DX: Chronic Granulomatous Villitis of Unknown Etiology = 96% of respondents
Other Diagnoses: Chorioamnionitis = 3% / Chorangiosis = 1%

Question answers:
Q1: (B) 87% (C)&(E) = 8% (A&D) = 5%
Q2: (D) 86% (C) = 9% (B&E) = 5%
Q3: (E) 83% (B) = 10% (D) = 5% (A&C) = 2%

The section shows a third trimester placenta with a patchy chronic villitis (CV) with a mixed lymphocytic and histiocytic infiltrate and, in some sections, giant cells. No organisms were identified using Cytomegalovirus (CMV), Herpes simplex virus (HSV) types 1 and 2, and Toxoplasma immunostains, a Steiner stain for spirochetes, and an acid fast stain. The etiology of CV includes viral infection, including TORCH organisms (toxoplasmosis, syphilis, CMV, HSV) and enteroviruses, Varicella, and non-viral organisms such as Chlamydia and Ureaplasma. When organisms are not identified, the etiology is often attributed to undiagnosed infection, an autoimmune process, or a graft-vs-host type response and is called chronic villitis of “unknown etiology” (CVUE). Bacterial infections are usually associated with acute maternal and fetal inflammation and acute chorioamnionitis and funisitis are not often seen with CV. A recent study identified no association between endometrial bacterial infection and CV [1]. In this regard, the clinical history of periodontal disease in this woman has been associated with acute amniotic infection due to oral flora, such as Fusobacterium, a gram-negative filamentous bacterium [2], but such an association has not been described in CV.

The involvement of placental villi by CV can vary between individual placentas. In some cases there is diffuse involvement with a majority of villi having lymphocytic and histiocytic inflammation with or without an intervillous component. A more diffuse involvement should trigger a higher suspicion for an infectious etiology. In many cases only scattered villi contain increased numbers of these chronic inflammatory cells. Often the villi involved become agglutinated, where the villi appear to be “stuck” together by intervening pink fibrinoid material. In severe cases it can be difficult to distinguish CVUE from massive perivillous fibrin deposition, an entity not usually associated with CVUE. Villi can also appear sclerotic, when the process can appear similar to villi affected by fetal thrombotic vasculopathy, but in that entity the sclerotic villi appear bland and without a chronic inflammatory infiltrate.

The infiltrate in CV can be predominantly lymphocytic, predominantly histiocytic, mixed lymphocytic and histiocytic, and lymphoplasmacytic. Syphilitic CV is histiocytic-predominant and is usually accompanied by necrotizing umbilical periphelebitis [3]. Congenital toxoplasmosis may also involve a histiocytic-predominant CV with areas of necrosis and often has an associated chronic deciduitis [3]. Congenital CMV usually has intranuclear and intracytoplasmic viral inclusions and a lymphoplasmacytic CV [3]. CVUE is generally lymphocytic predominant and is not accompanied by acute inflammation of the membranes or umbilical cord [3]. The presence of granulomatous inflammation with giant cells is not a marker for infection if it is in the background of a lymphohistiocytic response [3]. Finally, basal villitis is a subset of CVUE in which there is an associated chronic deciduitis [1].

CVUE is one of several placental lesions that have been described in recurrent spontaneous abortions with a recurrence risk of 10-25% [3]. These pregnancies are at risk for growth restriction, premature delivery, and intrauterine fetal demise. The other entities that can be recurrent include maternal floor infarction, thrombophilia-associated maternal vasculopathy, fetal thrombotic vasculopathy, and chronic histiocytic intervillitis [4], an entity considered distinct from CVUE.

Maternal lymphocytes and histiocytes are known to be the cell population that infiltrates the chorionic villi in CVUE and at least the syphilitic form of infectious chronic villitis [5, 6]. There is some evidence that CVUE may be a manifestation of fetal-maternal barrier compromise that generally permits the pregnancy to proceed without an allogeneic graft rejection response [7]. Increased numbers of CD4+ T cells, CD8+ cytotoxic T cells and macrophages have been identified at the sites of inflammation in CVUE. However, it is currently unclear whether the CD4+ T cells are regulatory T cells (CD4+/CD25+) or memory CD4 cells.
This is an important question, because regulatory T cells play a role in controlling autoimmune responses. Normally, trophoblasts lack expression of MHC class Ia and II molecules that are responsible for antigen presentation and this absence of expression contributes to maintaining a normal pregnancy [8]. Trophoblasts express HLA-G antigen, a non-polymorphic MHC class Ib molecule that appears to be an important player in moderating the effect of cytotoxic lymphocytes and NK cells in the placenta [9]. The finding that MHC class II antigen expression in syncytiotrophoblasts can be detected in CVUE supports the hypothesis that CVUE is a manifestation of compromise of the fetal-maternal “barrier” [10].

References


Pseudosarcomatous Myofibroblastic Proliferation / Inflammatory Myofibroblastic Tumor of the Urinary Bladder = 89 % of respondents

Other Diagnoses: Leiomyoma = 4% / Leiomyosarcoma = 4% / I Pseudotumor = 3%

Question answers:  Q1: (D) 27% (A) = 68% (B&C) = 5%
Note: Question not clear if answer pertains to this case or in general about this condition.
  Q2: (C) 44% (D) = 28% (B) = 16% (A) = 12%
  Q3: (C) 88% (D) = 7% (B) = 5%

The cut surface shows a transmural, relatively circumscribed, but infiltrative fasciculated, whorled, fleshy homogeneous stromal mass. No cysts, hemorrhage or necrosis where seen. The histologic section shows residual wall of urinary bladder (UB) with a myofibroblastic polygonal and spindle cell proliferation involving ulcerated and expanded mucosa, lamina propria and expanding-infiltrating the muscular wall of the urinary bladder. There are conspicuous numbers of inflammatory cells admixed with the spindle cells, predominantly plasma cells and in focal areas there are conspicuous numbers of mature eosinophils. The myofibroblastic cells grow as intersecting fascicles, diffuse sheets and focal myxoid areas, seen replacing the bladder wall, in some areas delimited by a dense fibroconnective tissue pseudocapsule. Other areas appear fasciitis-like, fibromatous and/or myosarcoma-like in morphology. No perivesical fat invasion is present. The nuclear morphology is variable, many large, open-chromatin nuclei with prominent nucleoli are noted, occasional cells show polylobated and hyperchromatic nuclei. No evidence of necrosis, vascular invasion or extension into perivesical fat. By immunohistochemistry the tumor shows evidence of keratin, actin, and vimentin positive cytoplasm diffusely, focal EMA and a low Ki67 index of <2%. The tumor also showed cytoplasmic expression of ALK1. No evidence of CD117 or CD34 expression by the lesional cells. Ultrastructurally, the cells showed features of myofibroblasts.

Pseudosarcomatous Myofibroblastic Proliferation (PMP) and Inflammatory Myofibroblastic Tumor (IMT) of the urinary tract appear to be the preferred designation for tumors showing a morphologic overlap with so-called Inflammatory Pseudotumor (IPT), Inflammatory Myofibroblastic Tumor, postoperative spindle cell nodule, reactive pseudosarcomatous response, pseudosarcomatous fibromyxomatous tumor and nodular fasciitis [1-3]. The spectrum of morphology is broad, but the common denominator is the sarcomatoid proliferation intermixed with inflammatory cells, in a spectrum similar to that of IPT/IMT described throughout the body.

Attempts to categorize these entities include various publications since the 1980’s, including series in children and adults [1, 2, 4-6]. The age range includes children as young as 2 years to the elderly. Patients usually present clinically with hematuria and or obstructive problems. The lesions are usually polypoid and have been described in all regions of the bladder; most are polypoid, ulcerated and intramural. The morphologic spectrum is as described above. The use of immunohistochemistry is helpful, most tumors co-express keratin in a diffuse fashion, actins, vimentin and ALK1 which is seen in approximately 50%-75% of cases [7-9]. This panel usually allows a distinction from smooth muscle tumors and other lesions in the differential diagnosis [7, 8]. Positivity for CD21, CD34, CD117, myogenin, myoglobin and S100 is usually not present. Other conditions entertained but usually only seen in older patients include sarcomatoid carcinomas and stromal reactions to invasive urothelial carcinomas. In the recent past, UB PMP was frequently confused with conventional embryonal rhabdomyosarcoma (ERMS) [4]. In the more recent classification of rhabdomyosarcoma, spindle cell “leiomyomatous” variant of ERMS would be a more likely differential consideration in this context. Supportive of ERMS would be a primitive or differentiated embryonal component with a cambium layer, lack of inflammation, striations and myogenin immunopositivity. ALK1 expression has been reported in RMS [7].

The larger published series of these tumors in both pediatric and adult populations consistently report an indolent or only rarely recurring behavior for these UB lesions, despite partial or incomplete resection, or
locally advanced tumor involvement at time of presentation [1-4, 6, 10]. In clinical practice, when
cystoscopic biopsy material establishes the diagnosis, then conservative tumor and adjacent bladder wall
resection should be advocated, particularly in children and adolescents.

As with pulmonary and extrapulmonary IPT/IMT’s, Pseudosarcomatous Myofibroblastic lesions whether
ALK1 positive or negative, appear to represent a heterogeneous group of lesions recapitulating similar
fibroblastic / myofibroblastic morphology, associated with inflammatory cell component. Nomenclature,
management and prognostic issues depend on the individual clinico-pathologic context [5, 6]. In the
urinary bladder, Pseudosarcomatous Myofibroblastic Proliferations should be considered a distinct
clinico-pathologic entity with an excellent prognosis.

References


2. Coffin CM, Humphrey P, Dehner LP. Extrapulmonary Inflammatory Myofibroblastic Tumor: A

3. Harik LR, Merino C, Coindre JM, et al. Pseudosarcomatous myofibroblastic proliferations of the

19:1224-1236.


6. Weidner N. Inflammatory (myofibroblastic) pseudotumor of the bladder: a review and differential

myofibroblastic tumor and its mesenchymal mimics: a study of 135 cases. Mod Pathol 2002;
15:931–938.


9. Tsuzuki T, Magi-Galluzzi C, Epstein JI. ALK-1 expression in inflammatory myofibroblastic tumor of

tract: a clinicopathologic study of 46 cases, including a malignant example inflammatory
fibrosarcoma and a subset associated with high-grade urothelial carcinoma. Am J Surg Pathol
DX: Disorder of surfactant - ABCA3 mutations = 14% of respondents
Other Diagnoses: Surfactant deficiency = 60% / Pneumonitis = 11% / Proteinosis 4 =%

Question answers:
Q1: (B) 74% (E) = 12% (C) = 9% (A&D) = 5%
Q2: (D) 51% (E) = 35% (C) = 9% (A&B) = 5%
Q3: (E) 89% (B) = 6% (A&C) = 5%

The explanted native lungs from this 2-month old girl were heavy and diffusely consolidated with a firm pale tan cut surface. Microscopically, the lungs show extensive lobular remodeling with interstitial widening and fibroplasia, diffuse alveolar epithelial hyperplasia, and alveolar filling by abundant alveolar macrophages, occasional multinucleate macrophages, and occasional aggregates of amorphous dense proteinosis material. Cholesterol clefts are inconspicuous in this case. This constellation of histologic features is one of the typical patterns seen in genetic disorders of surfactant metabolism. In light of these findings, electron microscopy was performed, showing abnormal small lamellar bodies with occasional central and eccentric round dense bodies, characteristic of surfactant metabolism defects due to ABCA3 gene mutations. Mutation testing in this case confirmed the presence of two sequence variations in the ABCA3 gene (Nt289InsA and Nt4648C>T), predicted to cause a premature stop codon and substitution of a highly conserved amino acid, respectively.

Genetic disorders of surfactant metabolism, also called “surfactant dysfunction disorders”, are caused by mutations in three known genes: SFTP B (surfactant protein B; chromosome 2), SFTPC (surfactant protein C; chromosome 8), and ABCA3 (ATP-binding cassette transporter, subfamily A, member 3; chromosome 16p13.3). Approximately 25% of cases with typical histologic features have no mutations identified, suggesting the presence of other unrecognized causative genes. Although the pathogenetic mechanism is not well-understood, the ABCA3 gene product appears to be required for normal lamellar body processing and transport, and is expressed on the surface of lamellar bodies and on the surface of type II alveolar epithelial cells. Other ABC transporters are implicated in diseases affecting lipid and bile acid transport, including Tangier disease (ABCA1), progressive familial intrahepatic cholestasis (PFIC) type 2 (ABCB11), PFIC type 3 (ABCB4), pseudoxanthoma elasticum (ABCC6), and adrenoleukodystrophy (ABCD1). Although only recently recognized in 2004 as a cause of surfactant dysfunction, ABCA3 has now become the most commonly implicated of the three known genes, resulting in lung disease in infants, older children, and young adults. Mutation testing is clinically available for all three genes, and research studies are ongoing for the discovery of new genes causing similar disease.

The histologic features associated with the surfactant disorders are variable, depending upon the gene affected and the age at biopsy. Described patterns of lung disease include “pulmonary alveolar proteinosis”, “desquamative interstitial pneumonia”, “chronic pneumonitis of infancy”, “non-specific interstitial pneumonia”, and “idiopathic pulmonary fibrosis”, with the first three more common in infants and the latter two more common in older children and adults. Although seen to variable degree, unifying characteristics which should suggest the diagnosis include: alveolar proteinosis, cholesterol clefts, increased macrophages, diffuse alveolar epithelial hyperplasia, and signs of chronic injury (lobular remodeling, interstitial widening, fibroplasia/fibrosis). Interstitial inflammation is variable and tends to be more prominent with increasing age at biopsy and severity of lobular remodeling. Periodic acid Schiff (PAS) stain may be helpful in highlighting proteinosis material and distinguishing it from edema or hyaline membrane material. Pulmonary alveolar proteinosis (PAP) material raises a differential diagnosis of Pneumocystis jiroveci pneumonia and the acquired forms of PAP due to macrophage dysfunction or antibodies to GM-CSF. Cholesterol clefts are a common feature in the surfactant dysfunction disorders, but may also be seen in chronic lung disease with poor clearance of secretions, obliterative bronchiolitis, chronic aspiration, resolving hemorrhage, and resolving pneumonia.

Infants with genetic disorders of surfactant metabolism are typically delivered at term and present in the first few weeks to months of life with progressive respiratory insufficiency. Chest x-ray typically shows
diffuse hazy opacity in bilateral lung fields, and chest CT shows ground glass opacity with interstitial markings (“crazy-paving” pattern), indicating patchy mixed alveolar-interstitial involvement. Diagnosis is typically made by lung biopsy, followed by mutation testing for confirmation. Surfactant protein B (SP-B) deficiency typically manifests in the neonatal period and is fatal in the first few months of life. Abundant alveolar proteinosis with early lobular remodeling (“pulmonary alveolar proteinosis” pattern) is typical. Surfactant protein C (SP-C) deficiency tends to manifest in late infancy with a pattern of “chronic pneumonitis of infancy” or “desquamative interstitial pneumonia”. However, some patients with SFTP C mutations may not be recognized until adolescence or adulthood, in these cases diagnosed with “non-specific interstitial pneumonia” or “idiopathic pulmonary fibrosis”. Like patients with SP-C deficiency, patients with ABCA3 mutations have more variable clinical presentation and prognosis. They may present either in the neonatal period with a fulminant course as seen in SP-B deficiency, or later in infancy and childhood as seen in SP-C deficiency. Family history of interstitial lung disease is an important clue to diagnosis, but is present in a minority of cases. SFTP C mutations are inherited in an autosomal dominant fashion, and have been described in successive generations of adults and children with chronic lung disease. SFTP B and ABCA3 mutations are inherited in an autosomal recessive fashion.

Due to the importance of electron microscopy in the evaluation of surfactant disorders, glutaraldehyde-fixed tissue should be obtained from all pediatric lung biopsies performed for diagnosis of diffuse lung disease. Although no characteristic ultrastructural abnormalities have been described in SP-C deficiency, electron microscopy has been diagnostically useful in recognizing abnormalities caused by SFTP B and ABCA3 mutations. SP-B deficiency is associated with abnormal multivesicular and composite bodies, while ABCA3 deficiency is typically associated with small round dense bodies in the type II alveolar epithelial cells.

Treatment for the genetic disorders of surfactant metabolism is largely supportive, as surfactant replacement has been ineffective. Lung transplantation has been performed successfully for the disorders of surfactant metabolism, both in infants with acute respiratory failure and in adolescents and adults with end-stage chronic lung disease.

References

Both kidneys are symmetrically and uniformly enlarged retaining their contour. They are equal in size to the liver. The examined kidney weighed 287 grams (expected wt = 15 grams) and is diffusely altered, showing a fusiform, uniform cystic tubular dilatation perpendicular to the cortex, affecting the cortical and the medullary regions where the cysts are more rounded. Isolated congested glomeruli appear as red dots. The calyceal system and pelvis appear unremarkable. The liver shows mild congestion and accentuation of interlobar connective tissue. No nodular transformation or cystic lesions grossly apparent, on close inspection, the parenchyma shows grossly recognizable subtle punctate pallor. Microscopic slide includes sections of kidney and liver. The kidney shows a generalized cystic dilation of the collecting ducts predominantly. There are residual proximal convoluted tubules that are better preserved and the glomeruli are without cystic alteration of specific glomerulopathy. The altered tubules are lined by cuboidal, sometimes attenuated epithelium. No complex or papillary epithelial structures are noted. The interstitium is edematous or with early fibrous expansion.

The liver shows a conspicuous portal fibrous expansion with complex, branching, dilated and malformed biliary structures, with intraductal fibrous polypoid projections. Some portal zones contain arterioles and small veins. At low magnification the expanded fibrous tissue interconnects in some areas, no nodular lesions or regenerative transformation is noted. There is variable cholestasis within smaller bile ducts and ductules. The hepatic limiting plate is well-defined, there is variable extramedullary hematopoiesis. The lobular relationships of the liver are maintained. The sinusoids, hepatocytes and central veins appear unremarkable.

The differential diagnosis involves an infantile presentation of ADPKD where cysts are found usually involving all segments of the nephron. Early presentation of ADPKD in infants usually manifests more with medullary cystic ectasia and fibrosis.

Autosomal recessive polycystic kidney disease (ARPKD) is a rare form of polycystic kidney disease (PKD) characterized by diffuse renal cystic transformation and portal biliary dysgenesis associated with portal tract fibrosis [1]. The incidence of ARPKD varies between 1:10 000 to 1: 60 000 live births [2]. The extreme manifestations are usually present at birth with marked bilateral nephromegaly, biliary dysgenesis, pulmonary hypoplasia secondary to compression and oligohydramnios. A significant proportion (30-50%) of infants affected with the severe infantile form die shortly after birth. The survival rate for neonates who survive the first month of life is approximately 90%, the most important prognostic factor being neonatal ventilatory support [3]. The most important causes of morbidity in surviving patients relate to progressive systemic hypertension, renal failure and portal hypertension [3]. Approximately 50% of children who survive the immediate perinatal period progress to end-stage renal disease in the first decade [4]. Currently, the diagnosis of ARPKD is established by ultrasound of the abdomen and tissue confirmation. Characteristic morphologic alterations have been identified in fetuses at 13 and 21 weeks of gestation [1, 5]. Since the cloning of the gene, the diagnosis can be confidently established by mutation analysis in up to 80% of patients surviving the neonatal period [6]. The hepatic alterations in ARPKD become a dominant component in patients presenting later in life. The advanced stage of hepatic fibrosis usually occurs in juvenile and adult presentations which manifestations related to portal hypertension. Morphologically there is gross pattern of “reticular fibrosis” affecting the entire liver. Microscopically it corresponds to an exaggerated and severe progression of the fibrous expansion of portal zones with encroachment of portal vein branches.
The ARPKD gene has been identified and termed PKHD1 (polycystic kidney and hepatic disease 1). It has been mapped to chromosome 6p21.1-p12 [7]. The PKHD1 gene, one of the longest human genes, encodes synthesis of the protein fibrocystin (also known as polyductin) [8]. This protein is expressed during fetal development and in mature tissues. In the kidney, it is present in the ureteric bud epithelium and in the collecting tubules; within the liver it is found in the intrahepatic bile ducts. It is expressed also in the ducts of the pancreas, variably in the lung and in the epididymis and seminiferous tubules. It is considered an integral membrane protein which acts as a "membrane receptor, interacting with extracellular protein ligands and transduction of intracellular signals to the nucleus" [2, 9] suggesting that multiple sites are targets for the scope of impact of this protein in differentiation and function.

Biliary dysgenesis accompanies several of the other renal cystic diseases including ADPKD and glomerulocystic disease, but it is an invariable component of ARPKD [1].

Current concepts of the pathogenesis of ARPKD suggest that all variants of the disease appear to relate to this single PKHDL gene locus, with a different pathogenesis accounting for the variation clinical expression, severity of kidney involvement and patterns of inheritance. Recent research points to the type of mutation as a significant factor in disease variations. Those infants with truncation type mutations appear to manifest more severe disease. Infants with amino acid substitution types of mutation, present with milder forms of the disease, suggesting the fibrocystin retains some function when mutated [4, 9, 10]. All patients carrying two truncating mutations displayed a severe phenotype with perinatal or neonatal demise, while patients surviving the neonatal period bear at least one missense mutation [6].

The mechanism of the clinical spectrum appears to be multifactorial, but at least the cystic transformation of tubules in PKD appears to be related to the impact of fibrocystin in the development and function of renal epithelial cell cilia as mechanosensors and chemosensors. Fibrocystin and other mediators are also involved in the development of calcium homeostasis, defects in cellular proliferation and apoptosis, defects in renal concentrating capacity, polarity of the sub-cellular components such as enzymes, ion transporters, channels, pores, growth factor, and matrix receptors and optimal distribution of Na$^+$/K$^+$-ATPase pump sites [2, 10]. Indeed the renal epithelial cell cilia are the focus of considerable attention in the elucidation of mechanisms of all renal cystic diseases [11]. The cellular distribution of fibrocystin is co-localized with tubulin along the apical portion of the cells and along the length of cilia. When these antibodies are applied to ARPKD tissues there is no evidence of binding [12].

References:


SPP 07-10

DX: Dysembryoplastic Neuroepithelial Tumor (DNET) - Non-specific Variant = 97% of respondents
Other Diagnoses: Desmoplastic Infantile Astrocytoma / Ganglioglioma / Low-grade Glioma = 3%

Question answers: Q1: (C) 96% (A&D) = 4%
Q2: (B) 96% (E) = 4%
Q3: (A) 80% (D) = 15% (E) = 5%

On MRI, the affected gyri are thickened; DNET’s are sharply circumscribed and may extend into the subcortical white matter. The tumor is hypo- or isointense on T1 and hyperintense on T2 weighted MRI. Unenhanced studies reveal a variable hypodense, hypo/isodense image with cyst formations of variable size. Tumor enhancement is seen in a minority of cases and appears as multiple rings. Cortical dysplasia may be identified. CT may reveal remodeling of the overlying bone, a sign of its slow growth. Calcifications may be detected. Cortical location, absence of peritumoral edema or mass effect (other than that caused by a cystic component) is important features that suggest the diagnosis and help in the differentiation of DNET from other low-grade infiltrative or malignant gliomas. MR Spectroscopy may be of use in separating DNET from other tumors such as pilocytic astrocytomas and gangliogiomas; they have relatively higher levels of creatine and myo-inositol and lower choline levels and lower glutamate glutamine.

The current case fulfills the clinical and radiological criteria required for the diagnosis of DNET. Histopathologic features however are non-specific, a distinct glioneuronal element and nodularity are not present. The tumor exhibits a diffuse pattern of growth with the subcortical white matter predominantly affected and cortical areas of diffuse infiltration. The tumor cells exhibit a round to oval to elongated nucleus with little cytoplasm. The background is rarified with focal fine vacuolation. There are scattered hypertrophic reactive astrocytes with moderate amount of cytoplasm. In areas of cortical infiltration, there is arguable architectural disarray of neuronal layers with apparent decrease of small neurons in the second and fourth layers; the adjacent cortex exhibits normal neuronal population and lamination. The number of neurons in the subcortical white matter is increased, they are scattered between tumor cells. Mitosis, necrosis, vascular proliferation or calcifications are not present.

The postoperative MRI showed a complete resection and follow-up studies have not revealed recurrent growth. Clinically there was significant improvement with resolution of seizure activity.

Gross examination is remarkable for broadening of affected gyri with occasional one or more bulging soft nodular areas. The leptomeninges are not involved. Cut sections disclose thickening and pallor of the cortical band with variable mucinous changes. The consistency may be heterogeneous and the tumor may extend into the subcortical white matter.

Dysembryoplastic neuroepithelial tumor (DNET) is a neoplasm composed of a mixed population of neuronal, oligodendroglial and astrocytic elements. The glial component is usually most conspicuous and the proportion of each cellular element varies from tumor to tumor. The WHO classification of tumors of the central nervous system includes DNET in the neuronal and mixed neuronal-glial group; histologically, DNET corresponds to WHO grade I. DNET occurs predominantly in children and young adults and is frequently associated with long standing, drug-resistant partial seizures. The histogenesis of this tumor is unclear, although initially was considered a hamartomatous condition.

DNET, described originally by Daumas-Duport et al. in 1988, presents typically in the cerebral cortex, predominantly in the temporal lobe. Notwithstanding, DNET has been described in extracortical locations such as septum pellucidum - lateral ventricle, caudate, brainstem and cerebellum. Multifocal presentation has been also described. Microscopically, DNET contains populations of glial and neuronal cells and perhaps a subset of biphenotypic tumor cells with immunoreactivity for both glial and neuronal markers. There are GFAP-immunoreactive astrocytes; the oligodendrocyte-like cells are immunoreactive for S100 and myelin oligodendrocyte glycoprotein. There are scattered cells positive for neuronal markers such as...
NSE, NeuN, synaptophysin, PGP 9.5 and N-methyl-D-aspartate receptor subunit NR1. Electron microscopic findings support a mixed population of astrocytic, oligodendroglial and neuronal components. Mitoses are absent or rare and proliferative indices (MIB-1) are low, usually less than 3%, however, occasional higher indices may be encountered.

The histopathologic concept has evolved to accommodate emerging simple, complex, and non-specific variants of DNET that are currently recognized, which result from the variable predominance of different cellular components and the histological features.

The simple form is characterized by cortical topography and the specific glioneuronal element.

The complex form is the originally described DNET which is characterized by a) cortical topography; b) multinodular architecture with areas reminiscent of oligodendroglioma, astrocytoma or mixed oligoastrocytoma; c) a morphologic feature termed “specific glioneuronal element” consisting of a proliferation of oligodendrocyte-like cells arranged along bundled axons and blood vessels, which are often perpendicular to the cortical surface, separated by a myxoid matrix rich in acid mucopolysaccharides containing well differentiated neurons; d) foci of cortical dysplasia.

The non-specific variants lack the multinodularity and specific glioneuronal element. Foci of cortical dysplasia, if present, may be helpful in identifying DNET. The tumor simulates other glial neoplasms extending into the subcortical white matter. The accurate diagnosis of this variant, irrespective of the histological features, depends on its correlation with the characteristic clinical and neuroimaging data namely: (1) association with partial seizures beginning prior to 20 years of age; (2) absence of associated neurologic deficits or presence of a nonprogressive congenital deficit only and (3) the typical neuroimaging features (vide supra).

Variants with more diffuse growth of the glial components may be indistinguishable from conventional oligodendroglioma, or from pilocytic or fibrillary astrocytoma, particularly in biopsies or in fragmented specimens. Occasionally, considerable cytologic atypia, some mitotic activity, microvascular proliferation and, rarely, necrosis may be seen. Examples of DNET combined with ganglioglioma, pilocytic astrocytoma, and pleomorphic xanthoastrocytoma and a melanotic DNET variant, have been reported.

While patients with DNET are cured by tumor resection and those patients with partially resected tumors remain stable, occasional rapid growth and an isolated case of malignant transformation has been described. There are reports of an occasional association to Neurofibromatosis I and a familial case.

References


