to progressive air-trapping, in some cases corresponding anatomically to proximal bronchial stenosis or bronchomalacia, with collapse of the affected bronchus during expiration. Bronchogenic cyst is a solitary unicystic lesion lined by respiratory epithelium and surrounded by smooth muscle and cartilage plates, replicating a normal bronchial wall. Bronchogenic cysts are typically related to the distal trachea or bronchial tree, and are only rarely intraparenchymal.

Based on clinical and imaging features, congenital pulmonary airway malformation is the most commonly suspected diagnosis for specimens containing bronchial atresia. The classification of CPAM initially proposed by Stocker has undergone re-evaluation in recent years, as our understanding of the pathogenesis of certain patterns has progressed. Most notably, it has been recognized that the pattern described in the small
cyst type CCAM (Stocker type II) is a histologic pattern common to bronchial atresia, as well as extralobar and intralobar sequestration. The pattern of microcystic maldevelopment is variable with respect to the relative proportion of airway-type structures and alveolar-type structures, with some examples showing almost entirely respiratory epithelial-lined cysts (as in this case) and other examples showing increased bronchiolar number and complexity, but with abnormally distended airspaces predominating.

While this microcystic pattern and evidence of mucus stasis may provide a presumptive diagnosis of bronchial atresia microscopically, critical evaluation during gross examination allows identification of the atretic segment in many cases. Close attention to detail at the hilum of the lung may reveal a “bulging” lesion corresponding to the underlying mucocele, or a small nodular area of cartilage corresponding to the atretic bronchus. The lobe should be sectioned in a parasagittal plane (parallel to the hila plane) from lateral to medial, so that the relationship of the cystic lesion to the hilum is preserved throughout examination. In bronchial atresia, the parenchyma is typically microcystic peripherally, often associated with branching mucus-filled small airways. As the hilum is approached from the lateral aspect, a large mucus-filled cyst is typically present near the point of atresia, corresponding to a markedly ectatic bronchus. The medial aspect of the central cyst can then be probed retrograde for any connection to other intact proximal airways at the hilum. This also offers an opportunity for re-examination of the hilum for any cartilage rests in the suspected site of bronchial atresia. It should be noted that the specific site of atresia is more easily identified if the affected airway is large and proximate to the hilum, but can be much more difficult if the atretic bronchus is small and deeper within the parenchyma. The lobe should also be examined for presence of absence of an artery branch entering the pleura outside of the hilum, often at the medial basal angle of a lower lobe specimen, which would suggest an intralobar sequestration (bronchial atresia with systemic arterial supply).

Children with Bronchial Atresia are often asymptomatic and come to medical attention after incidental detection of a lesion, either by routine prenatal ultrasound imaging or chest x-ray. Older children may present with asthma-like symptoms (wheezing) or symptoms related to secondary infection of the lesion (fever, pneumonia). Surgical resection can usually be accomplished by lobectomy.

References

DX: **Rhabdoid Tumor of the Kidney = 97% of respondents**
Other Diagnoses: Clear Cell Sarcoma of Kidney = 3%

Question answers:  
Q1:  (C) 96%  (B&D)= 4%  
Q2: (B) 91%  (C) = 7%  (D) = 2%  
Q3: (E) 1%  (D) = 47%  (B) = 20%  (A)= 16%  (C)= 16%

To summarize the radiographic and pathologic features of this mass, the interpreting radiologist’s impression of the mass on abdominal CT scan was that of a “heterogeneous mass occupying and expanding most of the right kidney” with probable subcapsular hemorrhage that markedly displaced the surrounding structures and compressed the inferior vena cava inferiorly. Grossly, the tumor was variegated (due to zones of hemorrhage interrupting an otherwise tan-yellow mass) and had apparent pushing borders. However, microscopically, the tumor was aggressive, with widespread angiolymphatic invasion and focal extension into perinephric adipose tissue, along with metastases to 4 regional lymph nodes (3 periaortic and 1 paracaval) The microscopic features of the tumor were distinctive and consisted of essentially monomorphous sheets of noncohesive cells with round to oval nuclei, vesicular chromatin, numerous prominent eosinophilic nucleoli, and ample pink cytoplasm that had a glassy appearance and, in places, appeared to form globular inclusions with a focally “whorled” appearance. Foci of single cell necrosis were observed. No blastemal or stromal elements were identified.

Rhabdoid tumor of the kidney (RTK) is a rare primary tumor of childhood, comprising approximately 2.0-2.5% of the approximately 500 pediatric renal tumors reported yearly in the United States. The median age at presentation is 11-13 months; the male/female ratio is approximately 1.5 to 1. Originally described as a variant of Wilms tumor in 1978, RTK was given its present name in 1981; ironically, its perceived similarity to rhabdomyoblasts has not been supported by either ultrastructural or immunohistochemical analysis. The association of RTK in approximately 15% of cases with central nervous system tumors (now referred to as atypical teratoid rhabdoid tumors, or ATRT) has led to the elucidation of the unique molecular genetic events that define RTK (namely, inactivation of the *hSNF5/INI1* gene on the long arm of chromosome 22 [22q11.2]).

The demographic, clinical and pathologic features of RTK are distinctive. RTK is a tumor of infants and young children; the median age at presentation is 11-13 months; the male/female ratio is approximately 1.5 to 1. Because >95% of children with RTK are under 3 years of age, the diagnosis of RTK should be regarded with high suspicion (and therefore, vigorously challenged) in any child older than 3 years. The clinical features that most commonly characterize RTK at presentation include either gross or microscopic hematuria (observed in 84% in one study), fever (~44% in the same study), signs or symptoms referable to metastatic disease (to the liver, lungs, or brain; present in ~80% of children), and hypercalcemia secondary to either parathyroid hormone (PTH) or prostaglandin E$_2$ secretion. Unfortunately, high tumor stage at the time of presentation is also common and is one of the strongest adverse risk factors.

The pathology of RTK has been discussed above to some degree, but a few features merit additional comment. The tumor derives its “rhabdoid” appearance from the distinctive “whorled” nature of the cytoplasmic inclusions, which ultrastructurally have been demonstrated to be dense perinuclear aggregates of intermediate filaments. However, it is critical to understand that the whorled structures are not a diagnostic feature of RTK, being present in neoplasms other than RTK and sparse in some genuine RTK. The immunohistochemical profile of RTK is polyphenotypic but also nondiagnostic, with uniform intense vimentin immunoexpression, and patchy but focally intense expression of cytokeratin or epithelial membrane antigen (EMA) against a background of nonexpression of these antigens; such focally intense immunoreactivity is observed in >90% of cases of RTK. Desmin and neurofilament are also occasionally expressed. One final
comment regarding the pathology of RTK is the existence of variant patterns, which were reported in the literature in 1989; such variations include sclerosing, epithelioid, spindled, and lymphomatoid patterns. Despite these departures from the typical RTK pattern, however, virtually all cases will have *some* areas of classic RTK, which, in addition to the accompanying clinical features and molecular genetics, will guide the careful pathologist to the proper diagnosis. Finally, the highly aggressive growth pattern and opportunistic angiolymphatic invasion distinguishes RTK from many of the less infiltrative pediatric renal tumors.

Although many entities belong in the differential diagnosis of RTK, including most of the other primary renal neoplasms of childhood (i.e., Wilms tumor, cellular mesoblastic nephroma, and clear cell sarcoma of the kidney), the most difficult entity to distinguish morphologically from RTK is renal medullary carcinoma (RMC), also a tumor with large nuclei, prominent nucleoli, and ample amounts of pink cytoplasm. However, RMC is characteristically a tumor occurring in individuals greater than 5 years of age with sickle cell trait.

The unfortunately dismal prognosis of RTK – with a 75-80% mortality from the time of diagnosis – is primarily a function of high stage at presentation (stage III or IV in 80% of patients), a predictable consequence of the inherent biological aggressiveness of the neoplasm. A recently identified additional factor is related to age at diagnosis; in a 2005 NWTSG study, infants <6 months of age had a 4-year survival of 8.8% as compared to children ≥ 2 years, whose survival was 41.1% (statistically significant at a P value of <0.0001). Even with intensified chemotherapeutic regimens, outcomes in RTK remain extremely unfavorable.

Undeniably, the most significant advance regarding RTK over the past decade has been the elucidation of the molecular genetic events that govern its clinical behavior (including presentation and course). In 1998, it was reported that derangements in the long arm of chromosome 22 (22q), including deletions and translocations, ultimately resulted in inactivation of the *hSNF5/INI1* tumor suppressor gene, which is thought to function by encoding a transcription control protein which alters the conformation of the DNA-histone complex in such a way that transcription factors gain access to target genes. It is this inactivation of the *hSNF5/INI1* gene, by means of mutations, homozygous deletions, or whole chromosomal loss (i.e., monosomy 22) that constitutes the “molecular hallmark” of RTK. Furthermore, it has been demonstrated that individuals with concomitant renal and CNS rhabdoid tumors possess germline mutations that involve one copy of the *hSNF5/INI1* gene but distinct molecular derangements in the second copy (allele) for each neoplasm (RTK and ATRT), thus confirming that RTK and ATRT are indeed independent neoplasms rather than a metastasis of a primary tumor. The discovery that rhabdoid tumors arising at separate (namely, renal and extrarenal) anatomic sites are linked by the common molecular genetic events of mutations or deletions of the *hSNF5/INI1* gene has provided a unified concept of rhabdoid tumors as a pathologic process arising from a distinct molecular genetic derangement.

The elucidation of the inactivation of the *hSNF5/INI1* gene as the molecular signature of RTK also has practical diagnostic utility in that an immunohistochemical stain for the INI-1 gene product (protein) has established consistent nuclear immunoexpression of the protein in virtually all pediatric renal tumors except RTK (and corresponding lack of expression in RTK). Thus, INI-1 immunohistochemistry appears to be a highly sensitive and specific method for detecting *hSNF5/INI1* protein loss of function. Only further studies will determine whether or not absence of INI1 protein immunooexpression is entirely specific to rhabdoid tumors. On a final note, a recent 2006 study addressing the classification of primary malignant pediatric renal neoplasms by gene expression demonstrated a 41.1-fold increase in expression of glucagon in RTK over that in the other primary tumors (i.e., Wilms tumor, congenital mesoblastic nephroma, and clear cell sarcoma of the kidney). Interestingly, it has been reported in some studies that genes in the glycolysis/glucogenesis pathway are upregulated in tumors that are more aggressive with a poor prognosis.
In conclusion, RTK, like many other pathologic entities, is entirely unrelated to its namesake; and, as our understanding of molecular genetics increases, pathologic processes will be classified according to their specific molecular genetic derangements along with their morphologic features.

REFERENCES


**DX:**  **Alveolar Capillary Dysplasia with misalignment of pulmonary veins = 94%**
Other Diagnoses: Persistent Pulmonary Hypertension NOS = 6%

Question answers:  
Q1: (C) = 93%  (A) = 7%  
Q2: (E) = 93%  (A) = 5%  (B&C)= 2%  
Q3: (B) = 29%  (D) = 56%  (C)= 9%  (E)= 5%  (A)= 1%

The characteristic gross pathologic features at autopsy were right ventricular (RV) enlargement (dilatation) and hypertrophy (RV wall thickness = 0.5 cm) with prominent intrapulmonary blood vessels. The most striking microscopic features were 1) misalignment of pulmonary veins, characterized by thin-walled, dilated, tortuous veins located adjacent to pulmonary arteries within bronchoarterial bundles (sheaths), rather than within interlobular septa (their customary anatomic location); and 2) significantly diminished numbers of alveolar capillaries, which were centrally placed within alveolar septa, several cell thicknesses away from the pneumocyte-lined alveolar spaces; and 3) marked medial hypertrophy of small muscular pulmonary arteries and pulmonary arterioles (muscularization of arterioles), with multiple layers of smooth muscle cells arranged in concentric rings.

Alveolar capillary dysplasia (ACD), either with or without misalignment of pulmonary veins, is a rare yet probably underreported cause of respiratory distress, persistent pulmonary hypertension, and early neonatal death that represents a derangement in pulmonary vascular development which leads to the formation of defective, nonfunctional air-blood interfaces. Originally described in 1981, ACD has been reported in >80 (approximately 85) neonates and has a fairly stereotypical mode of presentation. The history is classically (in >95% of cases) one of a term or near-term infant, with favorable Apgar scores, who succumbs within 48 hours of life (and within the first 4 hours of life in ~50% of cases) to respiratory distress, hypoxemia, cyanosis, and pulmonary hypertension. All of these complicating conditions are refractory to standard positive-pressure mechanical ventilatory strategies, including high-frequency oscillatory ventilation, as well as pulmonary vasodilator, namely, nitric oxide (NO), administration, although some infants do manifest a transient response to NO. The refractory, recalcitrant nature of the pulmonary hypertension invariably leads to one or more trials of extracorporeal membrane oxygenation (ECMO). Attempts at weaning off of ECMO are almost universally unsuccessful, and death supervenes within weeks (~4-6) to months (~2-3). Currently, ACD remains a uniformly fatal disease; however, some modifications in diagnostic approaches to the condition do at least create some hope of biding time until lung transplantation can be performed.

The pathology of ACD is fairly consistent from case to case. Typically, though not uniformly, the pulmonary veins accompany pulmonary arteries within the same adventitial sheath and become parts of the bronchovascular bundles within the centers of the lobules, rather than residing within the interlobular septa at the peripheries of the lobules, creating the so-called “misalignment of the pulmonary veins”. Several theories have been espoused regarding the basis for this phenomenon, none of which have been proven; nevertheless, it is present in the majority of cases of ACD. The other essential histopathologic features include 1) a significant reduction of alveolar capillaries in general; 2) prominently widened (thickened) alveolar septa, containing loose mesenchymal elements (spindled fibroblasts and myofibroblasts and extracellular matrix) and centrally placed alveolar capillaries that are at least several cell widths removed from the nearest alveolar spaces; 3) striking pulmonary vascular changes, in the form of medial hypertrophy of small muscular pulmonary arteries, with distal extension of smooth muscle to involve the walls of pulmonary arterioles beyond the terminal bronchioles, or so-called “muscularization” of pulmonary arterioles; and finally, 4) variable degrees of alveolar underdevelopment. These findings, while uniform (diffuse) in the majority of cases of ACD (~85%), may be patchy (focal) in the remaining 15%; such variation may account for the occasional delayed presentation of ACD in some infants, between 2 and 6 weeks of life (up to 14% in some series).
The basis for the pulmonary hypertension in ACD is not entirely known, and may, in fact, be multifactorial. Proposed explanations have included 1) hypoplasia or underdevelopment of the alveolar capillary bed, which may lead to intrapulmonary shunting; and 2) hypoxemia due to an increased alveolar diffusion gradient, resulting in pulmonary vasospasm.

One other generally consistent characteristic of ACD is the presence of associated extrapulmonary findings, particularly involving the cardiovascular, gastrointestinal, hepatobiliary, and genitourinary systems. In a 2004 study that examined clinical records and pathologic findings in 23 neonates with ACD, at least one major additional major structural derangement involving an extrapulmonary system was identified in 82% of infants. Such a substantial incidence of extrapulmonary anomalies provides further evidence for an underlying malformative process or derangement in development.

The genetic basis for ACD remains undetermined; however, pedigree studies in 30 families from the previously cited 2004 study, each with one or more infants diagnosed with ACD, favor an autosomal recessive mode of transmission in at least a subset of families. Furthermore, active research addressing the molecular mechanisms governing the development of the pulmonary vasculature has provided at least some insight into the underlying pathogenesis surrounding conditions characterized by aberrant vascular growth, including ACD. As stated previously, the basic underlying defect in ACD is the failure to form normal air-blood interfaces within the lung. It has been shown that the final fusion between basement membrane of the alveolar capillary endothelial and type I pneumocyte is markedly impaired in mice lacking expression of certain isoforms of vascular endothelial growth factor (VEGF), namely, 164 and 188 and expressing only VEGF 120 isoforms; a similar phenotype is observed in mice either deficient in endothelial nitric oxide synthetase (eNOS) or in those treated with ENOS inhibitors. The relationship between eNOS and VEGF is complex, with NOS both an upstream activator and a downstream target of VEGF. Probably the most plausible explanation is that the large abnormal capillaries within the alveolar septa are immature because they have been arrested at an earlier stage in vessel development; and because VEGF is believed to be the major regulator of mesenchymal-epithelial interaction during lung development, it follows somewhat logically that altered signaling by VEGF might play a decisive etiologic role in ACD. Admittedly, however, this theory remains to be proven.

Probably the most significant development with regard to practical management of infants afflicted with ACD relates to the aggressive stance adopted by most pediatric intensivists and pulmonologists regarding early open lung biopsy. While this procedure is by no means innocuous, the consensus of studies has demonstrated that open lung biopsy generally can be performed safely, even in neonates with significant pulmonary conditions. The diagnostic algorithm is as follows: in an infant who presents within the first 48 hours of life with persistent pulmonary hypertension and any combination of respiratory distress, cyanosis, hypoxemia, respiratory acidosis, and hypotension, following a term or near-term delivery with normal Apgar scores, ACD should be considered in the differential diagnosis of possible conditions, which may also include meconium aspiration, fetal or perinatal asphyxia, surfactant deficiency, polycythemia, extreme prematurity, and neonatal sepsis. Additional diagnostic considerations in infants presenting with persistent pulmonary hypertension that remains refractory to therapeutic intervention should include pulmonary hypoplasia and congenital pulmonary lymphangiectasia, another rare lung condition characterized by marked dilatation of subpleural and septal lymphatics. If medical management with high-frequency oscillatory ventilation, systemic alkalninization, NO, and prostacyclin is not effective, a trial of ECMO is initiated. If, after a 7- to 10-day course of ECMO, the child’s pulmonary status fails to improve, open lung biopsy should be entertained. The ability to make an early diagnosis of ACD at the very least optimizes that child’s chance of being conditioned or maintained until the time of lung transplant.

To summarize, a high index of suspicion for ACD should be maintained for infants with clinically significant pulmonary hypertension who fail to respond to medical therapy. A recent series of 7 cases of ACD
diagnosed between 1997 and 2002 from the Hospital for Sick Children in Toronto, reported an open lung biopsy diagnosis rate of 86% (6 of 7 patients); furthermore, the median interval between hospital admission and biopsy was only 6.5 days. The authors concluded that open lung biopsies in these infants was a low-risk, high-(diagnostic) yield procedure and that early diagnosis of ACD with continuous pulmonary vasodilator therapy might eventually “bridge a patient to transplantation”. Suffice it to say that while the present outlook for ACD is obviously unfavorable, there is at least some cause for optimism.

In conclusion, ACD is a rare yet devastating lung disease that cannot be diagnosed, anticipated or predicted prenatally, based upon the present body of knowledge regarding this entity. Hopefully, future advances relating to the molecular genetics, pathophysiology, and treatment of ACD will one day result in a more favorable prognosis for this condition.

References


