Congenital Tumors

19

Adrian K. Charles

Tumors presenting in the new-born period are rare, although any pathologist working with a busy obstetric or neonatal unit can expect to see occasional cases. The incidence is around 1 in every 12,000 to 27,500 live births. Many of these tumors are peculiar to infants or behave differently from their counterparts in older children [1, 2]. Lack of familiarity with neonatal tumors may lead to unnecessarily aggressive therapy or well-intentioned neglect. The neonate responds differently to therapy with immature and growing tissues and organs, is more sensitive, and the effect of many cancer therapies on the developing infant can be severe and permanent. Some neonatal tumors may appear to be aggressive lesions and yet behave in a benign manner; conversely, others look benign but may become aggressive malignant tumors if incompletely excised. Most, but not all, childhood neoplasms have been described in the perinatal period but the frequency of the different tumors varies greatly with the age of presentation between fetal and neonatal period, and later in childhood. Most of the more common childhood tumors are very rare in neonates. Tumors in the perinatal period (and children) are often mesenchymal rather than epithelial in histogenesis and knowledge of normal human development is often useful.

There are close links between development and oncogenesis as Willis noted [3]and his thoughts have been supported by the increasing recognition of the role of developmental genes in tumors. The genetic mechanisms such as chomatin status and imprinting and even marked genetic changes such as chromoanagenisis [4] occur in both tumours and development. Examples this overlap is seen in the Dicer-related and PTEN-related conditions, the ribosomopathies and SW1/SNF chromatin modeling-related complex with Rhabdoid tumors and the Coffin-Siris syndrome. The current classification of some of these neonatal tumors into a neoplasm or a hamartoma is also blurring [5, 6]. Indeed, some of these congenital lesions highlight that each of us is not genetically homogeneous and that non genomic changes can indeed be inherited. Hamartomas in children may represent the localized somatic mutation in a group of cells interacting with adjacent normal cells trying to replicate normal development.

This field is now changing rapidly as the genetic pathways involved in the pathogenesis group some lesions, separate other similar appearing lesions from one another, and the benefits of identifying druggable genetic changes leading to novel therapies for some of these lesions rather than mutilating surgery is changing the treatment options.

This chapter cannot be comprehensive but will concentrate on the special characteristics of neonatal tumors, which influence their diagnosis and management, and outline some areas where study of neonatal tumors is of interest to our understanding of neoplasia in general. Some characteristic lesions not mentioned elsewhere in the text are shown in Table 19.1. Neonatal tumors accounted for 2.6% of all children's tumors in one series, of which 40% were malignant [13]. About 40% of malignant tumors in neonates are evident on the first day of life, and 17% only discovered at autopsy [14]. Most malignant congenital tumors present in the first week.

A congenital tumor is one that is present at birth but it is reasonable to suppose that any tumor presenting in the first 3 months of life was congenital, and some later lesions were also congenital (Fig. 19.2). It is now becoming clear that other childhood tumors, including many leukemias, Wilms tumors, pleuropulmonary blastomas, neuroblastomas and some germ cell tumors, appear to arise from abnormal cells or lesions that are already present at the time of birth. Children who present with acute leukemia can be found to have identical genetic changes in their leukemia and in the DNA from their Guthrie card or in the leukemia in their monozygotic twin [15]. More neonates have these genetic changes than children who develop leukemia implying that many childhood leukemias have precursor cells that have

A. K. Charles (✉)
Department of Pathology, Sidra Medicine, Doha, Qatar
e-mail: Adrian.charles@health.wa.gov.au

T. Y. Khong, R. D. G. Malcomson (eds.), *Keeling's Fetal and Neonatal Pathology*,
https://doi.org/10.1007/978-3-030-84168-3_19

Table 19.1 Some lesions recognized in newborns, but not described elsewhere in the text

Anatomical site, tumor
Head and neck
Thymic cyst
Mouth and Nasopharynx
Gingival granular cell tumor/epulis (numerous case reports) (Fig. 19.1)
Hairy polyp of the oropharynx
Nasal glioma
Nasopharyngeal brain heterotopia
Foregut duplication cyst of tongue
Hamartoma of the tongue
Sialoblastoma [7]
Salivary gland anlage tumor
Skin and subcutis
Neurocristic hamartoma
Striated muscle hamartoma
Rhabdomyomatous hamartoma [8, 9]
Smooth muscle hamartoma [5]
Soft tissue
Neuromuscular choristoma
Primitive myxoid mesenchymal tumor [10]
Lung and thorax
Rhabdomyomatosis of lung
Pulmonary myofibroblastic tumor
Massive mesenchymal malformation of lung
Thymic hyperplasia
Heart
Cardiac fibroma
Rhabdomyoma
Gastrointestinal
Gastrointestinal stromal tumor
Leiomyosarcoma
Tailgut cyst
Pancreatoblastoma [11]
Juvenile polyposis of infancy
Gonads
Congenital ovarian cysts (mostly folicular cysts) [12]
Juvenile granulosa cell tumor
Gonadoblastoid dysplasia
Cystic dysplasia of testis
Testis adrenal rest with congenital adrenal hyperplasia
Spine
Spinal hamartoma
Tails
Bone
Osteochondromyxoma of bone
Infantile cartilaginous hamartoma of the rib
Brain
Hypothalamic hamartoma
Miscellaneous
Accessory scrotum

undertaken the initial genetic steps of neoplastic progression at birth but do not necessarily progress to malignancy, a situation well described with nephrogenic rests and Wilms tumor, neuroblastoma in situ and pleuropulmonary blastoma. Furthermore, studies are starting to show background genetic

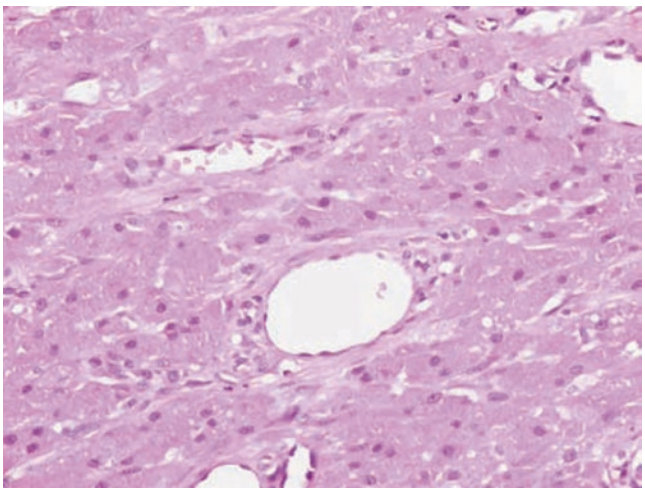

Fig. 19.1 Granular cell epulis/congenital granular cell tumor. Congenital presentation with a female neonate with a 20 mm mass arising from gingival margin

variants that increase the resistance or susceptibility to tumors though this is beyond the reach of this chapter.

Although there is no absolute distinction between the histological types of tumors presenting at birth and in early infancy, there are clinical differences that make the distinction worth preserving. For example, tumors are now regularly being diagnosed in utero by the anatomy scan in the second trimester [16]. This helps management of the pregnancy and delivery and novel approaches such as the ex-utero intrapartum treatment (EXIT) procedure have been introduced. Large tumors can rupture or obstruct delivery or give rise to fetal hydrops, if vascular, or affect the fetal cardiovascular system. The fetal circulation may be responsible for particular patterns of metastasis seen in the neonate. The outcome in this group often depends more on the size and site of the lesion than on the histology. Otherwise small benign tumors obstructing the larynx, or obstructing the venous return can easily be fatal [16]. Reduced tolerance to drugs and especially radiation may complicate therapy in very young babies. There are also tumors that are present in neonates and young infants but not later (e.g. sacrococcygeal teratomas) and conversely other tumors seen in children and adults but not (yet) described in neonates (e.g. synovial sarcoma) or are very rare (e.g. clear cell sarcoma of kidney).

Many of the tumors seen in the newborn are hamartomas, though the distinction between neoplasm, hamartoma and choristoma and even malformation is often unclear; many have localized somatic changes, and the categorisation is semantic in some cases. It is difficult to make a comprehensive classification system for these tumors: some segregate according to histological type, others according to usual site of presentation. Some of the true neoplasms of childhood are collectively referred to as blastomas or embryonic tumors. These include nephroblastoma (Wilms tumor), neuroblas-

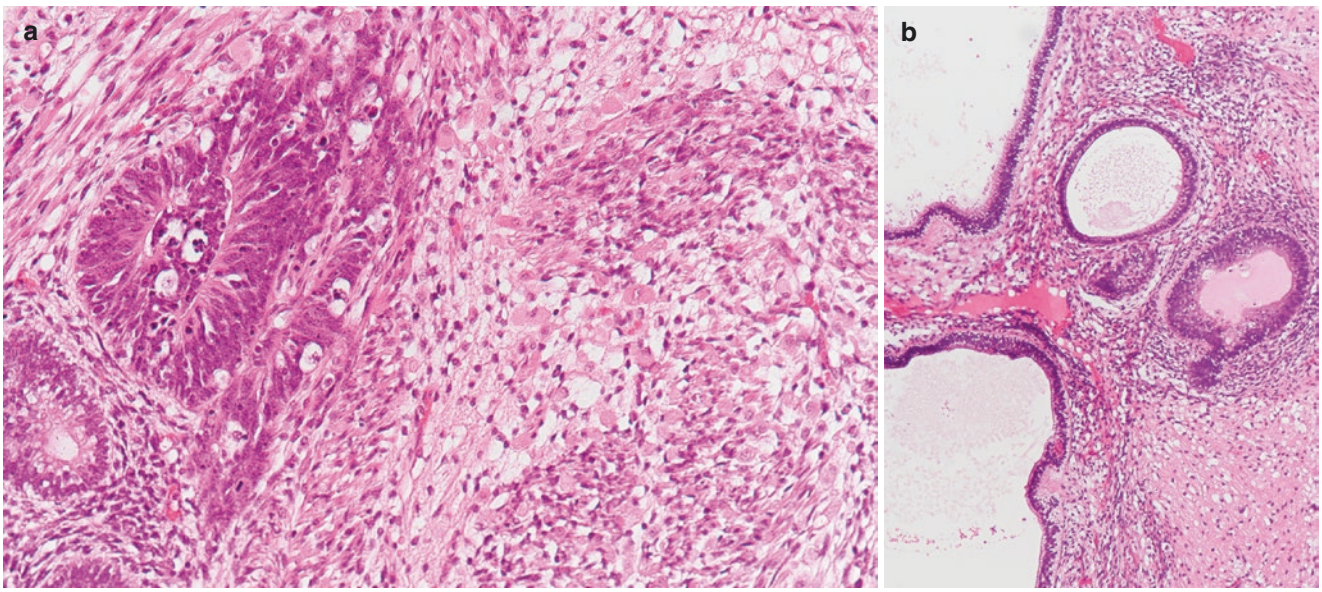

Fig. 19.2 A, B. Eye intraocular teratoma. A white eye reflex was noted since infancy. Tumor was seen arising by optic nerve. Epithelial (**a**), immature neural, rhabdomyoblastic and nephrogenic components (**b**) were identified

toma, retinoblastoma, hepatoblastoma, medulloblastoma, pleuropulmonary blastoma and embryonal rhabdomyosarcoma. These tumors tend to recapitulate embryonic tissues and are thought to arise from genetic changes in immature tissue, or persistent fetal stem cells. This explains their unique histology and restricted age range as the stem cell from which they arise matures and becomes more differerentiated or lost to apoptosis later in development.

Table 19.2 Benign and malignant tumors in newborn children and infants (percentage by tumor type)

Tumor	Perinatal tumors %
Teratoma	25
Neuroblastoma	26
Mesenchymal	9.6
Renal	4.9
Central nervous system	10.4
Leukemia	12.2
Number of cases	607

19.1 Incidence

Benign tumors of the newborn are common, and many are not formally recorded. Vascular nevi and hemangiomas are present in 6–25% of the pediatric population, most being congenital, although they often present after birth. Infantile hemangiomas are more common in very low birthweight babies than controls. While most infantile hemangiomas and many visceral hemangiomas regress, even benign hemangiomas may cause death, for example, by causing heart failure or a consumptive coagulopathy. Melanocytic nevi are found in a few percent of newborn white infants and more common of non-white infants in contrast to the extreme rarity of congenital malignant melanoma [17, 18] but the diagnostic features of malignancy and proliferative nodules within a congenital nevus are not absolute and even genetic studies are not always useful [19].

It is difficult to estimate the incidence of malignant congenital tumors from the literature. Most series are not population based, and many are not comparable because they include different age ranges (Table 19.2). Series extend over many years during which the treatment and classification of tumors have changed.

Teratomas are the commonest reported neonatal tumor but neuroblastoma is the commonest malignant tumor followed by leukemias (which is the commonest fatal congenital tumor) and mesenchymal tumors of various types, renal tumors and brain tumors [20]. Less-common conditions seen in the neonatal period include Langerhans' cell histiocytosis, hepatoblastoma and retinoblastoma. Lymphoma, clear cell sarcoma of kidney and anaplastic Wilms tumor are notable for their extreme rarity in neonates.

A study of 17,417 perinatal necropsies carried out in Melbourne over five decades revealed 46 congenital tumors, which included 24 teratomas, most frequently of the head and neck, followed by sacrococcygeal and mediastinal teratomas [21]. Vascular tumors, neuroblastoma and cardiac rhabdomyoma were next in frequency. Twenty percent of the affected babies had developmental anomalies, mainly associated with teratomas. Some babies presented with maternal polyhydramnios and/or fetal hydrops, most often with teratoma.

Standard histological criteria of malignancy such as high mitotic rate, immature cells, necrosis and even vascular invasion do not always indicate malignant behavior in congenital tumors. A large population-based study of infants up to 1 month old in the West Midlands from 1960–1989 showed an incidence of benign and malignant neonatal tumors of 0.07 per 1000 live births per year, also with a predominance of teratoma (mostly benign) followed by neuroblastoma and leukemia. The 5-year survival rate was 50%. Congenital tumors were associated with polyhydramnios which was not specific to any particular tumor type. Fifteen percent of patients had some congenital anomaly [22]

19.2 Etiology

Congenital tumors appear to offer a system in which to study oncogenesis free from the multiple environmental influences which complicate such studies in adults. However, the sperm, egg and the embryo and fetus are exposed to many chemical, physical and infective agents even in utero, and the intrauterine environment can alter the risk of infant and childhood neoplasia.

In recent years considerable insight has been gained into the pathogenesis of neoplasms in infants and young children, and the molecular pathogenetic pathways are beginning to be understood. Genetic accidents are part and parcel of human mitotic activity. The large number and rapidity of cell cycles required during embryonic and fetal growth provide ample opportunity for such mistakes. The genetic mechanisms involved in oncogenesis, which include small mutations, loss of heterozygosity and changes in genomic imprinting, are being shown to involve genes and non coding RNA which normally regulate the cell cycle, apoptosis and development (see also Chap. 3). Many generalized overgrowth syndromes such as Beckwith Wiedemann syndrome and more localized overgrowth syndromes are associated with increased risks of malignancy [23] and this extends to non syndromic large babies. The prevalence of growth factors may act as factors preventing the cells from undergoing apoptosis with the genetic changes. Genetic, chromosomal, syndromic and environmental associations that have been recognized in childhood cancer will be discussed below.

Many childhood and infant tumors have a normal or near normal karyotype and apart from the often characteristic translocations which involve oncogene activation, many of the pathogenetic pathways appear to involve more subtle, epigenetic and non genomic changes closely related to cell development and differentiation. This is also shown by recent studies of pediatric and adult tumor screening the genome for mutations showing few mutations in most childhood tumors [24]. Pediatric tumors have less time to acquire the more complex genomic changes more characteristic of adult tumors. It appears timing of the change in cell differentiation and the cell type in which the change occurs is crucial, and this may explain why the same translocation, the t(12;15) is seen in mesoblastic nephroma and infantile fibrosarcoma (essentially the same tumor type) and in the secretory analogue tumor of the breast and salivary gland, which are clearly otherwise unrelated tumors, indicating the genetic change and the epigenetic status are both important for tumorigenesis.

Many oncogenes and tumor suppressor genes are also implicated in development (e.g. retinoblastoma, MyoD1 and WT1 (WT1 can function as both oncogene and tumor suppressor). The evidence is showing that the more subtle non-genomic, epigenetic mechanisms such as imprinting (e.g. IGF2 locus at 11p15), chromatin remodeling (e.g SWNF1), and microRNA pathways (e.g DROSHA and DICER1), as well as cell-to-cell interaction and the cellular microenvironment are crucial in the oncogenesis of these tumors as well as being involved in development and cellular differentiation [25].

19.3 Inherited Tumors

Some childhood tumors are inherited and a greater proportion of pediatric tumors are associated with familial predispotion or a syndrome and this should be considered for all pediatric tumors. The frequency varies between tumors. For example, 40% of retinoblastomas and a small proportion (1–3%) of Wilms tumors are familial though 10–15% of Wilms tumor have a germline mutation [26]. Nine percent of retinoblastomas are present at birth, and these are almost always heritable and attributable to a mutation of the retinoblastoma gene on chromosome 13q. Sibships affected by leukemia, neuroblastoma, teratoma, hepatoblastoma or congenital fibromatoses have all been reported. Many inherited syndromes predispose to tumor development (Table 19.3), although such tumors are not usually present at birth.

19.4 Malformation Syndromes and Tumors

The association of trisomy 21 and leukemia is well known (see later), though children with Down syndrome appear to have a lower rate of solid tumors than those with a normal karyotype. A further group of infants have leukemia and constitutional aneuploidy, mainly trisomy 21. Neonatal tumors are reported with trisomies 13 and 18, the latter particularly with nephroblastoma and hepatoblastoma. The association of constitutional karyotypic abnormalities and childhood cancer can be helpful in localizing key genes involved in particular tumor oncogenesis. The most frequent associations likely to be seen by perinatal pathologists are congenital leu-

Table 19.3 Some inherited syndromes associated with childhood cancer

Inherited syndrome	Childhood cancer
Phakomatoses	
Neurofibromatosis type 1	Brain tumors; sarcomas; leukemia, carcinoid
Tuberous sclerosis	Brain tumors
Basal cell nevus syndrome	Medulloblastoma; basal cell carcinoma
Multiple mucosal neuroma syndrome	Medullary thyroid carcinoma; pheochromocytoma
Metabolic disorders	
Glycogenosis Type 1	Hepatocellular carcinoma
Hereditary tyrosinemia	Hepatocellular carcinoma
Alpha-1-antitrypsin deficiency	Hepatocellular carcinoma
Chromosome breakage and repair defects	
Bloom's syndrome	Leukemia; gastrointestinal tumors
Ataxia telangiectasia	Leukemia; lymphoma
Fanconi's anemia	Leukemia; hepatoma
Xeroderma pigmentosum	Skin cancers; melanoma
Chromatin related genes	
SWI/SNF	Rhabdoid tumors, Schwannomatosis
Non coding RNA related genes	
DICER1	Pleuropulmonary blastomas, Cystic Nephroma and many more
PTEN Hamartoma syndrome [27] (Cowden, Bannayani-Riley-Ruvalcaba, Proteus Group)	Lipomas, connective tissue and epidermal naevi, GI Polyps, vascular malformations, glial tumors, Adult breast and endometrial tumors
RASopathies (Neurofibromatosis type 1, Noonan, Costello, Cardio-facial cutaneous syndrome)	Various tumors, pediatric Rhabdomyosarcoma, Neural tumors, and Myeloid malignancies [28]
Ribosomopathies [29] (Shwachman-Diamond Syndrome, X-linked dyskeratosis congenita cartilage hair hypoplasia, Treacher Collins syndrome)	Risk of adult cancers
PIK3CA group (Cloves, MCAP, Fibroadipose hyperplasia, et al)	Pediatric lipomatous lesions, vascular and epidermal lesions, Mainly benign but some malignant tumors e,g. Rare Wilms tumor [30]
Immune deficiency disorders	
Wiscott–Aldrich syndrome	Leukemia; lymphoma (often in CNS)
Sex-linked lymphoproliferative syndrome	B-cell lymphoma
Severe combined immunodeficiency	Leukemia; lymphoma
Bruton's agammaglobulinemia	Leukemia; lymphoma
Rothmund Thompson syndrome	Osteosarcoma
Noonan syndrome	Juvenile muelomonocytic leukemia, giant cell tumors
Rubenstein Taybi syndrome	CNS tumors, rhabdomyosarcoma, leukemia
Carneys complex	Myxomas, Schwannomas, Osteochondromyxoma, Sertoli cell tumors

CNS central nervous system

kemia and transient myeloproliferative disorder associated with trisomy 21 if one excludes malformations caused by the tumor such as sacrococcygeal teratoma. (Table 19.4). Patients with congenital adrenal hyperplasia may develop testicular tumors from hyperplastic adrenal ectopic tissue.

Several dysmorphic syndromes and malformations carry significant risk of childhood cancer. (Table 19.5). The best known are hemihypertrophy and Beckwith–Wiedemann syndrome (BWS). Ten to 21% of children with Beckwith syndrome develop neoplasms, and the different genetic subtypes of BWS have different pheotypes and risk of malignancy [32]. The occasional occurrence of neuroblastoma in children with Hirschsprung's disease and Ondine's curse suggests that it may sometimes be part of a generalized disorder of neural crest development. The overlapping molecular pathology of tumors and malformations are seen in the different conditions associated with RET gene mutations, from Hirschsprung's disease to MEN2 syndromes and thyroid cancer.

Table 19.4 Constitutional chromosomal anomalies predisposing to childhood cancer

Chromosome anomaly	Childhood cancer
Down syndrome (trisomy 21)	Acute leukemia
Turner syndrome (45 XO)	Neurogenic tumors
13q-syndrome	Retinoblastoma
11p-syndrome	Nephroblastoma
Monosomy 7	Pre-leukemia and non-lymphoblastic leukemia
XY gonadal dysgenesis	Gonadoblastoma
Trisomy 18	Nephroblastoma
Variegated mosaic aneuploidy	Rhabdomyosarcoma, Wilms tumor, Leukemia
Klinefelter syndrome	Leukemia; teratoma; breast carcinoma

Table 19.5 Some congenital anomalies and malformation syndromes associated with childhood cancer [30, 31]

Congenital anomaly	Childhood cancer
Hemihypertrophy and Beckwith syndrome	Nephroblastoma, adrenal cortical tumors, hepatoblastoma
Sporadic aniridia (WAGR syndrome)	Wilms tumor
Denys–Drash syndrome	Wilms tumor
Perlman syndrome	Wilms tumor
Variegated aneuploidy	Wilms tumor and various others
Fanconi syndrome	Leukemia
Poland syndrome	Leukemia
Hirschsprung's disease	Neuroblastoma
Gorlin syndrome	Desmoplastic medulloblastoma, soft tissue rhabdomyoma

19.5 Malformations and Tumors

Several papers have examined the association of pediatic tumors and developmental anomalies, showing often an association between these especially in tumors in younger children, and not just in the well known tumor associated syndromes such as Beckwith-Wiedeman syndrome (BWS) [31, 33, 34].

The association of malformations and tumors is complex because there are different mechanisms underlying the association. In some cases such as congenital pulmonary adenomatoid malformation the anomaly appears to increase the risk of an adenocarcinoma developing. In BWS the same genetic changes that cause the anomaly and organ hyperplasia defect are also important in oncogenesis. In the WAGR syndrome the constitutional loss of the contiguous genes PAX 6 and WT1 gives rise to the aniridia and the Wilms tumor respectively (OMIM 194072). Diethyl stilbestriol gives rise to abnormal development that is prone to secondary malignant change. In the variegated aneuploidy syndrome the underlying genetic instability gives rise to the malformations and the tumors (OMIM 257300). Another area of malformations and tumors is the relationship of spinal dysraphisms with a range of tumors including adipose and fibrous lesions and, somewhat surprisingly, renal tissues [35].

A review of the records of 20,304 children with cancer in Britain from 1971–1986 showed the frequency of anomalies to be 4.4% in children with solid tumors, and only 2.6% in those with leukemia/lymphoma [36]. The cancers most frequently associated with anomalies were Wilms tumor (8.1%), Ewing's sarcoma (5.8%), hepatoblastoma (6.4%) and gonadal and germ cell tumors (6.4%). The rate of malignant tumors in low birth weight children and twins is close to that of the general population, although very low birthweight infants are predisposed to hepatoblastoma. Twins had a higher rate of renal tumors in one study but another showed a lower rate of tumors in twins [37]. There appears to be a general association with increased birth weight and tumors (apart from the notable exception of hepatoblastoma and also rhabdoid tumors which are associated with small fetuses) suggesting fetal growth factors promote childhood malignancy as discussed above.

19.6 Prenatal Exposure to Environmental Agents, Maternal Medical Therapies and Tumors

There is good experimental evidence that teratogenesis and oncogenesis are closely linked. However, agents that induce tumors postnatally may produce malformations when given earlier in gestation. There are three phases of risk: the pre- and peri-implantation period, the (embryonic) organogenesis phase and the fetal phase. The first phase is resistant to teratogenesis, but may abort; the second phase is sensitive to teratogens, and the third phase is more resistant to teratogenesis. Experimental studies show the organogenesis phase of development is relatively resistant to tumor development but this risk increases after organ formation. Ionizing radiation shows a similar gestational age-related effect. The fetus usually tolerates maternal chemotherapy in pregnancy. Irradiation for maternal malignant disease does cause some fetal damage depending on the gestational age and the amount of irradiation but is not necessarily dire but it increases the risk of childhood leukemia by around 40% [38].

There are many examples of exogenous teratogens in humans and some evidence that intrauterine exposure to chemical agents induces tumors. The association of maternal ingestion of diethylstilbestrol during pregnancy with genital tract malformations and subsequent development of clear-cell adenocarcinoma of the vagina and cervix is well known. Anecdotal reports describe nephroblastomatosis after in utero aspirin intoxication, mesothelioma in a child exposed to isoniazid prenatally and neuroblastoma in fetal hydantoin syndrome and after exposure to maternal carbamazepine. USA studies of pediatric tumor epidemiology showed few environmental risk factors for pediatric tumors though some reports of increased risk of pediatric tumors (Wilms tumor and hepatoblastoma) with paternal occupational exposure to hydrocarbons suggesting a prezygotic influence and possibly pesticide exposure with acute myeloblastic leukemia.

Cell culture models have suggested a mechanism of genetic mutations for the insecticide Permethrin and 11q23/MLL gene changes and because MLL gene changes are seen post chemotherapy, maternal exposure to bioflavonoids has been postulated a risk factor for infants with leukemia with MLL changes. Smoking appears not to be a risk factor for childhood leukemia [39] whereas exposure to petroleum products does [40]. It is now accepted that prenatal radiation predisposes to childhood cancer. The Chernobyl incident has demonstrated that fetal and infant thyroid is more sensitive than adult thyroid to radiation [41]. RET gene mutations are usually involved in both follicular and papillary thyroid tumors following radiation. The debate about overhead powerlines and childhood cancer is still ongoing though the evidence at the moment is that this risk is, at most, small.

There is some evidence that an infection may be needed for the "second hit" to allow progression of already genetically abnormal cells to progress to leukemia [42]. There is evidence in-vitro fertilisation pregnancies have an increased risk of imprinting abnormalities including Beckwith-Wiedemann syndrome. The increasing incidence of undescended testis, hypospadias and germ cell tumors of the testis (testicular dysgenesis syndrome) appears to be due to envi-

ronmental changes with chemicals causing hormone effects [43]. Folate may have a protective effect for childhood acute leukemia as well as the reduction of neural tube defects and cleft palate [44].

19.7 Oncogenesis

In 1971 Knudson proposed a two-hit theory of carcinogenesis. From studies of retinoblastoma he postulated that two separate random and rate-limiting genetic events or "hits" are required to transform a cell and produce a tumor. In patients with hereditary retinoblastoma the first "hit" has already affected the genome, thus explaining the predisposition of these children to develop retinoblastomas which often arise early and may be multifocal. Knudson later included Wilms tumor and neuroblastoma in his two-hit hypothesis. The hypothesis does not explain all the observed facts but it has had a profound effect on theoretical oncology. The various dysmorphic syndromes, focal tissue abnormalities, chromosomal anomalies and inherited disorders predisposing to childhood cancers may be evidence that the first genetic event has already occurred and that the child (or at least cells within the child) are vulnerable to any subsequent "hit" or oncogenic event. In retinoblastoma, evidence of the first hit may be a positive family history or the 13q-phenotype. For Wilms tumor the visible evidence may be nephroblastomatosis, hemihypertrophy, the Beckwith–Wiedemann syndrome or aniridia. The development of both retinoblastoma and nephroblastoma is associated with further genetic events resulting in loss of heterozygosity for regions of chromosome 13 and 11, respectively. These regions contain genes involved in control of normal growth and development of the retina and kidney. Although it is not their usual function, these genes have been called "tumor suppressor genes" because their homozygous loss or mutation results in tumors.

The genetic mechanisms involved in the majority of tumors are more complex than two hits of a tumor suppressor gene. Oncogenes, growth promoter, cell cycle regulator, apoptosis-related, and differentiation genes are all involved and of growing importance are epigenetic changes including chromatin remodeling and acetylation, methylation and also non coding RNA acting as master regulators of both the genome and mRNA. The genetic mechanisms include loss of function, increased function, gene regulatory (promoter and suppressor coding regions), methylation and non-coding RNA changes as well as translocations that either affect gene regulation or give rise to novel genes (e.g. the t(12;15) in mesoblastic nephroma), gene amplification and chromosomal structural changes. These translocations are very helpful diagnostically but not always tumor-specific, as described above. We remain ignorant of the molecular mechanisms responsible for the phenotype of most malformations and dysmorphic syndromes. The Beckwith–Wiedemann syndrome is one example of the close relationship between dysmorphic syndromes, genes and cancer. The segment involved, 11p15 embraces a cluster of imprinted genes and includes insulin-like growth factor-2 (IGF2), the insulin gene, H19 and CDKN1C ($p57^{KIP2}$), offering possible explanations for the abnormalities of growth, carbohydrate metabolism and tumor susceptibility seen in this syndrome. Many individuals with the syndrome show paternal trisomy or isodisomy for this region of 11p15 and over-expression of IGF2 but the syndrome is genetically and phenotypically heterogeneous.

A growing area of interest is the role of nuclear organization of the chromosomal DNA, with histones and the stem cell phenotype with epigenetic changes related to chromatin structure and the effects of non coding RNAs acting as master regulators of gene expression. The chromatin pattern may also be the time window when oncogenic translocations occur as a result of splicing errors. In pediatric tumors the tumors are developing in cells with less differentiation, with stem cell-like characteristics. Many primary pediatric tumors have a near normal karyotype or frequently characteristic changes such as translocations with few other changes. They are in general unlike adult cancers which typically have complex karyotypes, many probably secondary and not oncogenic changes, and some with chromothripsis [45], with extensive chromosomal disordering occurring as a single event. Recent studies with deep sequencing support the largely epigenetic model of pediatric tumors with few genomic changes, suggesting the epigenetic features of a differentiating cell and with only limited genomic changes that are sufficient for oncogenesis, for example rhabdoid tumors where only a single genetic locus may be affected as discussed above.

The cell of origin of some pediatric tumors is more clear, in retinoblastoma from the developing retina, and in Wilms tumors, probably from the metanephric blastema that normally regresses during development. However, for acute leukemia, for example, the stem cells persist through life (hence bone marrow transplant) and the reasons why pediatric leukemia is predominantly acquired in utero, may be related to the fetal environment and hematopoetic development which differs from later being predominantly hepatic and extramedullary location. Some types of tumors in infants such as the germ cell tumors arise from a different mechanism than tumors called the same (and may look the same) in older children and adults, with different locations, histological features, genetic changes and prognosis.

Recent studies in acute lymphoblastic leukemia are also starting to understand what some of the background genetic polymorphisms are involved in susceptibility to tumors. This is indicated by the racial differences for example in perilobar nephrogenic rests and methylation pathway changes in Wilms tumors.

19.8 Investigation of Congenital Tumors

The management of these tumors is dealt with in routine texts but retention of appropriate samples for genetic and molecular studies from tumor and non-tumor tissue may be needed and should be taken, (electron microscopy now rarely needed). Histological markers with important implications such as adrenal cytomegaly, pancreatic islet-cell hyperplasia and nephroblastomatosis should be sought in both postmortem and surgical material. In stillbirths, it is important to establish whether the tumor is part of a syndrome with genetic implications for subsequent pregnancies or a sporadic condition. This requires an autopsy, including examining the placenta and retaining samples of both tumor and non tumor tissue for cytogenetics and molecular studies. A surgical specimen requires similar considerations. An accurate tumor diagnosis is needed and the possibility of a syndromic cause considered.

Many histologically malignant appearing tumors behave in a relatively benign way in neonates, for example neuroblastoma, whereas as a histological identical tumor would have a poor prognosis in a 5 year old. (Table 19.6). Advice must be based on knowledge of the behavior of the tumor in children of the same age and should be dealt with by a pathologist with pediatric expertise and access to pediatric oncologists.

19.9 Teratomas

Teratoma has been the subject of numerous reviews. In infancy, most are extragonadal. Sacrococcygeal teratomas outnumber all others (Table 19.7). The origin of teratomas is controversial and it is likely that not all arise in the same way. Extragonadal germ cell tumors appear to arise from either totipotent somatic cells or premeiotic germ cells. Isochromosome 12, seen in many germ cell tumors in older children and adults, is not seen in teratomas of the newborn while neonatal germ cell tumors may show 1p and 6q deletions and translocations involving 12q13, again suggesting they are biologically different [46]. There is some evidence from mouse models that ectopic germ cells can persist.

Table 19.6 Some tumors of early life showing benign tendencies

Nephrogenic rests
Neuroblastoma:
In situ neuroblastoma
Stage IV-S neuroblastoma
Neuroblastoma under 1 year of age
Immature neuroepithelium in congenital Teratoma
Congenital myeloproliferative disorder in trisomy 21*
Congenital fibromatosis (myofibromatosis)
Congenital fibrosarcoma
Yolk sac tumor of testis under 2 years of age
Hereditary retinoma.

*(though may relapse as leukemia)

Table 19.7 Percentage of childhood teratomas by site; 578 cases pooled from nine series (after Gonzalez-Crussi 1982

Sacrococcygeal	44.8%
Ovary[a]	29.7%
Mediastinum	7.0%
Testis	5.8%
Neck	3.4%
Retroperitoneum	3.4%
CNS	2.7%
Head (extracranial)	1.7%
Abdomen	0.69%
Perineum	0.34%

[a]The proportion of ovarian tumors is much less in neonates

The majority of congenital teratomas contain tissues from all three germ layers although about one-quarter does not. Highly differentiated teratomas with limbs and organoid development may have features of a parasitic twin or fetus in fetu. Teratomas have been defined as being different from fetal development as they lack a notochordal or vertebral axis and have an inherent tendency towards progressive uncoordinated growth. However, teratoma and fetus in fetu have been reported occurring together and the distinction between these two entities is not be as clear-cut as has been suggested. Intracranial teratomas with multiple "fetuses" have been described. It is likely that the difference reflects the degree of linear (homeobox) early embryonic differentiation of the tumor.

The most important prognostic factors in teratomas of the newborn period (age is, of course, an important factor), are presence or absence of a yolk sac component, site and completeness of excision. Immature neural elements are not malignant though often associated with yolk sac elements. Wilms tumors are seen as part of a malignant teratoma occasionally whereas choriocarcinomas and germinomas appear vanishingly rare in this entity. Other immature elements should be related to the maturity of the host. Even teratomas with a high degree of organoid differentiation occasionally recur. Overall, 5–6% of congenital teratomas contains yolk sac elements [47].

19.9.1 Sacrococcygeal Teratomas

Sacrococcygeal teratomas occur in 1:30000–1:170000 live births with a male to female ratio of 1:3. Most sacrococcygeal teratomas are sporadic but familial cases occur. A strong family history of twinning is described. Associated malformations of the hindgut, caudal spinal cord and distal genitourinary tract are often present. A recent review of teratomas summarises the current thinking on the pediatric tumors, noting the difference from adult type of germ cell tumors and

that they arise from germ cells at an earlier stage of differentiation [46]

Most sacrococcygeal teratomas are apparent at birth and many are now diagnosed at the time of the antenatal anatomy scan though it is likely that many will be undetectable in the second trimester. Sacrococcygeal teratomas are a cause of raised maternal serum alpha-fetoprotein. Management includes planned delivery in a center with expert pediatric surgery. Unfavorable factors are presentation before 30 weeks' gestation, rapid tumor growth and the development of fetal hydrops or placentomegaly. Fetal presentation is associated with increased immature elements and also a high proportion with yolk sac elements [48]. Extensively cystic tumors are usually benign but a predominantly solid tumor raises the possibility of malignancy, though most are histologically benign if resected soon after delivery. The tumor may be so large as to obstruct labor, cause maternal injury or rupture during delivery. The overlying skin is sometimes ulcerated and occasionally bears a rudimentary tail or digit. Some tumors are highly vascular, and telangiectasia in the overlying skin should warn of the risk of hemorrhage into the tumor or high-output heart failure. They are usualy supplied by a median sacral artery to be identified by the surgeon at removal. Occasionally adrenal cortical tissue may produce secondary effects as a result of secretion of steroid hormones. Sometimes the tumor is inconspicuous, marked externally only by a skin tag, dimple or tuft of hair. Internal tumors may present with delayed passage of meconium. Tumors may not lie in the midline and can present as a lateral mass in the buttock.

Sacrococcygeal teratoma may be entirely postsacral (external), presacral (internal), or dumbbell shaped. The risk of malignancy is increased when the tumor is internal and when the diagnosis is delayed beyond the newborn period. Benign tumors are usually well defined with a solid and cystic cut surface. Some tumors are highly differentiated with well-formed bronchial or intestinal cysts. Neuroglial tissue, with or without choroid plexus, is seen in most cases and may predominate. Twenty to thirty percent of tumors contain immature tissue, usually neural and resembling neuroblastoma or the developing neural tube. The amount of this has been graded, as in the ovary, but presence does not indicate malignancy in this context but should stimulate a close look for yolk sac elements. Immature renal tissue, striated muscle and other tissues are also seen (Fig. 19.3). Tumors with immature tissue have an increased risk of local recurrence. Neural elements may recur as local implants (dermal–subcutaneous gliomatosis) without ominous significance. About 10–20% of sacrococcygeal teratomas presenting in the newborn period are malignant, including all those with yolk sac elements or embryonal carcinoma, and produce alpha-fetoprotein. Small foci of yolk sac tumor may be hard to recognize, resembling other immature epithelial structures such as intestine. It may have a variety of growth patterns, including reticular, festoon, polyvesicular, vitelline and solid areas. Hepatoid variant of solid type may resemble fetal liver. Immunohistochemistry (particularly glypican) can be useful as alpha feto-protein expression can be very focal by immunohistochemistry, and correlation with the serology can be helpful.

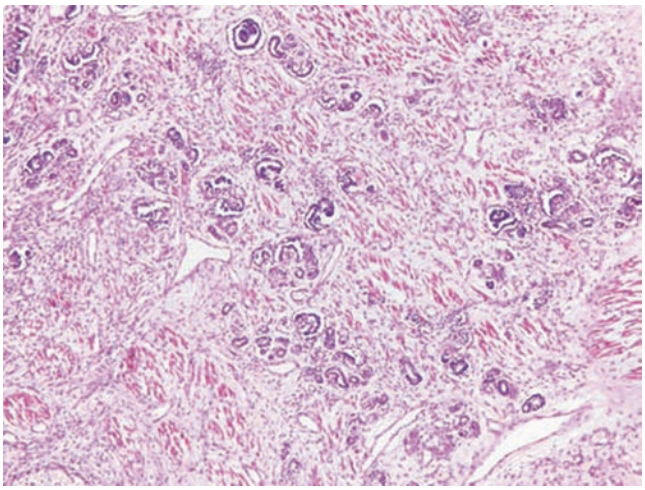

Fig. 19.3 Sacrococcygeal teratoma. Term neonate with large external mass showing skeletal muscle and renal elements. Abundant neuroglial elements present in other fields

The main objectives of pathological examination are to assess the completeness of excision and to offer a guide to prognosis [49]. Failure to remove the coccyx results in an increased risk of recurrence and it is important to identify and record this structure in the surgical specimen. However, failure to achieve full excision does not always lead to recurrence. The tumor must be adequately sampled, including areas of hemorrhage and necrosis, which may indicate malignancy. Maturation and regression of sacrococcygeal teratomas in the interval between debulking and definitive resection has been described. However, despite the good outcome of most immature sacrococcygeal teratomas it is important to recognize that an occasional tumor without frankly malignant elements at presentation may recur with malignant elements and cause death. Retrospective analysis in some of these cases has revealed occult foci of yolk sac tumor in the original tumor. In other cases there may have been foci of yolk sac tumor separate from the main tumor mass. Follow-up for at least 2 years is recommended regardless of histological type although late recurrence may occur even in adulthood.

Lemire and Beckwith [50] and Bale [51] described an extraordinary variety of developmental abnormalities and tumor-like conditions of the sacrococcygeal region in children and related them to the complex embryology of this area, which probably underlies the predilection of this site for congenital teratoma. A large range of tumors associated

with embryological remnants can be found [51], including tailgut lesions [52], ependymomas and other normally intra-axial tumors, meningocele and related lesions, chordomas and paccinian corpuscle. Currarino syndrome (anorectal anomalies, coccygeal anomaly and a pre-sacral mass) should also be considered.

19.9.2 Teratomas and Germ Cell Tumors at Other Sites

Other teratomas that affect the newborn include orbital, facial, intracranial (see later), cervical, mediastinal, intrapericardial and gastric teratomas [53]. Orbital teratoma is peculiar to the newborn and has often reached a large size by the time of birth this is usually extraocular, but very rare intraocular tumors occur [54] (see later). There is usually exophthalmos of striking proportions with the orbital tumors. The extrinsic muscles of the eye are stretched over a retrobulbar mass, which may have an intracranial extension. Differential diagnosis includes hemangioma, lymphangioma, epidermal inclusion cyst and metastatic neuroblastoma.

Teratoma involving the pharynx and base of the skull arises from pluripotent cells around Rathke's pouch and the oral membrane at the point of contact of the buccopharyngeal membrane and the rostral notochord. It frequently prevents fusion of the palatal processes, resulting in clefting. Large tumors project from the mouth (epignathus) and cause polyhydramnios by preventing fetal swallowing (Fig. 19.4). The tumor site often precludes complete excision and death occurs from asphyxia or from meningitis if the base of the skull is involved. Teratomas also arise in the tongue. A possibly related lesion peculiar to infancy is the hairy polyp of the pharynx (Fig. 19.5). This tumor-like lesion consists of a mass of fibroadipose tissue covered by hair-bearing skin projecting into the mouth or pharynx. This entity is best regarded as a hamartoma. Meningoepithelial elements have been described.

Germ cell tumors arising in the neck account for 3–4% of childhood teratomas and are usually evident as a large mass at birth. Seventeen percent of affected babies are stillborn and 35% die before surgery. The EXIT procedure where the baby is delivered by cesarean section and maintained on the placenta until a surgically protected airway is established may be used if a large obstructive tumor has been identified by prenatal scans. Many tumors are intimately related to the thyroid, resulting in post-operative hypothyroidism and hypoparathyroidism. Of interest there has been recent identification of Dicer1 mutation in the rare adult thyroid malignant teratomas [55]. Congenital cervical teratomas are usually benign but yolk sac tumors and metastases have been described. Lymph nodes draining cervicothyroid teratomas may contain foci of neural tissue without ominous significance.

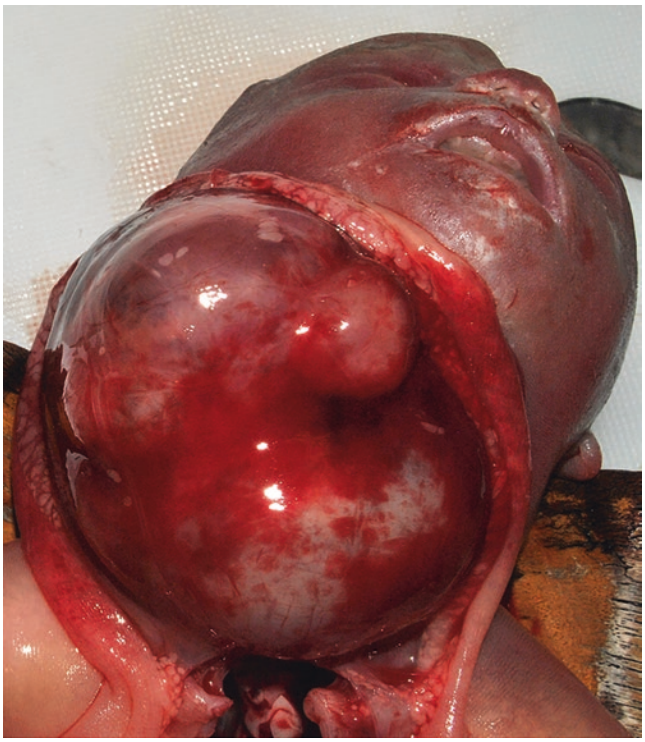

Fig. 19.4 Nasopharyngeal teratoma. Termination of pregnancy at 23 w gestation with large well-circumscribed and vaguely lobulated mass arising from the right side of the neck

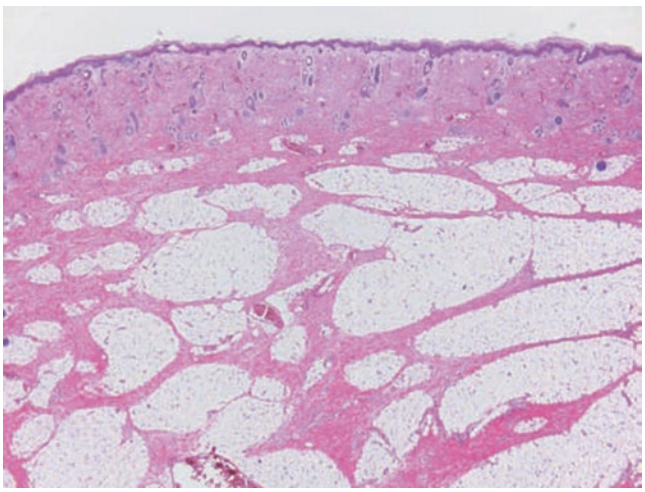

Fig. 19.5 Hairy polyp. Term neonate with mass in the mouth arising from the soft palate consisting of skin-like tissue with hair and adnexal glands over fibroadipose tissue. A cartilage bar was present deep in the lesion

Mediastinal tumors may present with hydrops fetalis or respiratory obstruction caused by compression of adjacent structures. These tumors also usually have a benign behavior in infants, even when histologically immature. Intrapericardial

tumors present in infancy with cardiomegaly, muffled heart sounds and cardiac tamponade caused by a pericardial effusion. These tumors arise close to the root of the great vessels, often on the right side, and may be fatal because of their location or, very rarely, malignant behavior.

Gastric teratomas are notable because, unlike other congenital teratomas, they occur almost exclusively in males [56]. Malignancy is very rare and treatment is by local excision. Yolk sac tumor is sometimes found at extragonadal sites including the vagina, the head and neck and the retroperitoneum. Various chromosomal abnormalities have been demonstrated and are different from those seen in yolk sac tumor in adults.

Teratomas may occasionally be described in the umbilical cord and associated with other anomalies [57].

The infantile choriocarcinoma usually arises from the placenta and presents in the first few weeks with varying features including anemia, organomegaly, and sometimes precocious puberty (see later). The mother may present before the baby with metastatic disease and the disease in the placenta may be very focal and easily overlooked resembling a small infarct macroscopically.

19.10 Congenital Neuroblastoma

Neuroblastoma has been diagnosed before birth by ultrasound scanning when it may rarely produce symptoms in the mother due to secretion of catecholamines. It is the commonest malignant solid tumor presenting in the neonatal period, accounting for 30–50% of cases. The majority has an abdominal primary, either in the adrenal gland or retroperitoneum. Pathological management is well summarised in textbooks and reviews. Some cases are familial and associated with germline PHOX2B (paired-like homeobox 2b), ALK (anaplastic lymphoma receptor tyrosine kinase), and ATRX (alpha thalassemia/mental retardation syndrome X-linked) [58].

Rare cases are may be part of a disorder of neural crest such as neurofibromatosis type 1, Hirschsprung's disease, nesidioblastosis or Ondine's curse. There also appears to be an association with congenital heart disease. There may be placental involvement with widespread plugging of villous capillaries and hydrops fetalis. Concordance for neuroblastoma in twins may be due to transplacental metastasis or simultaneous onset tumors in each twin. Metastasis to the skin is common in neonates. Hepatic involvement may be massive and is common. The terms "Pepper's syndrome" and "Hutchinson's syndrome" are no longer fashionable; the former described massive liver involvement by adrenal neuroblastoma, which is virtually confined to young infants. It has been suggested that the liver may be reseeded from the placenta via the umbilical vein while the lungs are spared by diversion of blood through the foramen ovale and ductus arteriosus. Congenital neuroblastoma undergoes spontaneous regression more commonly than any other tumor. Regression is usually the result of necrobiosis but maturation to ganglioneuroma may occur. This remarkable phenomenon has been well documented and accounts in part for the relatively good prognosis of neuroblastoma in young children. A cystic variant of neuroblastoma is uncommon (2% of neuroblastomas) and appears to present predominantly in neonates.

The diagnosis of neuroblastoma in neonates poses the same diagnostic problems as in older children. The microscopic appearance does not differ significantly from that in older children although often is only poorly differentiated, but its behavior and metastatic pattern are distinctive. Diagnostic aids such as the measurement of catecholamines and their metabolites in body fluids can be useful. Immunohistochemistry is useful confirming a neuroendocrine differentiation and differentiating from other small round blue cell tumors in poorly differentiated tumors. N-myc amplification is not always present, but denotes a poorer prognosis, but this molecular finding can be seen in other tumors such as some alveolar rhabdomyosarcomas.

Artefactually dispersed neural tissue in macerated fetuses has been mistaken for metastatic/multifocal neural tumors in several older case reports.

The prognosis of neuroblastoma depends on site, stage, grade and, particularly, age. Pathological grading systems which correlate with prognosis were proposed by Beckwith and Martin in 1968 and Shimada et al. in 1984 and 1995 and are updated [59]. Favorable prognosis correlates with low N-myc copy number, aneuploidy and no loss of chromosome 1p and are reviewed in recent reviews and protocols for the main childrens cancer study groups. A modified Shimada classification is currently preferred with the age, stage, histology and molecular markers taken into account for management [60]. N-myc amplification may be focal and localized to areas with undifferentiated morphology. It has recently been found that activating ALK mutations in neuroblastoma have their effect through increased N-myc transcription [61]. However, newer technologies examining the genome for changes including for chromothripsis (where there are massive chromosomal rearrangements) mean samples of tumors need to be stored for these techniques [62].

Various explanations have been advanced for the relatively benign behavior of neuroblastoma in neonates. About 10% of children and at least 30% of neonates with neuroblastoma have a special pattern of metastasis termed Stage IV-S neuroblastoma, which has a particularly favorable outlook. It describes patients with small primary tumors and dissemination to liver, skin and bone marrow but without bone lesions [63]. Survival has been reported as 93% in babies with skin metastases compared with 32% survival

when these are absent. Newborns have a poorer survival than babies presenting later with lV-S disease because of massive liver enlargement causing respiratory failure. Stage IV-S neuroblastoma does not usually show N-myc amplification but, when it does, it often behaves aggressively. Telomerase is also not usually present in stage IV-S tumors unlike more aggressive neuroblastomas but has been reported in a IV-S tumor that was fatal. Thus, it appears that most IV-S neuroblastomas lack the genetic mechanisms for fully malignant behavior. Even incidentally discovered connatal localized neuroblastomas may progress, and though some caution against a "wait and see" strategy, such an approach, especially for cases detected by screening is advocated by others.

Small nodules of neuroblasts up to 400 μm in diameter with a modal size of 60 μm are seen in the adrenal glands of all fetuses. They become less frequent after 20 weeks' gestation and are uncommon at birth. "In situ neuroblastoma" refers to larger nodules of undifferentiated neuroblasts a few millimetres in diameter situated in the adrenal medulla ~~(Fig. 19.6)~~. Some are visible to the naked eye.

The natural history of in situ neuroblastoma is unknown but it is not found after 3 months of age. Systematic search shows in situ neuroblastoma in 1–2% of routine perinatal necropsies. However, other congenital abnormalities (often cardiac) have been found in 30% of these cases and it has been argued that it is part of a generalized dysontogenic process. If normal newborn population has the same frequency of this lesion as in the necropsied population, then the majority of in situ neuroblastomas must regress spontaneously, very few becoming malignant tumors. The favorable prognosis of neuroblastoma in infancy has stimulated screening programmes based on catecholamine metabolites in urine to detect the tumor before it is clinically manifest. Such programmes in Japan have not been successful in reducing mortality but do detect favorable prognosis neuroblastomas that would not otherwise have come to medical attention. In the Québec Neuroblastoma Screening Project, most screening positive cases were of favorable histology while most unfavorable histology tumors were missed by screening. Screening for neuroblastoma does not therefore appear to be of benefit. Although the effectiveness of these programmes in preventing death is still in question, it is clear that a majority of neuroblastomas are detectable by 6 months and so many may, in fact, be congenital. Most authors favor on theoretical grounds that almost all childhood neuroblastomas arise in utero.

19.11 Small Round Blue Cell Tumors

The differential of these tumors in infants is wide, from leukemia, to undifferentiated neuroblastoma, and areas in Rhabdoid tumor. Ewings sarcoma is rare in infants, but has been described [64, 65] including "blueberry Muffin" presentation. Other entities include a cellular infantile fibrosarcoma, but some are new entities and require molecular testing [66]. Some small round cell sarcomas tumors show CIC arrangement (immunohistochemistry with WT1 and ETV may assist) [67] BCOR anomalies [68], and a variant is the primitive myxoid mesenchymal tumor of infancy [69].

19.12 Hematological Tumors

19.12.1 Congenital Leukemia

Congenital leukemia is rare but is the major cause of cancer deaths in the first month of life [70]. Congenital leukemia has very different features from older children [71–73]. The prognosis is poor though has improved with aggressive therapy and recent international collaboations are developing newer protocols with around 44% 2 year survival (but very low with KMT2A/MLL changes). Acute non-lymphoblastic leukemia (ANLL) is more common than Acute lymphoblastic leukemia (ALL) and, once in remission, ANLL cases have a better prognosis than the ALL cases, and a few percent are biphenotypic. The ALL cases have a disease free survival of under 10% in many series. Sixty three percent of patients have shown skin involvement and this can present before the leukemic phase and even appear to regress before presenting with the leukemia. Organomegaly is often a prominent feature and with skin (Blueberry Muffin change) and CNS involvement iscommon. A differential diagnosis of skin lesions is the Blastic plasmacytoid dendritic cell neoplasm (BPDCN) rarely reported in infants with CD4 and CD56 positivity [74]. Congenital leukemia/myeloproliferative may be a cause of spontaneous stillbirth in up to 7% of Down syndrome. The fetuses are usually hydropic and the placentas large and edematous [71].

Abnormalities of the mixed-lineage leukemia (MLL now called *KMT2A*) gene are seen in 37% or more congenital leukemias (only around 5% in other childhood leukemias and in BPDCN), both ANLL and ALL types. This gene is also often involved in post chemotherapy related leukemias and has given rise to the suggestion that maternal ingestion of flavonoids may be a factor. Congenital leukemia is often CD10 negative and leukemias and may show lymphoid and myeloid marker positivity (mixed lineage or biphenotypic leukemia). Leukemias with MLL gene translocations usually cluster together in gene profile experiments suggesting a separate pathogenetic group. They may not infrequently show CD4 and CD56 positivity (and BPDCN needs to be considered).

Leukemia must be distinguished from the florid leukemoid reactions seen in fetuses and neonates (see parvovirus reaction). Four diagnostic criteria have been suggested: birth proliferation of immature cells of the myeloid or lymphoid series; infiltration of non-hemopoietic tissues; and absence

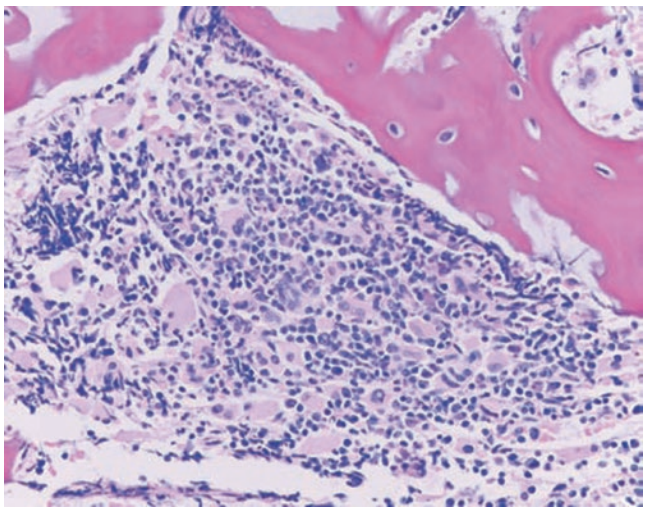

Fig. 19.6 Transient leukemia. A 2-week-old with leukemic blood film. Bone marrow trephine biopsy showing excess atypical megakaryoblasts. Cytogenetics showed trisomy 21 from the blood. The infant was not dysmorphic and had a normal skin karyotype. Leukemia resolved without treatment

of other diseases that might cause diagnostic confusion such as erythroblastosis fetalis, congenital syphilis, or viral and bacterial infections and presentation before 4 weeks of age. Leukemia is associated with Down syndrome, Bloom's syndrome, Turner's syndrome, trisomy 13, Fanconi's anemia, Ellis–van Creveld syndrome, Schwachman's syndrome and Rubenstein–Taybi syndrome.

A condition variously called transient abnormal myelopoiesis (TAM), or transient myeloproliferative disorder (TMD) is now often called transient leukemia. This condition resembles the megakaryoblastic leukemia (M7) which is usually seen in trisomy 21 but commonly remits spontaneously (Fig. 19.6). This association with trisomy 21 appears to be a complex relationship involving GATA1 [75], with truncating mutations and also involvement of other genes [76]. The infants are generally healthy but with hepatosplenomegaly. The transient leukemia may be managed expectantly unless there is life-threatening progression. It may induce severe hepatic fibrosis as a result of the production of fibrogenic cytokines. Bone marrow tends not to show the fibrosis, perhaps because it is not the major site of hemopoiesis in fetal life. There are genetic differences in the genetic signatures of transient leukemia and acute megakaryoblastic leukemia associated with trisomy 21. Telomerase activity is present in the leukemia but usually not in the non fatal transient form. However, a high proportion with the transient leukemia (25% or so) relapse with leukemia by the age of 4 and a number of others will succumb to complications, such as infection or hematological complications. A similar syndrome is seen in children with trisomy 21 mosaicism, the leukemoid reaction being confined to trisomic cells with other somatic cells having a normal karyotype and this has a relatively good prognosis. Occasionally congenital leukemia without trisomy 21 remits without treatment. Older children with Down syndrome have a 20 times increased risk of acute leukemia more than children with a normal karyotype. It is thought that leukemia occurs only in those children who had transient luekemia and involves the same clone of cells. Genes present on chromosome 21 such as AML1 and TIAML may have a role in this association. Transient leukemia has also been asscociated with Noonan syndrome.

Care must be taken not to overdiagnose leukemia in chylous effusions in infancy which can contain numerous lymphocytes and raise cytological concerns of leukemia, and in viral and other fetal infections with massive erythroblastosis (Fig. 19.7).

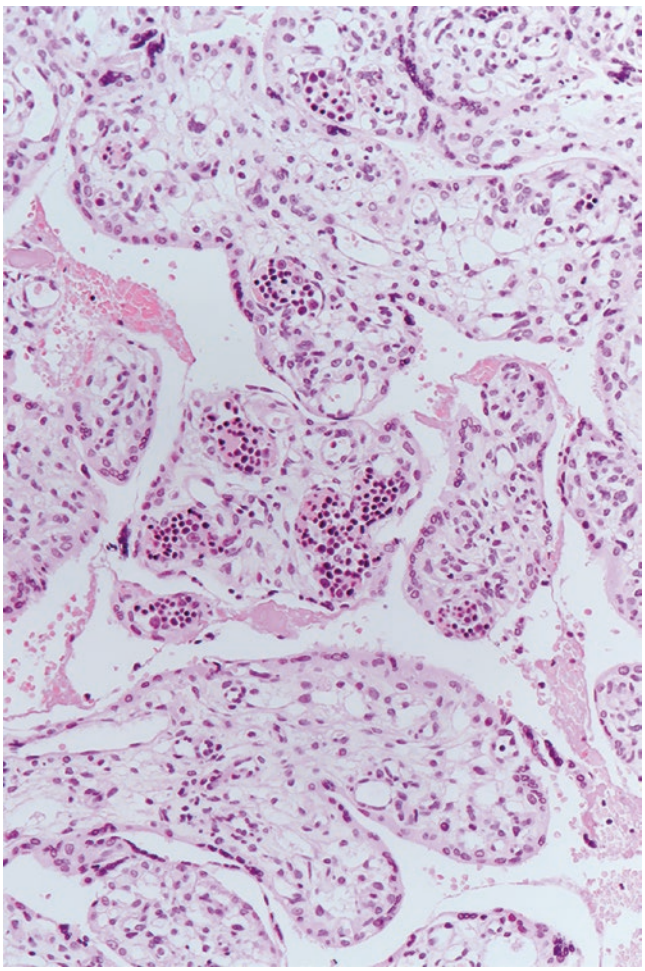

Fig. 19.7 Leukemoid reaction associated with Parvovirus (Mother IgM positive) in the placenta

19.12.2 Lymphoma

Lymphomas are rare in infants and almost unknown in the newborn. Congenital immunodeficiency syndromes predispose to lymphoma and leukemia in older children.

19.12.3 Histiocytic Disorders

The biology, classification and diagnosis of the histiocytic disorders of childhood have been clarified in recent years [77–79] and although most cases are straightforward, many are not so simple. Patients may present with lesions that change in phenotype from LCH to non LCH. In the newborn period Langerhans' cell histiocytosis, hemophagocytic lymphohistiocytosis and juvenile xanthogranuloma all pose diagnostic and prognostic problems. The localized histiocytoma shows a mixed cell lineage, and various mutations, including *BRAFv600E*, *HRAS* and *PTEN* changes [80]. Rosai-Dorfman disease (SHML Sinus histiocytosis with massive lymphadenopathy) has also rarely been described in neonates. Autoimmune lymphoproliferative syndrome—another disease due to defective apoptosis—usually presents later but splenomegaly and SHML-like changes can present shortly after birth. A rare recently described entity in infants is the ALK positive histiocytosis [81].

19.12.4 Langerhans' Cell Histiocytosis

Langerhans' cell histiocytosis (LCH) presenting in neonates has been reviewed recently. Multifocal disease is common and has a poor prognosis. The incidence is around 1 in a million neonates. Around 90% of cases have skin involvement, 40% single system disease (with a 94% 5 year survival), 60% with multiple organ disease and 75% have involvement of the liver, spleen, lung or hematological system and have less than a 50% survival. Those presenting with multiple nodules confined to the skin in the newborn period often regress spontaneously and this form has been called congenital self-healing reticulohistiocytosis or Hashimoto–Pritzker disease. Skin involvement with LCH can be also present as a recalcitrant excema. Congenital LCH with systemic involvement has a less favorable outlook, but occassionally even this can regress. The liver involvement may give rise to secondary sclerosing cholangitis. GI involvement in neonates and infants is probably under reported and can cause diarrhoea, bleeding, protein-losing enteropathy and perianal disease and histologically resembles inflammatory bowel disease.

Studies using X-linked markers show that unifocal and multifocal LCH is clonal. A definitive diagnosis of Langerhans' cell histiocytosis requires positive immunostaining for CD1a and Langerin (identification of Birbeck granules by electronmicroscopy is not now routine). Clinical behavior is determined by the extent of organ involvement and dysfunction. More aggressive disease may be indicated by age under 1 year old and multiple bone and organ involvement. Occasional associations of LCH with congenital abnormalities, leukemia and other neoplasms are recognized and molecular similarities between the tumors have been shown.

19.12.5 Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis (HLH) is a familial (autosomal recessive) or sporadic syndrome usually affecting infants and young children characterized by fever (> 7 days), splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis [82, 83]. It is becoming more recognized in older children and adults and the current understanding is that the disease is a continuum of risk factors with variable genetic components and environmental triggers.

Familial cases may have a background of consanguinity and the disease is usually triggered by an infection, and is due to a defect in the perforin dependent cytotoxic pathway. Histology of many organs shows an infiltrate of lymphocytes, activated non-Langerhans' histiocytes and hemophagocytosis (Fig. 19.8). In some cases, neurological symptoms may be prominent with meningeal, perivascular and parenchymal infiltration. Skin involvement may be the presenting feature. The disease was often missed and, as it is fatal unless treated, was diagnosed only at autopsy.

HLH appears to be due to uncontrolled activation of T cells producing interleukin-2 and other cytokines due to impaired apoptosis of target cells. Defective natural killer (NK) cell function has been found. Familial HLH (FLH) has been subdivided according to the genetics. FLH2 forms around 20–40% of FLH and is due to mutations of the perforin gene. A second gene, *Munc 13-4*, causes FLH3 which presents later. The treatment for primary genetic HLH is chemotherapy to suppress the ineffective immune response followed by bone marrow transplantation with a 60–70% cure rate.

19.12.6 Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) usually presents at birth or in infancy usually with a single (less frequently multiple) dome-shaped nodule in the skin of the head, neck or trunk. Biopsy shows histiocytes, foam cells, Touton giant cells and eosinophils in varying proportions and can be classified into

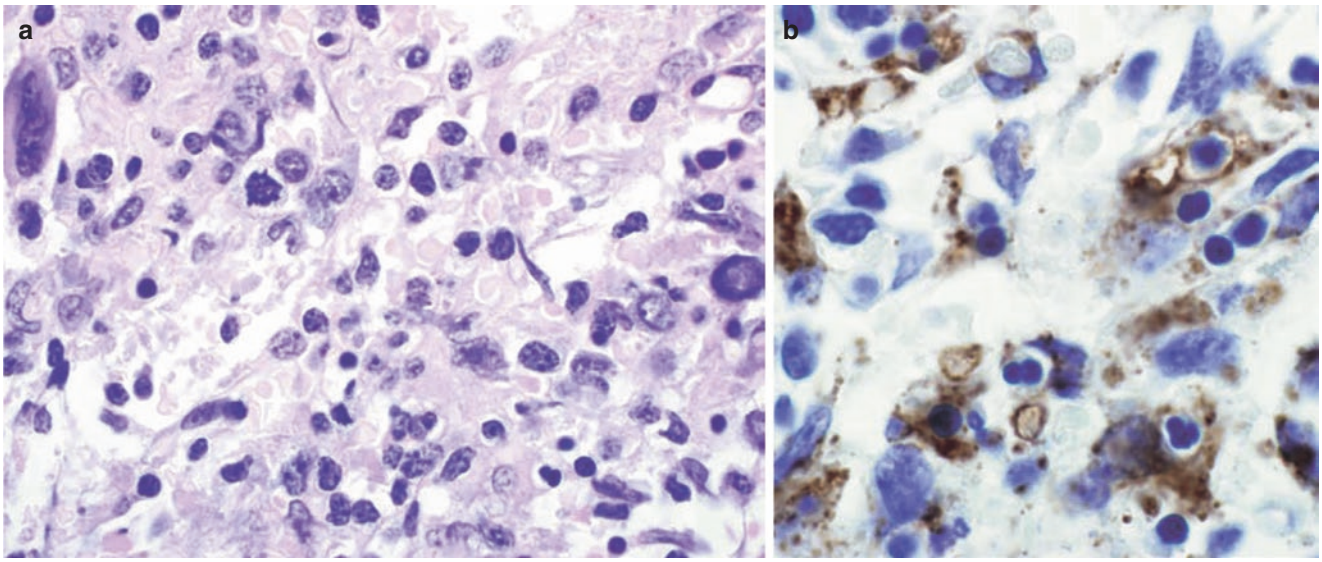

Fig. 19.8 (**a**) Familial hemophagocytic lymphohistiocytosis. A 3-month-old with history of pallor, skin rash, hepatosplenomegaly, and pancytopenia. Bone marrow aspirate shows numerous histiocytes with hemophagocytosis. (**b**) Immunohistochemistry for CD68 confirms the changes. The serum triglycerides were high

the early, classic, transitional and combined subtypes. The proliferating cell is the dermal dendrocyte which is CD68 and fascin positive, usually expresses Factor Xllla, LCA, CD4, rarely S100 and is negative for CD1a. Birbeck granules are not identified. The non-cutaneous lesions tend not to have multinucleate cells, may have spindle cells, and can be difficult to diagnose. Most lesions regress spontaneously by 3 years. There is a reported association between NF1, juvenile xanthogranuloma and juvenile chronic myeloid leukemia.

JXG also occurs in a systemic form involving subcutaneous tissue, muscle, central nervous system, liver, spleen and other sites. About 10% of babies with cutaneous JXG have extracutaneous involvement and most, but not all of those with multifocal disease have cutaneous lesions. Liver involvement with giant cell hepatitis can be fatal. A third of patients have lesions at birth and it appears more common in males. Treatment may be difficult and the systemic form of JXG carries significant morbidity and mortality, particularly if the brain is involved. LCH type chemotherapy has been used for systemic disease. There may be overlap with some of the non Langerhans'0 histocytoses.

19.13 Congenital Soft Tissue Tumors

19.13.1 Mesenchymal Tumors

Mesenchymal lesions comprise about 10% of neonatal tumors. Kauffman and Stout in 1965 reported 125 congenital mesenchymal tumors of soft tissue. Fibromatoses, mesenchymoma, rhabdomyosarcoma, smooth muscle tumors and hemangiopericytoma were the commonest types in their series. Since that time, a number of new entities have been described which might necessitate reclassification of some of their cases [84]. However, their conclusion that congenital mesenchymal tumors seldom behave in a malignant way and differ biologically from those in adults is still valid. Malignant neonatal soft tissue tumors are divided equally between congenital fibrosarcoma, rhabdomyosarcoma and other non-rhabdomyosarcoma malignant soft tissue tumors including rhabdoid tumors.

19.13.2 Vascular Tumors

The classification of hemangiomas is complicated as cases do not always readily fit into single entities and some cases appear to be a neoplasm, others reactive and others are a malformation [85–88]. The classification of vascular lesions is complex and covers developmental anomalies, benign, intermediate and malignant tumors and there is an international association (ISSVA- https://www.issva.org) devoted to this with an update produced in 2018, which includes a list of genes and also related syndromes, some of which may present in the neonatal/early infantile period [89]. A vascular malformation should prompt clinical consideration of many syndromes, including PHACE, CLOVES, PTEN related, Proteus, and FAVA though the full features may present later in childhood [87–89]. Recent developments also include the use of specific drugs based on the genetic basis of the lesions [90].

The (Capillary) Infantile Hemangioma is well known [91]. It classically presents as a strawberry nevus, increasing in size for a few months before regressing. Treatment, which includes intralesional steroids and interferon, is usually reserved for those cases which affect sight, feeding or cause other significant symptom. Diffuse involvement of the tissues—angiomatosis—is well recognised though may present later in childhood. The placenta may also be involved with chorangiomas. GLUT1 can be used to distinguish the involutional hemangioma from the other entities. GLUT1 is also expressed in the placenta and some have suggested a relationship between these tumors and a placental origin. New infantile capillary hemangioma variants, the Rapidly Involutional (RICH) and the Non Involuting (NICH) and the partially involuting (PICH) variant have histological appearances that overlap the common infantile hemangioma, although are GLUT1 negative, though some NICH may show post natal growth [92]. Recent newer treatments such as propranolol and sirolimus or other mTOR inhibitors are leading to a major change in therapy. A growing recognition is that some of these vascular lesions, which can appear to be malformations, carry somatic mutations [93].

The Tufted Hemangioma often appears more plaque-like and generally develops after birth and the closely related or same tumor, the Kaposiform Hemangioendothelioma is a tumor often presenting in infancy and increasingly recognised in adults (Fig. 19.9). It may present at birth as a mass or a cause of hydrops or Kasabach-Merritt syndrome [94]. It does not fully regress. It may closely resemble infantile hemangiomas, especially in small biopsies, but has a lymphatic component, and it is negative for GLUT1 and the lymphatic marker D2-40 stains the spindle cell and lymphatic components. Rarely, they appear to be the cause of hypothyroidism.

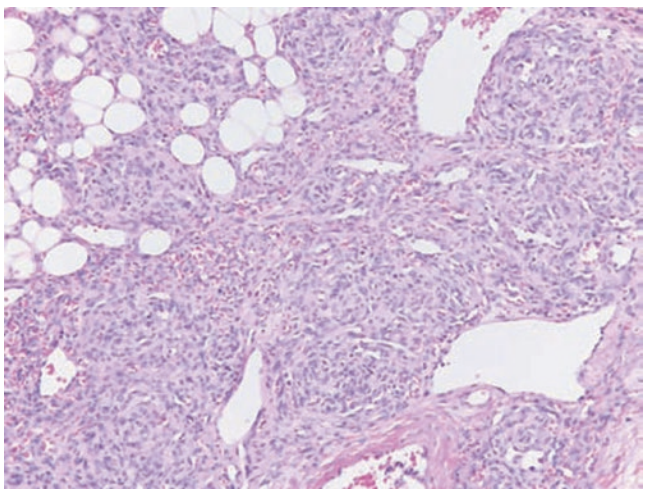

Fig. 19.9 Kaposiform hemangioendothelioma. A 3-month-old with soft tissue mass increasing in size since birth, who also developed Kasabach-Merritt syndrome. Adipose tissue infiltrated by vascular nodules with spindle cells and with larger vessels adjacent to the nodules

There are several syndromes associated with hemangiomas including the PHACE syndrome in which facial hemangiomas are associated with arterial malformations, cardiac, eye, and brain anomalies. This syndrome may be a concern for the use of beta blockers. Another recently described entity in infants includes the Giant Cell Angioblastoma [95].

Lymphangiomas are common tumors in neonates. They are often diffuse, poorly localised and difficult to remove and often recur.

19.13.3 Fibromatoses

The fibrous proliferations of infancy and childhood include a number of distinctive lesions unique to this age group which are recognizable as much by their clinical presentation as by their histology (Table 19.8) [96]. All have in common the proliferation of spindle cells resembling fibroblasts, which are locally invasive, but generally lack the capacity to metastasize. However, they can be fatal and lead to extremely disfuring surgery. Fibromatoses seen in infancy are usually more cellular than adult types although the latter also occur in childhood. Discussion will be restricted to the fibrous proliferations that are seen in neonates and young infants. Infantile fibromatosis, myofibromatosis, and congenital fibrosarcoma, often show considerable histological overlap and an immunohistochemical panel and molecular testing may be required [97]. Most authorities now regard hemangiopericytoma of infancy as a myofibromatosis.

Table 19.8 Fibrous proliferations of infancy and childhood

Congenital myofibromatosis:
Solitary
Multicentric
Infantile desmoid-type fibromatosis
Gardner-associated fibroma
Nuchal Fibroma
Fibromatosis colli (sternomastoid tumor)
Infantile digital fibromatosis (recurring digital fibroma)
Cranial fasciitis
Inflammatory myofibroblastic tumor
Infantile Fibrosarcoma
Giant cell fibroblastoma/Dermatofibrosarcoma protuberans
Fibrous hamartoma of infancy
Calcifying aponeurotic fibroma
Plantar fibromatosis
Juvenile hyaline fibromatosis
Gingival fibromatosis
Fibrodysplasia (myositis) ossificans progressiva
Plexiform fibrohistiocytic tumor
Fibrolipomatosis
Gastrointestinal stromal tumor (GIST) (See above)

19.13.4 Congenital Myofibromatosis (Solitary and Multicentric)

This distinctive lesion of neonates has been described under a variety of synonyms. Congenital myofibromatosis may be solitary, usually involving the soft tissues of the head, neck and trunk, and is more common in males. Multicentric involvement of the skin, soft tissue and bone is less common but usually has a good outcome with spontaneous regression. The third and rarest type, generalized myofibromatosis with visceral organ involvement is often fatal. Sixty percent of lesions are congenital. Autosomal dominant (with variable penetrance) and possibly recessive modes of inheritance have been suggested in some cases (OMIM #228550). Various chromosomal changes have been reported in the tumors.

Myofibromatoses are more or less well-demarcated, often vascular nodules up to several centimetres in diameter. Occasional examples are cystic. Microscopically, they tend to be cellular and are composed of nodules of plump spindle cells showing mitotic activity. The center of the lesion characteristically has a hemangiopericytomatous pattern while the periphery of the tumor appears mature with more collagen. Giant cells may rarely be present. Necrosis, intravascular growth, trapped fat and an infiltrative margin may be present but are not of adverse significance. Congenital myofibromatoses are immunohistochemically positive for smooth muscle actin, vimentin and desmin and the histogenesis is believed to be from pericytic myofibroblasts [98]. CD 34 may be positive [99]. Coffin suggested that the generalized type arises multifocally from subintimal mesenchymal or smooth muscle cells with a myofibroblastic phenotype [100]. One case has been associated with fibromuscular dysplasia of the arteries.

Although solitary lesions sometimes recur, they do not metastasize and the outlook is excellent. The prognosis is less good for patients with multicentric visceral lesions due to involvement of vital organs, particularly the lungs where there may be occlusion of pulmonary veins. New lesions may continue to appear after birth. Spontaneous regression, which may be by apoptosis, can occur even in patients with multiple lesions.

19.13.5 Infantile Desmoid-type Fibromatosis

Infantile desmoid-type fibromatosis is the childhood equivalent of the desmoid tumor (musculoaponeurotic fibroma) of adults. It arises in muscle, aponeurosis or fascia. Muscles of the head and neck, shoulder, upper arm and thigh are favored sites. The macroscopic appearance is of an ill-defined mass of grey–white tissue that infiltrates surrounding tissues at the periphery. The histological appearance varies. Some resemble the adult desmoid tumor but more cellular examples are indistinguishable from infantile fibrosarcoma. Another pattern seen in very young infants is of immature cells, intermediate in form between primitive mesenchymal cells and fibroblasts, scattered in a myxoid background and surrounded by abundant reticulin. This appearance may be confused with other myxoid tumors such as a lipoblastoma or rhabdomyosarcoma. This fibromatosis characteristically infiltrates muscle when it may be accompanied by adipocytes.

Infantile desmoid-type fibromatosis tends to recur and infiltrate locally but does not metastasize. It may spontaneously regress. Local recurrence is correlated with the presence of numerous slit-like blood vessels and undifferentiated mesenchymal cells. Local excision is the treatment of choice but may be difficult because of the involvement of vital structures. Chemotherapy or hormone therapy have also been tried and the tumors may express hormone receptors. Some patients may have congenital abnormalities and 15% are associated with Familial polyposis (FAP)/Gardners syndrome. This association should be particularly considered with less dense fibromas with features of nuchal type fibroma (Beta catenin negative), and Gardners fibroma (Beta catenin positive). Patients may have other features of this syndrome and the lesion has a high risk of recurrence [101]. Immunohistochemistry and investigations for underlying FAP should be considered in children with these tumors as a significant proportion especially with nuclear staining of beta catenin will have mutations of the *APC* gene [102].

19.13.6 Fibromatosis Colli

Fibromatosis colli (sternomastoid tumor) typically occurs as a horizontally mobile mass in the sternomastoid muscle of an infant presenting between the second and fourth week of life. After a period of growth it becomes static and may regress, to be followed by shortening of the sternomastoid muscle resulting in torticollis. The rapid growth can cause considerable concern leading to surgical biopsy. In over 50% of cases there is a history of complicated delivery or trauma and some cases also have congenital dislocation of the hip. Occasional cases occur in families. Microscopy shows proliferating fibroblasts surrounding regenerating residual striated muscle cells, and thus mimics fibromatosis but the location and the history are important diagnostic clues (Fig. 19.10). This lesion never behaves aggressively and may well be a reaction to trauma to the sternomastoid. Treatment is by passive stretching or division of the sternomastoid muscle.

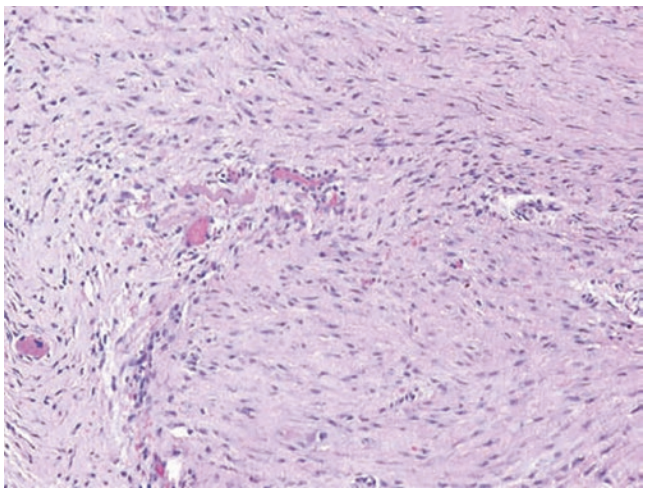

Fig. 19.10 Sternomastoid tumor. A 3-week-old with mass lying arising from the anterior aspect of the sternomastoid muscle. Entrapped skeletal muscle present

19.13.7 Infantile Digital Fibromatosis

Another lesion unique to young children is the infantile digital fibromatosis (recurring digital fibroma) [103]. It appears as a dome-shaped swelling on the sides or dorsum of the middle and distal interphalangeal joints of the fingers and toes (usually sparing the great toe and thumb). More than one lesion may be present. Most patients are less than 1 year of age and, is congenital in one-third of cases. Microscopic examination shows a uniform proliferation of fibroblasts and myofibroblasts. A characteristic feature is the presence of a variable number of eosinophilic cytoplasmic inclusions with filamentous ultrastructure staining immunohistochemically for actin. A histologically identical lesion has been described in an extradigital location and occasionally in adults.

The lesions tend to regress and surgery is only required for diagnosis or if function is affected. As the synonym implies, there is a tendency to local recurrence after excision. They may be syndromic with limb eye and skin malformations and some may not have inclusions.

19.13.8 Cranial Fasciitis

Cranial fasciitis affects infants and young children and may be congenital. It presents as a rapidly growing mass in the soft tissue of the scalp often eroding the outer and even inner table of the skull. Histologically, it is composed of a proliferation of loosely arranged fibroblast-like cells and shares features with nodular fasciitis. Other fasciitis-like lesions can occur in extracranial sites in young children, mainly in the head and neck, and like cranial fasciitis tend to have a more consistently uniform myxoid appearance than nodular fasciitis.

19.13.9 Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor is occassionally seen in infants with the same histology as children and adults. Younger children often have abnormalities involving the *ALK* gene at 2p23 and the increased expression of this gene can be detected immunohistochemically with the pattern of staining reflecting the translocation partner. Some translocation partners have been associated with a more aggressive prognosis. Intravascular tumors have been described [104].

19.13.10 Giant Cell Fibroblastoma/ Dermatofibrosarcoma Protruberans (DFSP)

Giant cell fibroblastoma is an uncommon benign tumor of the subcutaneous tissue and dermis that has rarely been reported in the newborn, most cases being diagnosed by 10 years. The histological appearance is distinctive with solid areas composed of bland spindle cells, and "angiectoid" areas with irregular branching spaces lined by mononuclear cells and bizarre giant cells containing pale amorphous material staining as acid mucopolysaccharide. This lesion has infiltrative margins and frequently recurs after surgery. This lesion has been described with dermatofibrosarcoma protruberans which has also been described in neonates. They share a specific translocation, t(17;22), involving the *COL1A1-PDGFB* gene fusion. Giant cell fibroblastoma and dermatofibrosarcoma protruberans are closely related clincally, histologically and genetically.

19.13.11 Congenital (Infantile) Fibrosarcoma

Congenital fibrosarcoma is a different entity from adult-type fibrosarcoma and has a better prognosis. About half the cases of infantile fibrosarcoma described by Chung and Enzinger in 1976 were present at birth and occurred preferentially in the extremities. Some lesions are very large and grow rapidly. The tumor is poorly circumscribed and tends to infiltrate adjacent tissues. The microscopic appearance may vary from that of an adult-type fibrosarcoma to a tumor composed of immature spindle cells with little evidence of fibroblastic differentiation (Fig. 19.11). An infiltrate of chronic inflammatory cells is commonly seen. There may be hemangiopericytomatous areas and foci of necrosis. Congenital fibrosarcoma characteristically shows trisomy of chromosome 11 and a typical translocation, t(2;15)(p13;q25), has been identified. This translocation is also found in cellular mesoblastic nephroma and is also seen in mammary analogue secretory carcinoma of the salivary gland and the secretory breast carcinoma but not in adult

type fibrosarcoma, myofibromatosis or infantile hemangiopericytoma.

Metastases occur in less than 10% of cases and the 5-year survival rate is 84%. Two fatal cases are reported in which the recurrence showed transition to a malignant fibrous histiocytoma-like appearance. The recommended treatment is wide local excision or combined with chemotherapy. Exceptional cases do not recur after incomplete excision or regress spontaneously. The distinction between congenital fibrosarcoma and other cellular spindle cell lesions of infancy may sometimes be difficult or impossible by microscopy alone and infantile fibrosarcoma has probably been over-diagnosed in the past. The overlap with some of the round blue cell tumors is described above including the BCOR group of tumors.

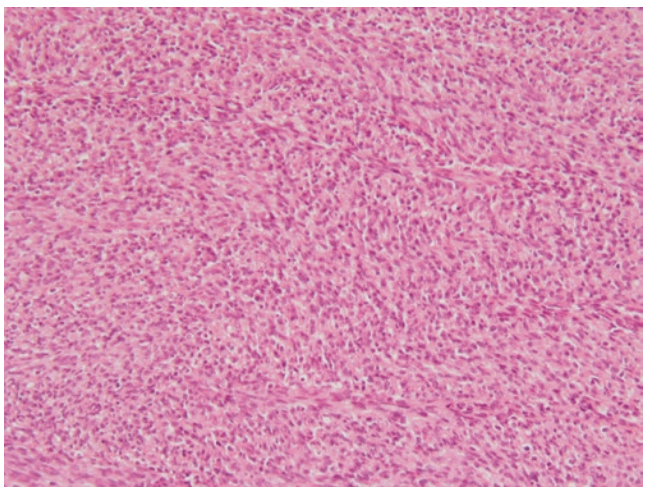

Fig. 19.11 Congenital fibrosarcoma in the hand of a 7-day-old child showing vague herring-bone arrangement of spindly tumor cells. Numerous mitotic figures and lymphocytes are seen on higher power

19.13.12 Fibrous Hamartoma of Infancy

Fibrous hamartoma of infancy occurs in the lower dermis and subcutaneous tissue as a rapidly growing solitary soft mass which rarely involves the superficial aspect of underlying muscle About 20% of cases are congenital. Favored sites are around the shoulder and upper arm, particularly the axillary folds, thigh and inguinal region. Grossly it appears as an ill-defined fibro-fatty lump. Microscopically it is made up of variable amounts of three components; trabeculae of fibrous tissue, mature fat and areas of immature mesenchymal cells often arranged in nests. A recent publication of a large number of cases showed a male predominance and also highlighted that there may be a prominent pseudoangiomatous pattern (Fig. 19.12) [105]. The presence of thick, wide capillaries and lymphocytes in these immature areas has been emphasized. This lesion is benign but may rarely recur locally. The natural history of untreated lesions seems to be rapid growth until 5 years, after which growth slows. It is unclear whether it is a true hamartoma or a benign neoplasm though a t(2;3) translocation has been found. The differential diagnosis of fibrous hamartoma of infancy includes lipoblastoma and three recently described entities. These are the Plexiform Fibrohistiocytic Tumor, Lipofibromatosis and the Congenital Lipofibromatosis Hamartoma. The last may be familial. The precalcified phase of calcifying aponeurotic tumor is also a differential.

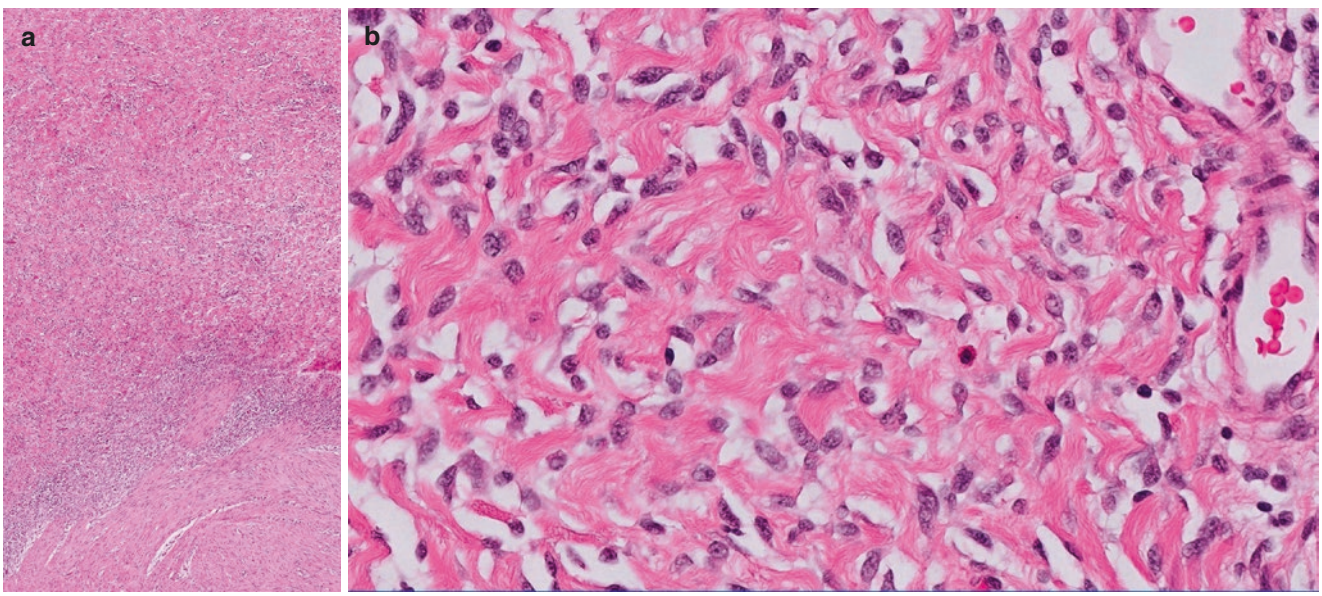

Fig. 19.12 Fibrous hamartoma of infancy. This lesion was predominantly (>95%) showing the sclerotic component with the typical adipose, fibromatosis areas and immature mesenchyme at the margin (low magnification **a**, high magnification **b**)

19.13.13 Hyalinosis and Juvenile Hyaline Fibromatosis

Two overlapping autosomal recessive syndromes are described in the literature: Infantile Systemic Hyalinosis and Juvenile Hyaline Fibromatosis. They appear due to a mutation in the capillary morphogenesis protein 2. They are characterized by multiple dermal and subcutaneous nodules with onset in early infancy. Other features include gingival hypertrophy, flexion contractures, muscle weakness, intraosseous lesions and tumorous involvement of internal organs with the systemic type presenting earlier and with more severe features. The lesions consist of fibroblasts and thick collagen bundles widely separated by eosinophilic hyaline material due to the disrupted cell to matrix interaction and basement membrane formation.

19.13.14 Others

A rare entity sometimes associated with other syndromic changes is Gingival Fibromatosis. Fibrodysplasia Myositis Ossificans Progressiva can present very early in infancy. The soft tissue swellings may be misdiagnosed if the characteristic skeletal changes have not been identified by the referring clinician.

19.14 Extrarenal Rhabdoid Tumor

The rhabdoid tumor group includes the renal and liver rhabdoid tumor, the atypical teratoid/rhabdoid tumor of the brain and the soft tissue extra renal rhabdoid tumor in infants. Extrarenal rhabdoid tumor has been a less well-defined entity than its renal counterpart, though is more common than renal or cranial. It has also been associated with a lower birthweight [106, 107]. Congenital disseminated malignant rhabdoid tumor has been described as a distinct entity, placental involvement and rapid progression to death.

In the skin the tumor can be plaque-like and have very bland hamartomatous histological features with few apparent mitoses, small nuclei, such that it is worth considering immunohistochemistry for any skin lesion with increased immaure appearing undifferentiated mesenchymal cells, even with relatively low or patchy cellularity [108]. This group of tumors is associated with INI gene mutations and has a poor prognosis. In older children and adults the phenotype is less specific and so-called rhabdoid tumors in older children often prove to be a result of dedifferentiation of many other tumor types. However, there are also groups of different tumors such as the medullary carcinoma of the kidney and the proximal epithelioid sarcoma which also show the same mutation. Some non-rhabdoid undifferentiated sarcomas of infants and young children [109] have been described with INI loss. The same gene is also associated with inherited schwannomatosis.

19.15 Rhabdomyosarcoma

Rhabdomyosarcoma is unusual in the first month of life. In an older review, half the tumors were caudal (buttock, sacrococcygeal, perirectal, urogenital) and the rest involved different sites. Rhabdomyosarcoma may arise in the eyelid in the newborn. Most rhabdomyosarcomas in babies are embryonal and behave as in older children. Alveolar rhabdomyosarcoma, which may rarely present in early life, can present with skin nodules and is a highly malignant tumor. Alveolar rhabdomyosarcoma has a characteristic traslocation, but there are some cases with an alveolar phenotype and no translocation [110, 111]. Recently, more cases of sclerosing rhabdomyosarcoma are being recognized in young infants [112]. Infantile rhabdomyo-fibrosarcoma also needs to be considered [113].

It is important to distinguish rhabdomyosarcoma from fetal rhabdomyoma, which resembles fetal muscle and is benign. Fetal rhabdomyoma is sometimes associated with Gorlin's nevoid basal cell carcinoma syndrome.

19.16 Neural Tumors

Plexiform neurofibromas are usually congenital but may appear in the first year of life and are almost pathognomonic of neurofibromatosis type 1 (NF1). Other stigmata such as multiple *café-au-lait* spots and freckling of the axillary and inguinal skin folds are highly suggestive of NF1 but may be absent in young babies. *Café-au-lait* spots are also seen in Noonan syndrome and Watson's syndrome. Other tumors developing in children with NF1 include congenital peripheral neuroectodermal tumor (PNET), malignant schwannoma, optic nerve glioma, astrocytoma, rhabdomyosarcoma and leukemia. The *NF1* gene is a tumor suppressor gene on chromosome 17 encoding neurofibromin. Neurofibromatosis type 2 is rare and usually manifests in later childhood or adult life, often with bilateral acoustic neuromas. The gene responsible is on chromosome 22 and codes for schwannomin. Occasional patients present with segmental NF1 or NF2 affecting only part of the body as a result of somatic mosaicism.

Meningothelial remnants in the scalp and glial hamartomas around the nose may be seen in young infants, probably reflecting inclusion in closure lines.

Congenital malignant peripheral nerve sheath tumors are vanishingly rare. The congenital and childhood plexiform (multinodular) cellular schwannoma should be considered in

this age group. It can have a histological appearance that can lead to being overcalled as being malignant.

Peripheral Primitive Neuroectodermal Tumor (PNET) is rare in neonates though occassionally reported. Benign Triton Tumor/Neuromuscular Hamartoma may present as a congenital tumor, usually in the trunk, and is composed of bundles of skeletal muscle fibers and nerves.

19.17 Melanotic Neuroectodermal Tumor of Infancy (Retinal Anlage Tumor)

Another tumor of neuroectodermal origin virtually confined to infancy is the melanotic progonoma, or melanotic neuroectodermal tumor of infancy. It has features suggesting a relationship to retinal development. Over 90% occur in the head and neck region and characteristically involve the maxilla. Other sites include the epididymis, mediastinum, thigh and brain. The histological appearance is striking. It is a biphasic tumor composed of nests of neuroblast-like cells and groups of larger cuboidal cells containing melanin, sometimes forming gland-like structures, set in a connective tissue stroma (Fig. 19.13). Although the local recurrence rate is 15%, metastasis is rare and most cases follow a benign course. The small neuroblast-like cells may stain for vimentin and neurone specific enolase, the larger cells for HMB 45 [114]. Increased mitotic activity may correlate with behavior. Chemotherapy may be of benefit in some cases.

19.18 Adipose Tumors

Lipoblastoma is a tumor of early childhood, occasionally present at birth, composed of lobules of immature adipose tissue containing lipoblasts with a prominent capillary network and myxoid foci reminiscent of adult myxoid liposarcoma. Liposarcomas are virtually unknown in infants, and do not show the lobulation characteristic of lipoblastoma, though liposarcomas can rarely be found in children, mainly of the myxoid subtype [115]. Lipoblastoma may mature to resemble lipoma in sequential biopsies, and may be considered an embryonal tumor of soft tissue recapitulating organogenesis. Diffuse lesions termed lipoblastomatosis have a less lobular architecture and commonly infiltrate muscle and involve deep structures. Both lesions are benign, but the diffuse form has a tendency to recur locally. Lipoblastoma shows a consistent rearrangement of chromosome 8 distinct from the rearrangement described at 12q14 in childhood and adult lipomas.

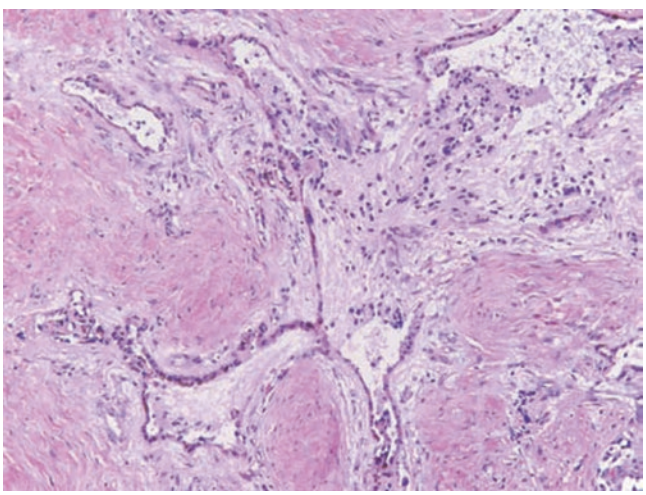

Fig. 19.13 Melanotic neuroectodermal tumor. Mass started to become prominent around ear from 6 weeks of age

Lipomas are uncommon in children and hamartomatous entities such as PTEN should be considered. Lipomatosis of the nerve (Neural Lipofibroma) may be associated with macrodactyly. Multiple congenital lipomatous hamartomas occur in Haberland syndrome.

19.19 Chest Wall Hamartoma

This expansile extrapleural lesion of the chest wall involving one or more ribs most often presents in newborns. It consists of nodules of proliferating hyaline cartilage, immature mesenchyme, reactive bone and prominent vessels with hemorrhage giving an aneurysmal bone cyst-like appearance. A similar lesion has been described in the upper respiratory tract of newborns and young infants.

19.20 Renal Tumors

Between 5 and 7% of congenital tumors arise in the kidney (see also Chap. 24). Some may be detected by antenatal ultrasound. Although in the past most were called Wilms tumors, it is now recognized that nephroblastoma is extremely rare in neonates, and that other renal tumors predominate in this age group. Pathological management is well summarised elsewhere.

19.20.1 Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma is the commonest neonatal renal tumor [116]. It is genetically unrelated to Wilms tumor and usually does not have the same associations although occasional cases have been described with nephrogenic rests and one with Beckwith syndrome. Pregnancy may be complicated by polyhydramnios or fetal hydrops. Mesoblastic nephroma may cause hypertension or hypercalcemia in the affected baby which resolve rapidly on removal of the tumor. The tumor is usually found on routine examina-

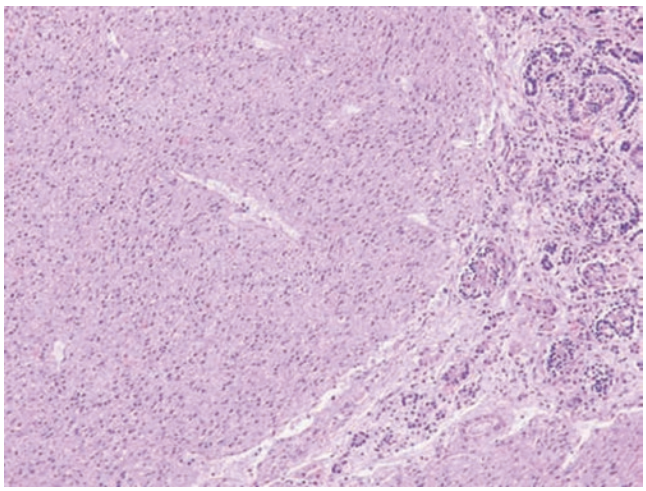

Fig. 19.14 Mesoblastic nephroma. Mildly macerated stillbirth with renal mass identified at autopsy

tion in the neonatal period and presentation is unusual beyond 3–6 months of age.

The kidney is enormously enlarged by an intrarenal mass whose cut surface resembles a uterine fibroid although the cellular variant can be extremely soft and friable. About 25% extend beyond the kidney and nephrectomy with complete removal of the tumor is usually adequate therapy though chemotherapy may reduce the size. Histology shows a spindle cell tumor composed of bland myofibroblasts infiltrating normal kidney at its margins (Fig. 19.14). Entrapped renal tubules and glomeruli may show nuclear atypia which is without adverse significance. Renin can be demonstrated by immunohistochemistry in these entrapped renal elements. Included renal tissue may also explain why this tumor takes up Tc99m dimethylsulphonic acid (DMSA) and excretes contrast medium. Negative immunohistochemistry for WT1 and Bcl-2 may help distinguish mesoblastic nephroma from stromal Wilms tumor (which is positive for both). It must also be distinguished from metanpehric stromal tumor (see below). Marsden has drawn attention to foci of cartilage, squamous islands, large multinucleated cells, and adrenal cytomegaly in occasional cases.

Mesoblastic nephromas with increased cellularity and mitotic activity are called cellular variants or atypical mesoblastic nephroma. The latter term is a misnomer because the cellular variant is more common than the so-called classic type, particularly in older infants. Mixed classic and cellular tumors are not uncommon, suggesting the possibility of a clonal progression from classical to cellular mesoblastic nephroma. The cellular or atypical tumors may be aneuploid and show both trisomy 11 and the translocation t(12;15). The same translocation which results in ETV6–NTRK3 gene fusions and the trisomy 11 are also seen in infantile fibrosarcoma and these two tumors are now considered to be essentially the same entity. Both genetic changes are needed for transformation. Although infantile fibrosarcoma and cellular mesoblastic nephroma generally behave benignly, there are occasional reports of local recurrence of congenital mesoblastic nephroma and metastasis to lung and brain. The finding of positive surgical margins predicts recurrent disease. A conservative approach is therefore generally advocated, reserving chemotherapy for those few cases which recur or are not amenable to resection.

19.20.2 Metanephric Tumors

A review of the US National Wilms tumor study series led to the recognition that a significant number of the tumors originally diagnosed as mesoblastic nephromas were actually metanephric stromal tumors. The main histological difference between the two is in the nodular cellularity, onion skin like cuffs around entrapped tubules and the characteristic vascular changes, that have been associated with surgical complications. The metanephric adenofibroma and the metanephric adenoma are the other members of the metanephric group of tumors and are associated with BRAF mutations [117], which tend to occur in children and young adults and not neonates. The latter needs to be distinguished from Wilms tumor, nephrogenic rests and embryonal hyperplasia of Bowmans epithelium.

19.20.3 Nephroblastoma (Wilms Tumor)

Of the 30 renal tumors in the first year of life seen by Marsden and Lawler in 1983, 15 were classic Wilms tumors, and 1 of these might be considered congenital. The US National Wilms Tumor Study 1969–1993 found only 0.16% of nephroblastomas occurred in the first month of life. A high proportion (64%) of these babies had associated nephrogenic rests. Special histological types such as the fetal rhabdomyomatous nephroblastoma (in which the major component is differentiating striated muscle), pure epithelial Wilms tumor and cystic partially differentiated nephroblastoma are more common in the first year of life. Wilms tumor with anaplasia is rare under a year of age. Nephroblastoma in the first month of life is usually of low stage and has an excellent prognosis with current therapy.

19.20.4 Nephroblastomatosis and Nephrogenic Rests

Nephroblastomatosis has been defined as the persistence of metanephric blastema beyond 36 weeks' gestation when

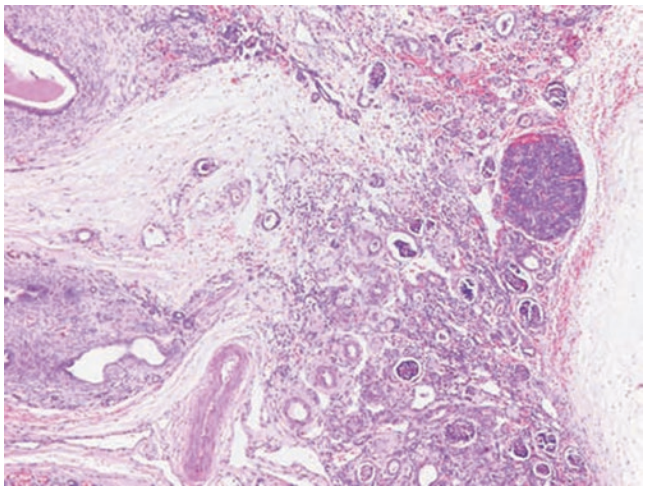

Fig. 19.15 Perilobar nephrogenic rest associated with renal dysplasia. Small infant with removal of nonfunctional kidney

nephrogenesis ceases, or in an inappropriate location or amount before that time. It is of great interest as a putative precursor of Wilms tumor, being present in less than 1% of neonatal necropsies but in 20–40% of kidneys with Wilms tumor. In the neonatal period rests present in two ways, either as a rare cause of bilateral renal enlargement, or as an incidental macroscopic or microscopic postmortem finding, when it should alert the pathologist to the possibility of associated syndromes. It has been described after in utero aspirin intoxication. In older children it is seen in kidneys removed for Wilms tumor and occasionally in association with cystic renal dysplasia (Fig. 19.15).

Commonly, nephroblastomatosis involves the periphery of the renal lobe in a subcapsular position or along the columns of Bertin. Microscopic and discrete nests of embryonal renal epithelial cells with minor tubular differentiation and no embryonal stromal component situated beneath the renal capsule, sometimes with immature glomeruli, are termed perilobar rests. Bove and MacAdams in 1976 described differentiation or maturation into other types with the formation of tubules or sclerotic changes. Hyperplastic lesions arise within rests with progression from adenoma to incipient Wilms tumor. In 1990, Beckwith et al. proposed a new and unifying classification using the term nephrogenic rest for a single focus of persistent nephrogenic cells and restricting the use of nephroblastomatosis to cases with multiple or diffuse nephrogenic rests [118]. Nephrogenic rests are divided according to their location (intralobar or perilobar) and subclassified by gross and microscopic appearance (dormant, maturing, hyperplastic or neoplastic). Nephroblastomatosis may be perilobar, intralobar, combined or universal. This authoritative scheme is comprehensible, biologically relevant and clinically meaningful and so has been generally adopted. There are racial variations in prevalence of perilobar rests, with fewer seen in the Far East, which appears to be associated with fewer methylation changes in these populations.

Perilobar rests are seen in patients with Beckwith–Wiedemann syndrome, hemihypertrophy, pseudohermaphroditism, trisomy 18 and 13 and some familial cases of Wilms tumor. The nephroblastomas that develop in this form of nephroblastomosis tend to show epithelial or blastemal predominance, with scanty stroma and rare heterotopic tissues such as striated muscle. Rarely, persistent blastema forms a continuous layer around each renal lobe resulting in considerable renal enlargement. There may be tubule formation but no stromal elements. Perilobar type rests are also seen associated with renal dysplasia, and occasionaly with mesoblastic nephroma.

Intralobar nephrogenic rests involving the juxtamedullary cortex are associated with germline WT1 mutations (WAGR and Denys–Drash syndrome) and development of nephroblastoma with a predominant striated muscle component. These rests have a higher malignant potential than perilobar rests. These rests are found in the lobule sometimes in the medulla and tend to be less well cirumscibed and blend with the adjacent kidney. Both the cortex and the medulla may be diffusely affected, resulting in marked nephromegaly.

The microscopic appearance of nephrogenic rests and nephroblastoma is often indistinguishable in a biopsy and so the macroscopic appearance of the lesion is critical. The precise risk of developing Wilms tumor in each type of rest is unknown but most nephrogenic rests probably do not become neoplastic, particularly those found incidentally (which are usually perilobar rests). Nephroblastomatosis in the presence of Wilms tumor is usually bilateral and indicates the possibility of bilateral nephroblastoma, so renal tissue should be conserved whenever possible.

Juxtarenal and extrarenal Wilms tumors are believed to arise from heterotopic nephrogenic tissue. Renal elements resembling nephrogenic rests or cystic renal dysplasia are occasionally seen in the sacral region in association with spinal dysraphism and extrarenal Wilms tumor has been reported at this site in a patient with spina bifida. Mesoblastic tissue can also occasionally be seen adjacent to the gonads at fetal autopsy. Nephrogenic tissue may be seen in teratomas (see Fig. 19.16) and lesions associated with spinal dysraphism.

19.20.5 Cystic Nephroma and Anaplastic Sarcoma of the Kidney

Cystic Nephroma is a multicystic tumor which has no solid areas is associated with the DICER1 syndrome, especially if they are bilateral or familial and is discussed below. It is not

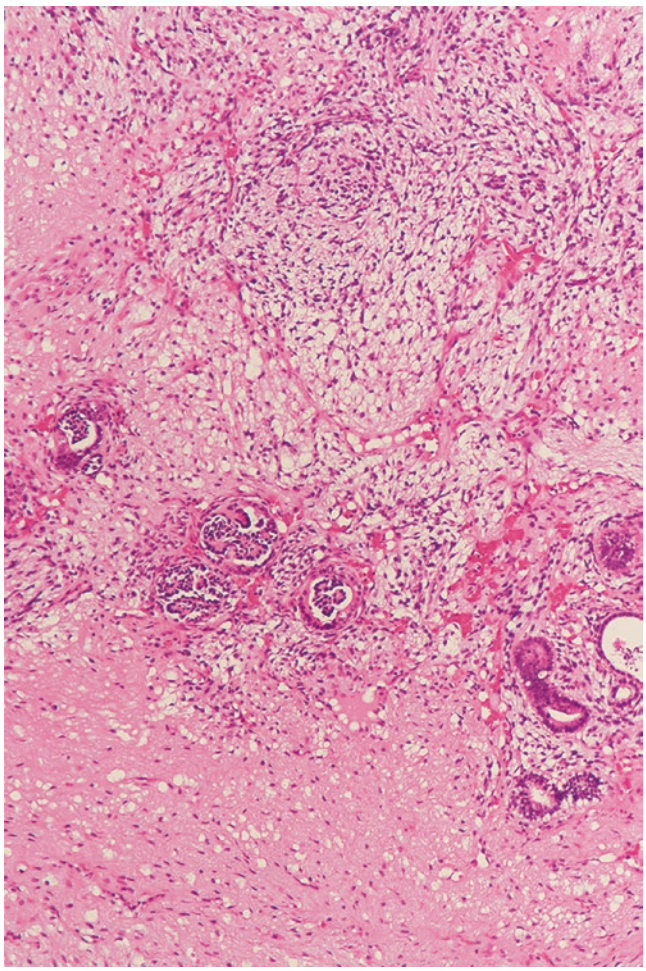

Fig. 19.16 Nephrogenic tissue in an intra-ocular teratoma

to be confused with the adult tumor of the same name, which is a different entity with a variety of synonyms. Anaplastic sarcoma may arise from cystic nephroma and is also part of the Dicer group of tumors [119].

19.20.6 Rhabdoid Tumor of Kidney

This highly malignant renal tumor is unrelated to Wilms tumor and usually presents in the first few months of life. The tumor is genetically related to the other rhabdoid tumors of infancy, with loss of function mutations involving the gene *SMACB1/INI1*. Immunohistochemistry for detecting the lack of production of this gene in rhabdoid tumors and the fact that the gene is otherwise widely expressed in normal tissues is a useful diagnostic test. This gene appears to act as a classical tumor suppressor gene and a minority of the patients have a germline mutation and familial cases are recognised. It appears that this biallelic mutation of this gene may be the sole genetic change required [120]. This also explains the association of two primary tumors, viz. the renal rhabdoid and the brain atypical teratoid/rhabdoid (AT/RT) tumor, which have been shown to be the two separate tumors and not a metastasis.

The tumor classically has a discohesive, infiltrative pattern of growth and is recognized by the presence of so-called "rhabdoid" cells. These have large open nuclei containing a single very prominent eosinophilic nucleolus. Classic rhabdoid cells have large cytoplasmic inclusions consisting of aggregates of whorled intermediate filaments. These give positive staining for vimentin and cytokeratin by immunohistochemistry and other antibodies may also be positive in a non-specific manner. Rhabdoid cells may only be focally represented in a tumor and the tumor may have a variety of growth patterns. Rhaboid tumors can resemble other tumors, e.g. clear cell sarcoma of kidney, and conversely other tumors, including mesoblastic nephroma, metanephric stromal tumor and Wilms tumors, can focally resemble rhabdoid tumors.

Hypercalcemia is seen in some cases. The tumor is highly malignant and aggressive and tends to respond incompletely to chemotherapy before relapse and is the subject of studies with novel chemotherapuetic regimes.

19.20.7 Ossifying Renal Tumor of Infancy

Ossifying renal tumor of infancy is a rare and apparently benign tumor described in neonates. The tumor is usually partly intracalyceal and may resemble a staghorn calculus attached to the renal medulla. Microscopy shows islands of partly mineralized osteoid separated by polygonal cells and often separate areas of spindle cells resembling blastema or nephrogenic rest.

19.20.8 Other Renal Tumors

Other rare tumors of the kidney include the presentation of acute myeloid leukemia. Clear cell sarcoma of kidney is very rare in neonates. A congenital sarcoma exactly resembling clear cell sarcoma of kidney has been described in the terminal ileum.

19.21 Liver Tumors

The incidence of metastatic neuroblastoma or leukemia involving the liver exceeds that of primary liver tumors in the first month of life [121]. Vascular tumors, mesenchymal hamartoma and hepatoblastoma are the only primary lesions seen with any frequency [121, 122], though sometimes in a fetus a vascular lesion and mesenchymal hamartoma can be difficult to differentiate. Most tumors are vascular (60%),

with Mesenchymal Hamartoma and Hepatoblastoma next in frequency [123]. Teratoma, yolk sac tumor and rhabdoid tumor are also described. Some tumors are difficult to classify. A combined yolk sac tumor and hepatoblastoma has been reported in a 6-month-old infant. Choriocarcinoma is also described. Congenital hepatic adenomas are rare. In later childhood they are associated with congenital disorders such as Fanconi's anemia and glycogen storage disorders. Undifferentiated sarcomas may be seen in infancy though it appears to not be reported in a neonate.

19.21.1 Hepatic Vascular Tumors

Hepatic hemangiomas have been called a variety of names including hemangioendothelioma, but there is a push to standardize nomenclature to congenital hemangiomas and infantile hemangiomas [124]. The congenital hemangiomas tend to be localised and are GLUT1 negative; the infantile hemangiomas are GLUT1 positive, may respond to propranolol, and also associated with hypothyroidism, due to enzymatic inactivation of thyroid hormone. Large tumors present with an abdominal mass, high-output heart failure, hepatic failure or intra-abdominal hemorrhage following rupture during delivery. Occasionally, sequestration of platelets causes a bleeding diathesis (Kasabach–Merritt syndrome). Multiple liver tumors are frequent with the infantile hemangiomas, and 11–40% of patients also have cutaneous hemangiomas. Small tumors may be encountered as an incidental necropsy finding.

The surface of the liver over the tumor may be umbilicated and the cut surface shows red, brown or tan, soft or firm tissue often with focal fibrosis or flecks of calcification. Microscopy shows small vascular channels, included bile ducts, extra- medullary hemopoiesis and focal involutionary changes. Poor prognostic features are congestive heart failure, jaundice, multiple tumor nodules and absent cavernous differentiation. Most deaths occur within a month of diagnosis. Spontaneous regression is less common in visceral than in cutaneous hemangiomas but is said to occur in approximately 60% of cases.

19.21.2 Mesenchymal Hamartoma

Mesenchymal hamartoma is a tumor of infants and young children usually arising in the right lobe of the liver. Of 30 cases reported by Stocker and Ishak in 1983, seven patients were less than 3 months old. A few patients had adrenal cytomegaly and pancreatic islet hyperplasia. Mesenchymal hamartoma has been diagnosed antenatally. The microscopic appearance is characterized by progressive expansion of portal tracts by mesenchymal tissue, which becomes confluent, entrapping hepatocytes and sometimes prominent bile ducts proliferation resembling bile duct plate anomaly. Cysts may be lined by biliary epithelium or devoid of an epithelial lining. Enlargement of cystic spaces after birth may lead to rapid growth and suspicion of malignancy. Surgical excision is curative although marsupialization of the cysts is also a treatment option. The pathogenesis is uncertain and a vascular etiology has been suggested. A genetic change at 19q13 originally found in two tumors points to a neoplastic process and this may give rise to non coding RNA changes [125]. Rare reports describe progression to sarcoma, which in one case also showed a 19q13 anomaly.

19.21.3 Hepatoblastoma

Hepatoblastoma is the commonest malignant liver tumor of infancy and is occasionally found in neonates. It has also been described with glomerulocystic disease. A recent increase in incidence of hepatoblastoma has been attributed to the increased survival of low birthweight babies. There is a definite association with intrauterine growth restriction and maternal preeclampsia, and with the familial adenomatous polyposis. It occurs in children with hemihypertrophy, and Beckwith–Wiedemann syndrome and it has also rarely been reported in siblings, in conjunction with nephroblastoma. Association with maternal use of oral contraceptives, and fetal alcohol syndrome have been reported. Multiple hepatoblastomas have been described in a patient with trisomy 18. Genetic changes in hepatoblastoma include translocations of chromosome 1q12-2. Serum alpha-fetoprotein is usually but not always markedly elevated, and may be differentiated from that produced by yolk sac tumor by subfractionation.

The histological pattern of hepatoblastoma has prognostic significance. Survival is commoner in children with predominantly fetal tumors (these have a very low mitotic rate) than in those with conspicuous embryonal or mesenchymal components. Variants with an unfavorable prognosis are the anaplastic type, small cell variant and the macrotrabecular pattern.

19.22 Tumors of the Central Nervous System

Congenital tumors of the brain and spinal cord are rare and amount to only 10% of all congenital tumors [126–129]. Only 1% of childhood brain tumors occur in the neonatal period. Ten—25% of brain tumors diagnosed in the first year of life are evident at birth. The commonest presentation, regardless of tumor type, is enlargement of the head because of hydrocephalus or the mass of the tumor itself. The ability of the neonatal skull to expand enables some of these tumors

to grow very large indeed. One in four cases is stillborn and decompression of the skull may be required to effect vaginal delivery. Choroid plexus tumors may produce hydrocephalus by hypersecretion of cerebrospinal fluid. Occasionally, a hemorrhagic tumor mimics intracerebral hemorrhage and this possibility should be considered in term infants with unexplained intracerebral bleeding. In children less than 1 year of age the majority of intracerebral tumors are supratentorial, in contrast to the infratentorial position of the majority of tumors in older children. Modern diagnosis into the subtypes is aided by methylation studies [130].

The commonest congenital brain tumors are teratomas. Teratomas usually arise either in the pineal region or in continuity with a pharyngeal teratoma. They are often very large but, with few exceptions, histologically benign. Other tumor types seen in the neonatal period include astrocytoma, (including high grade lesions), medulloblastoma, choroid plexus papilloma and carcinoma, atypical teratoid/rhabdoid tumor (AT/RT), medulloepithelioma, ependymoma and ependymoblastoma, craniopharyngioma, suprasellar PNET and ganglioglioma. The astrocytomas have a varying prognosis, and include high grade glioblastoma (GBM), subependymal giant cell astrocytomas and low grade tumors such pilocytic astrocytomas [131]. Some of the GBM have targetable mutations such as ALK [132].

Pituitary blastoma occurs in very young infants, often associated with infantile Cushing syndrome and is associated with the DICER1 syndrome [133].

Medulloblastomas comprises a genetically heterogeneous group of brain tumors composed of small round blue cells showing little differentiation. These tumors are highly malignant and may metastasise widely within the CNS. They often show loss of chromosome 22. Young infants with medulloblastoma have a particularly poor survival. Some of these cases need to be distinguished from AT/RT (the immunohistochemistry for INI is worth undertaking on any poorly differentiated neoplasm in infants). The desmoplastic variant of medulloblastoma occurs in infants with Gorlin's syndrome who carry a mutation of the *PTCH* gene. The large cell/anaplastic variant of medulloblastoma carries a poor prognosis.

Intracranial rhabdoid tumors—the atypical teratoid/rhabdoid tumors—are described above. There may be only focal rhabdoid change and the lesions may resemble medulloblastoma. Immunohistochemistry for INI is useful. Cytogenenetic abnormalities of chromosome 22 may be found in the infant type and the INI gene is located on the long arm of chromosome 22. Although generally highly aggressive, some have responded to treatment. Different subtypes of rhabdoid tumors are being identified, and rhabdoid tumors also appear to have very few other changes [130]. Choroid plexus carcinomas and the AT/RT tumor have overlapping histological features.

Desmoplastic infantile ganglioglioma is a distinctive supratentorial tumor of infants with a usually favorable outcome. It has a prominent fibrous stroma with neural and astrocytic elements seen with GFAP and S100 stains, respectively. Although originally thought to be benign, some recent cases of a more aggressive type have been described. Congenital glioblastoma multiforme may have a better survival than in older patients. The dysembryoplastic neuroepithelial tumor usually presents with epilepsy in infants or older children, and is presumably often present at birth. Hypothalamic hamartoblastoma is associated with several syndromes, including the Pallister–Hall syndrome. Intracranial lipomas are rare and are a maldevelopment usually associated with brain abnormalities, including the absence of the corpus callosum. They are associated with epilepsy and with Goldenhar's syndrome and frontonasal dysplasia.

Choroid plexus tumors are also seen and include papillomas and occasional carcinomas (one of the rare carcinomas presenting in infancy), the latter need to be distinguished from AT/RT tumors [134].

Intraocular tumors include retinoblastoma and medulloepithelioma, which can be teratoid, and arises from the ciliary body [135]. Very rare intraocular teratomas are described, but the distinction between these and teratoid type medulloepithelioma is unclear apart from possible site of origin (See Fig. 19.2).

It is worth noting that the cerebrospinal fluid of infants may be cellular and contain granular cells from the cerebellum, that can mimic a small blue round cell tumor.

Occasional cases of extra-axial CNS tumors may be found usually associated with embryological closure site such as the nasopharynx, dorsal to the spine and the sacral area, suggesting a congenital, developmental origin.

19.23 Gonadal Tumors

One not uncommon lesion of infancy is the cystic follicular cyst of the ovary, not infrequently hemorrhagic with torsion of the ovary and the fallopian tube, making the diagnosis difficult [12].

Yolk sac tumor is the commonest tumor of the infant testis and is adequately treated by orchidectomy alone if confined to the testis. Juvenile granulosa cell tumor can have a similar histologial appearance, and testis sparing surgery is to be considered. Germ cell tumors of the neonate are biologically and genetically different from older patients. Occasionally teratoma presents in the infant testis, and is composed of mature elements with or without immature neuroglia. Some benign mucinous cysts in the infant testis probably represent a benign monodermal teratoma. Unlike its counterpart in

adolescents and adults, the teratoma behaves in a benign manner. Sporadic germ cell tumors of the infant testis are not accompanied by intratubular germ cell neoplasia in the absence of gonadal dysgenesis. Gonadoblastoma has been described at birth and is usually associated with XY gonadal dysgenesis. It has also been described in a phenotypic female with XY karyotype and campomelic dysplasia.

19.24 Skin Tumors

Skin tumors presenting in the neonate include hemangiomas, neuroblastoma, leukemia and rhabdoid tumors, as described above. Congenital melanocytic nevii occur in around 1% of newborns, although large congenital nevi (>20 cm in diameter) are very uncommon. The congenital melanocytic naevi are associated with abnormalities of the MAPK pathway, with *NRAS* and *BRAF* mutations [136]. The large nevi not infrequently contain nodules, sometimes larger than 1 cm. These may show a variety of appearances with cellular proliferative and/or hamartomatous appearances, and neural-like patterns that may mimic benign peripheral nerve sheath tumors and other mesenchymal elements like cartilage may be seen. The larger proliferative nodules may mimic melanoma, especially on frozen section. Some nodules may show genetic changes suggesting malignant progression. Congenital melanomas are very rare, but can be fatal with metastases. The histological features of these tumors can be very difficult and even genetic studies do not always provide clarity. The risk of malignant melanoma developing in congenital naevi overall is low <1%, but in giant nevi is up to around 10–15%, particularly if satellite nodules are present [137]. Giant nevi may be associated with neurocutaneous melanosis and significant morbidity, and also may involve the placenta.

The term of blueberry muffin baby has unfortunately become a term used for a neonate with multiple blue skin nodules. This can be seen in congenital tumors (e.g. neuroblastoma, leukemia, rhabdomyosarcoma, chroiocarcinoma), extramedullary hemopoesis (due to a cause for fetal anemia such as rhesus disease, infection or myeloproliferative disorder), histiocytoses (e.g. LCH, Griscelli syndrome), infection (e.g. CMV and rubella) and also mimicked by vascular tumors (hemangiomas, and blue rubber bleb syndrome). The bland hamartomatous skin presentations of rhabdoid tumor are mentioned above

19.25 Lung Lesions

The lung is more often the site of metastatic or multifocal disease including hemangiomas and myofibromatosis. Cystic lesions of the lung need careful evaluation. Cystic pulmonary airway malformation (CPAM, used to be termed CCAM, is dealt with elsewhere, see Chap. 21), and pulmonary sequestration and congential emphysema, but apparently benign cysts of the lung all need careful exclusion of being a Pleuropulmonary blastoma. In infancy this is usually predominantly cystic with no macroscopic solid areas (type I) through to solid (type III) and the the tumors in the older infants and children tend to be more solid and behave in a malignant fashion [138]. Useful information is present at the registry website (http://www.ppbregistry.org). The type 1 tumors have at least a focal cambium cellular area, but in some cases this appears to involute to become the type 1r. It is recognized that in the majority of these lesions there is a germline mutation of DICER1, that is critical in the processing of non coding RNA [139]. The tumor is associated with cystic nephroma in the patient or a sibling and family history of malignancies including a variety of unusual tumors, sex cord tumors, nasal chondromesenchymal hamartomas, pituitary tumors and childhood multinodular goitre. The family therefore needs careful genetic counseling.

These lesions may be mistaken for congenital pulmonary airway malformation (CPAM) especially types 1 and 4 and this misclassification explains probably all the previous reports of rhbdomyosarcoma arising in CPAM. CPAM has been associated with epithelial malignancies and atypical goblet cell hyperplasia has been described in infancy with features both morphological and genetic suggesting mucinous adenocarcinoma and a precursor of adenocarcinoma [140].

Congenital peribronchial myofibroblastic tumor is a rare tumor that may present with a mass lung lesion and hydrops [141].

Another recently described entity is the Fetal Lung Interstitial Tumor, a lesion with a fibrous capsule, and numerous cysts with widened septa containing glycogen [142].

19.26 Cardiac Lesions

The rhabdomyoma is the most common and is associated with tuberous sclerosis, especially if multiple. Other tumors include the teratoma, fibroma and oncocytic cardiomyopathy. Myxomas are associated with Carney's triad and Lamb syndrome.

19.27 Tumors of the Cord and Placenta

Umbilical cord and placenta may also be affected by tumors from the fetus and the mother, and have tumors of their own, including chorangioma and teratomas, but are discussed elsewhere.

19.28 Maternal Malignant Disease in Pregnancy

Cancer in pregnant women is commoner than primary malignant tumors in their offspring. Figures for maternal cancer range from 1 per 1000 pregnancies to 1 per 6000 livebirths. The coexistence of pregnancy and maternal malignancy imposes difficult therapeutic dilemmas which are beyond the scope of this chapter. Around 60% of the tumors are diagnosed in the 12 months after delivery. Fetal and placental metastasis from maternal disease has been reviewed by several authors. True placental involvement with villous invasion has to be distinguished from tumor in the intervillous space which is more common. Melanoma appears to have a particular propensity to metastasize to the placenta and fetus although metastatic breast tumor within the fetal blood vessels is well described in several series. The prognosis for the mother is dismal because placental involvement by cancer indicates disseminated disease but survival data are historical. Management may be influenced by the supposed risk of metastatic spread of the maternal tumor to the fetus. Available evidence shows that this concern is largely unjustified. Although a wide range of tumor types metastasised to the placenta, most do not cross, and melanoma appeared most likely to affect the fetus. Rarely maternal leukemia, lymphoma, small cell carcinoma of the lung, and pulmonary adenocarcinoma have been described presenting as a metastasis in the fetus or infant.

The placenta is probably always affected if there are metastases in the fetus. The placenta appears to act as a barrier to maternal tumors, and the fetus may be able to recognize and reject foreign maternal antigens expressed by the tumor. Maternal malignant melanoma metastatic to the fetus has regressed spontaneously after birth, perhaps as a result of a fetal immune response. Although fetal tumors such as neuroblastoma may involve the placenta, there is no report of a fetal tumor metastatic to the mother.

There is a rare but characteristic syndrome of infantile choriocarcinoma caused by metastatic placental choriocarcinoma. The young infant develops anemia, hepatomegaly, bleeding and endocrine abnormalities, such as breast enlargement, with signs of disseminated tumor, especially in the liver and lungs, and sometimes skin nodules. Evidence of spread of choriocarcinoma to the mother may precede or follow its appearance in the child or she may be unaffected. Choriocarcinoma in the placenta may not have been noticed in these cases but may resemble an infarct or cause fetomaternal hemorrhage. Choriocarcinoma of the placenta is occasionally an incidental finding.

References

1. Orbach D, Sarnacki S, Brisse HJ, Gauthier-Villars M, Jarreau PH, Tsatsaris V, et al. Neonatal cancer. Lancet Oncol. 2013;14:e609–20.
2. Isaacs H Jr. Tumors of the fetus and infant. An Atlas. New York: Springer-Verlag; 2002.
3. Willis RA. The borderland of embryology and pathology. Bull N Y Acad Med. 1950;26:440–60.
4. Zepeda-Mendoza CJ, Morton CC. The iceberg under water: unexplored complexity of chromoanagenesis in congenital disorders. Am J Hum Genet. 2019;104:565–77.
5. Tjarks BJ, Gardner JM, Riddle ND. Hamartomas of skin and soft tissue. Semin Diagn Pathol. 2019;36:48–61.
6. Wick MR. Hamartomas and other tumor-like malformations of the lungs and heart. Semin Diagn Pathol. 2019;36:2–10.
7. Choudhary K, Panda S, Beena VT, Rajeev R, Sivakumar R, Krishanan S. Sialoblastoma: a literature review from 1966–2011. Natl J Maxillofac Surg. 2013;4:13–8.
8. Solis-Coria A, Vargas-González R, Sotelo-Avila C. Rhabdomyomatous mesenchymal hamartoma presenting as a skin tag in the sternoclavicular area. Pathol Oncol Res. 2007;13:375–8.
9. Mazza JM, Linnell E, Votava HJ, Wisoff JH, Silverberg NB. Biopsy-proven spontaneous regression of a rhabdomyomatous mesenchymal hamartoma. Pediatr Dermatol. 2015;32:256–62.
10. Allagio R. Primitive myxoid mesenchymal tumor of infancy. Am J Surg Pathol. 2006;30:388–94.
11. Klimstra DS, Wenig BM, Adair CF, Heffess CS. Pancreatoblastoma. A clinicopathologic study and review of the literature. Am J Surg Pathol. 1995;19:1371–89.
12. deSa DJ. Follicular ovarian cysts in stillbirths and neonates. Arch Dis Child. 1975;50:45–50.
13. Isaacs H Jr. Tumors of the fetus and newborn. Philadelphia: WB Saunders; 1997.
14. Campbell AN, Chan HS, O'Brien A, Smith CR, Becker LE. Malignant tumours in the neonate. Arch Dis Child. 1987;62:19–23.
15. Greaves M. In utero origins of childhood leukaemia. Early Hum Dev. 2005;81:123–9.
16. Cho JY, Lee YH. Fetal tumors: prenatal ultrasonographic findings and clinical characteristics. Ultrasonography. 2014;33:240–51.
17. Kinsler VA, Birley J, Atherton DJ. Great Ormond Street Hospital for Children Registry for congenital melanocytic naevi: prospective study 1988–2007. Part 1-epidemiology, phenotype and outcomes. Br J Dermatol. 2009;160:143–50.
18. Lambie M, Nadler C, Glat P, Van Duzer S, Halligan G, Geller E. Infantile melanoma—a triple threat: diagnosis and management. Ann Plast Surg. 2011;67:85–9.
19. Phadke PA, Rakheja D, Le LP, Selim MA, Kapur P, Davis A, et al. Proliferative nodules arising within congenital melanocytic nevi: a histologic, immunohistochemical, and molecular analyses of 43 cases. Am J Surg Pathol. 2011;35:656–69.
20. Moore SW, Satge D, Sasco AJ, Zimmermann A, Plaschkes J. The epidemiology of neonatal tumours. Report of an international working group. Pediatr Surg Int. 2003;19:509–19.
21. Werb P, Scurry J, Ostör A, Fortune D, Attwood H. Survey of congenital tumors in perinatal necropsies. Pathology. 1992;24:247–53.
22. Parkes SE, Muir KR, Southern L, Cameron AH, Darbyshire PJ, Stevens MC. Neonatal tumours: a thirty-year population-based study. Med Pediatr Oncol. 1994;22:309–17.

23. Brioude F, Toutain A, Giabicani E, Cottereau E, Cormier-Daire V, Netchine I. Overgrowth syndromes—clinical and molecular aspects and tumour risk. Nat Rev Endocrinol. 2019;15:299–311.
24. Paltiel O, Tikellis G, Linet M, Golding J, Lemeshow S, Phillips G, et al. Birthweight and childhood cancer: preliminary findings from the International Childhood Cancer Cohort Consortium (I4C). Paediatr Perinat Epidemiol. 2015;29:335–45.
25. Bellacosa A. Developmental disease and cancer: biological and clinical overlaps. Am J Med Genet Part A. 2013;161A:2788–96.
26. http://www.ncbi.nlm.nih.gov/books/NBK1294/
27. Ciaccio C, Saletti V, D'Arrigo S, Esposito S, Alfei E, Moroni I, et al. Clinical spectrum of PTEN mutation in pediatric patients. A bicenter experience. Eur J Med Genet. 2019;62:103596.
28. Rauen KA. The RASopathies. Annu Rev Genomics Hum Genet. 2013;14:355–69.
29. Kampen KR, Sulima SO, Vereecke S, De Keersmaecker K. Hallmarks of ribosomopathies. Nucleic Acids Res. 2020;48:1013–28.
30. Coffin CM, Davis JL, Borinstein SC. Syndrome-associated soft tissue tumours. Histopathology. 2014;64:68–87.
31. Johnson KJ, Lee JM, Ahsan K, Padda H, Feng Q, Partap S, et al. Pediatric cancer risk in association with birth defects: a systematic review. PLoS One. 2017;12:e0181246.
32. Rump P, Zeegers MP, van Essen AJ. Tumor risk in Beckwith-Wiedemann syndrome: a review and meta-analysis. Am J Med Genet A. 2005;136:95–104.
33. Botto LD, Flood T, Little J, Fluchel MN, Krikov S, Feldkamp ML, et al. Cancer risk in children and adolescents with birth defects: a population-based cohort study. PLoS One. 2013;8:e69077.
34. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, Hennekam RC. Prevalence and patterns of morphological abnormalities in patients with childhood cancer. JAMA. 2008;299:61–9.
35. Coli A, Angrisani B, Chiarello G, Massimi L, Novello M, Lauriola L. Ectopic immature renal tissue: clues for diagnosis and management. Int J Clin Exp Pathol. 2012;5:977–81.
36. Narod SA, Hawkins MM, Robertson CM, Stiller CA. Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet. 1997;60:474–85.
37. Inskip PD, Harvey EB, Boice JD Jr, Stone BJ, Matanoski G, Flannery JT, et al. Incidence of childhood cancer in twins. Cancer Causes Control. 1991;2:315–24.
38. Arnon J, Meirow D, Lewis-Roness H, Ornoy A. Genetic and teratogenic effects of cancer treatments on gametes and embryos. Hum Reprod Update. 2001;7:394–403.
39. Slater ME, Linabery AM, Blair CK, Spector LG, Heerema NA, Robison LL, et al. Maternal prenatal cigarette, alcohol and illicit drug use and risk of infant leukaemia: a report from the Children's Oncology Group. Paediatr Perinat Epidemiol. 2011;25:559–65.
40. Slater ME, Linabery AM, Spector LG, Johnson KJ, Hilden JM, Heerema NA, et al. Maternal exposure to household chemicals and risk of infant leukemia: a report from the Children's Oncology Group. Cancer Causes Control. 2011;22:1197–204.
41. Williams D. Radiation carcinogenesis: lessons from Chernobyl. Oncogene. 2008;27(Suppl 2):S9–18.
42. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer. 2006;6:193–203.
43. Lymperi S, Giwercman A. Endocrine disruptors and testicular function. Metabolism. 2018;86:79–90.
44. Cantarella CD, Ragusa D, Giammanco M, Tosi S. Folate deficiency as predisposing factor for childhood leukaemia: a review of the literature. Genes Nutr. 2017;12:14.
45. Ly P, Cleveland DW. Rebuilding chromosomes after catastrophe: emerging mechanisms of chromothripsis. Trends Cell Biol. 2017;27:917–30.
46. Mosbech CH, Rechnitzer C, Brok JS, Rajpert-De Meyts E, Hoei-Hansen CE. Recent advances in understanding the etiology and pathogenesis of pediatric germ cell tumors. J Pediatr Hematol Oncol. 2014;36:263–70.
47. Isaacs H Jr. Perinatal (fetal and neonatal) germ cell tumors. J Pediatr Surg. 2004;39:1003–13.
48. Heerema-McKenney A, Harrison MR, Bratton B, Farrell J, Zaloudek C. Congenital teratoma: a clinicopathologic study of 22 fetal and neonatal tumors. Am J Surg Pathol. 2005;29:29–38.
49. Heerema-McKenney A, Bowen J, Hill DA, Suster S, Qualman SJ. Members of Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from pediatric and adult patients with extragonadal germ cell tumors. Arch Pathol Lab Med. 2011;135:630–9.
50. Lemire RJ, Beckwith JB. Pathogenesis of congenital tumors and malformations of the sacrococcygeal region. Teratology. 1982;25:201–13.
51. Bale PM. Sacrococcygeal developmental abnormalities and tumors in children. Perspect Pediatr Pathol. 1984;8:9–56.
52. Haider N, Shaheen I, Squire R, Stringer MD. Tailgut cysts in children: a report of two cases and literature review. Pediatr Surg Int. 2015;31:597–60.
53. McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. Adv Anat Pathol. 2007;14:69–92.
54. Zhelnin KE, Gebhard GM, Mirsky DM, Oliver SC, Lovell MA, Galambos C, et al. Pediatric intraocular immature teratoma associated with sacrococcygeal teratoma. Pediatr Dev Pathol. 2017;20:240–4.
55. Agaimy A, Witkowski L, Stoehr R, Cuenca JCC, Gonzalez-Muller CA, Brutting A, et al. Malignant teratoid tumor of the thyroid gland: an aggressive primitive multiphenotypic malignancy showing organotypical elements and frequent DICER1 alterations-is the term "thyroblastoma" more appropriate? Virchows Arch. 2020;477:787–98.
56. Kharga B, Kumar V, Prabhu PS, Sundeep PT, John SK. Neonatal gastric teratoma: a rare entity. J Clin Diagn Res. 2014;8:185–6.
57. Adams KV, Bernieh A, Morris RW, Saad AG. Umbilical cord teratomas associated with congenital malformations. Arch Pathol Lab Med. 2020;144:156–9.
58. Sridhar S, Al-Moallem B, Kamal H, Terrile M, Stallings RL. New insights into the genetics of neuroblastoma. Mol Diagn Ther. 2013;17:63–9.
59. Shimada H, Ikegaki N. Neuroblastoma pathology and classification for precision prognosis and therapy stratification. In: Ray SK, editor. Neuroblastoma: molecular mechanisms and therapeutic interventions. London: Academic Press; 2019. p. 1–22.
60. Shimada H, Umehara S, Monobe Y, Hachitanda Y, Nakagawa A, Goto S, et al. International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group. Cancer. 2001;92:2451–61.
61. Schönherr C, Ruuth K, Kamaraj S, Wang CL, Yang HL, Combaret V, et al. Anaplastic Lymphoma Kinase (ALK) regulates initiation of transcription of MYCN in neuroblastoma cells. Oncogene. 2012;31:5193–200.
62. Ambros IM, Brunner C, Abbasi R, Frech C, Ambros PF. Ultra-high density SNP array in neuroblastoma molecular molecular diagnostics. Front Oncol. 2014;4:202.
63. Joshi VV. Peripheral neuroblastic tumors: pathologic classification based on recommendations of International Neuroblastoma Pathology Committee (Modification of Shimada classification). Pediatr Dev Pathol. 2000;3:184–99.

64. Jin SG, Jiang XP, Zhong L. Congenital Ewing's Sarcoma/Peripheral Primitive Neuroectodermal Tumor: a case report and review of the literature. Pediatr Neonatol. 2016;57:436–9.
65. Krenova Z, Kren L, Blatny J, Falk M, Kazakov DV, Grossmann P, et al. Extraosseal Ewing sarcoma as a rare cause of the blueberry muffin baby syndrome: a case report and the review of the literature. Am J Dermatopathol. 2011;33:733–5.
66. Xiong J, Zhu K, Mao J, Cai J, He M, Li L, et al. Ewing-like sarcoma/undifferentiated round cell sarcoma in an infant with APC and MSH6 variation: a case report. Medicine (Baltimore). 2019;98:e17872.
67. Hung YP, Fletcher CD, Hornick JL. Evaluation of ETV4 and WT1 expression in CIC-rearranged sarcomas and histologic mimics. Mod Pathol. 2016;29:1324–34.
68. Kao YC, Sung YS, Zhang L, Jungbluth AA, Huang SC, Argani P, et al. BCOR overexpression is a highly sensitive marker in round cell sarcomas with BCOR genetic abnormalities. Am J Surg Pathol. 2016;40:1670–8.
69. Santiago T, Clay MR, Allen SJ, Orr BA. Recurrent BCOR internal tandem duplication and BCOR or BCL6 expression distinguish primitive myxoid mesenchymal tumor of infancy from congenital infantile fibrosarcoma. Mod Pathol. 2017;30:884–91.
70. Brown P. Treatment of infant leukemias: challenge and promise. Hematology Am Soc Hematol Educ Program. 2013;2013:596–600.
71. Isaacs H Jr. Fetal and neonatal leukemia. J Pediatr Hematol Oncol. 2003;25:348–61.
72. Zhang Q, Ren Z, Yang J, Yin A. Analysis of 59 cases of congenital leukemia reported between 2001 and 2016. J Int Med Res. 2019;47:4625–35.
73. Roberts I, Fordham NJ, Rao A, Bain BJ. Neonatal leukaemia. Br J Haematol. 2018;182:170–84.
74. Sapienza MR, Pileri A, Derenzini E, Melle F, Motta G, Fiori S, et al. Blastic plasmacytoid dendritic cell neoplasm: state of the art and prospects. Cancers (Basel). 2019;11:595.
75. Gamis AS, Smith FO. Transient myeloproliferative disorder in children with Down syndrome: clarity to this enigmatic disorder. Br J Haematol. 2012;159:277–87.
76. Labuhn M, Perkins K, Matzk S, Varghese L, Garnett C, Papaemmanuil E, et al. Mechanisms of progression of myeloid preleukemia to transformed myeloid leukemia in children with Down Syndrome. Cancer Cell. 2019;36:123–38. e10
77. Weitzman S, Jaffe R. Review: uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. Pediatr Blood Cancer. 2005;45:256–64.
78. Black J, Coffin CM, Dehner LP. Fibrohistiocytic tumors and related neoplasms in children and adolescents. Pediatr Dev Pathol. 2012;15(1 Suppl):181–210.
79. Isaacs H Jr. Fetal and neonatal histiocytoses. Pediatr Blood Cancer. 2006;47:123–9.
80. Dupeux M, Boccara O, Frassati-Biaggi A, Helias-Rodzewicz Z, Leclerc-Mercier S, Bodemer C, et al. Langerhans Cell Histiocytoma: a benign histiocytic neoplasm of diverse lines of terminal differentiation. Am J Dermatopathol. 2019;41:29–36.
81. Chan JK, Lamant L, Algar E, Delsol G, Tsang WY, Lee KC, et al. ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood. 2008;112:2965–8.
82. Risma K, Jordan MB. Hemophagocytic lymphohistiocytosis: updates and evolving concepts. Curr Opin Pediatr. 2012;24:9–15.
83. Jordan MB, Allen CE, Greenberg J, Henry M, Hermiston ML, Kumar A, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the North American Consortium for Histiocytosis (NACHO). Pediatr Blood Cancer. 2019;66:e27929.
84. WHO classification of tumours of soft tissue and bone, 4th ed. Geneva: World Health Organization; 2013.
85. Bruder E, Alaggio R, Kozakewich HP, Jundt G, Dehner LP, Coffin CM. Vascular and perivascular lesions of skin and soft tissues in children and adolescents. Pediatr Dev Pathol. 2012;15(1 Suppl):26–61.
86. North PE. Classification and pathology of congenital and perinatal vascular anomalies of the head and neck. Otolaryngol Clin N Am. 2018;51:1–39.
87. Johnson CM, Navarro OM. Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 1: classification, sonographic approach and vascular tumors. Pediatr Radiol. 2017;47:1184–95.
88. Johnson CM, Navarro OM. Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 2: vascular malformations. Pediatr Radiol. 2017;47:1196–208.
89. https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf
90. Nguyen V, Hochman M, Mihm MC Jr, Nelson JS, Tan W. The pathogenesis of Port Wine Stain and Sturge Weber Syndrome: complex interactions between genetic alterations and aberrant MAPK and PI3K activation. Int J Mol Sci. 2019;20:2243.
91. Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: an update on pathogenesis and therapy. Pediatrics. 2013;131:99–108.
92. Cossio ML, Dubois J, McCuaig CC, Coulombe J, Hatami A, Marcoux D, et al. Non-involuting congenital hemangiomas (NICH) with postnatal atypical growth: a case series. Pediatr Dermatol. 2019;36:466–70.
93. Lalonde E, Ebrahimzadeh J, Rafferty K, Richards-Yutz J, Grant R, Toorens E, et al. Molecular diagnosis of somatic overgrowth conditions: a single-center experience. Mol Genet Genomic Med. 2019;7:e536.
94. Putra J, Gupta A. Kaposiform haemangioendothelioma: a review with emphasis on histological differential diagnosis. Pathology. 2017;49:356–62.
95. Yu L, Lao IW, Wang J. Giant cell angioblastoma of bone: four new cases provide further evidence of its distinct clinical and histopathological characteristics. Virchows Arch. 2015;467:95–103.
96. Coffin CM. Alaggio R Fibroblastic and myofibroblastic tumors in children and adolescents. Pediatr Dev Pathol. 2012;15(1 Suppl):127–80.
97. Parham DM. Fibroblastic and myofibroblastic tumors of children: new genetic entities and new ancillary testing. F1000Res. 2018;7 https://doi.org/10.12688/f1000research.16236.1.
98. Oudijk L, den Bakker MA, Hop WC, Cohen M, Charles AK, Alaggio R, et al. Solitary, multifocal and generalized myofibromas: clinicopathological and immunohistochemical features of 114 cases. Histopathology. 2012;60:E1–11.
99. Kiyohara T, Maruta N, Iino S, Ido H, Tokuriki A, Hasegawa M. CD34-positive infantile myofibromatosis: case report and review of hemangiopericytoma-like pattern tumors. J Dermatol. 2016;43:1088–91.
100. Coffin CM, Neilson KA, Ingels S, Frank-Gerszberg R, Dehner LP. Congenital generalized myofibromatosis: a disseminated angiocentric myofibromatosis. Pediatr Pathol Lab Med. 1995;15:571–87.
101. Cates JM, Stricker TP, Sturgeon D, Coffin CM. Desmoid-type fibromatosis-associated Gardner fibromas: prevalence and impact on local recurrence. Cancer Lett. 2014;353:176–81.
102. Wang WL, Nero C, Pappo A, Lev D, Lazar AJ, López-Terrada D. CTNNB1 genotyping and APC screening in pediatric desmoid tumors: a proposed algorithm. Pediatr Dev Pathol. 2012;15:361–7.
103. Reye RD. Recurring digital fibrous tumors of childhood. Arch Pathol. 1965;80:228–31.
104. Sebire NJ, Ramsay A, Sheppard M, Malone M, Harding B. Risdon RA Intravascular inflammatory myofibroblastic tumors in infancy. Pediatr Dev Pathol. 2002;5:400–4.

105. Saab ST, McClain CM, Coffin CM. Fibrous hamartoma of infancy: a clinicopathologic analysis of 60 cases. Am J Surg Pathol. 2014;38:394–401.
106. Isaacs H Jr. Fetal and neonatal rhabdoid tumor. J Pediatr Surg. 2010;45:619–26.
107. Brennan B, Stiller C, Bourdeaut F. Extracranial rhabdoid tumours: what we have learned so far and future directions. Lancet Oncol. 2013;14:e329–36.
108. Perez-Atayde AR, Newbury R, Fletcher JA, Barnhill R, Gellis S. Congenital "neurovascular hamartoma" of the skin. A possible marker of malignant rhabdoid tumor. Am J Surg Pathol. 1994;18:1030–8.
109. Kreiger PA, Judkins AR, Russo PA, Biegel JA, Lestini BJ, Assanasen C, et al. Loss of INI1 expression defines a unique subset of pediatric undifferentiated soft tissue sarcomas. Mod Pathol. 2009;22:142–50.
110. Anderson JR, Barr FG, Hawkins DS, Parham DM, Skapek SX, Triche TJ. Fusion-negative alveolar rhabdomyosarcoma: modification of risk stratification is premature. J Clin Oncol. 2010;28:e587–8.
111. Parham DM, Alaggio R, Coffin CM. Myogenic tumors in children and adolescents. Pediatr Dev Pathol. 2012;15(1 Suppl):211–38.
112. Whittle SB, Hicks MJ, Roy A, Vasudevan SA, Reddy K, Venkatramani R. Congenital spindle cell rhabdomyosarcoma. Pediatr Blood Cancer. 2019;66:e27935.
113. Lundgren L, Angervall L, Stenman G, et al. Infantile rhabdomyofibrosarcoma: a high-grade sarcoma distinguishable from infantile fibrosarcoma and rhabdomyosarcoma. Hum Pathol. 1993;24:785–95.
114. Soles BS, Wilson A, Lucas DR, Heider A. Melanotic neuroectodermal tumor of infancy. Arch Pathol Lab Med. 2018;142:1358–63.
115. Coffin CM, Alaggio R. Adipose and myxoid tumors of childhood and adolescence. Pediatr Dev Pathol. 2012;15(1 Suppl):239–54.
116. Gooskens SL, Houwing ME, Vujanic GM, Dome JS, Diertens T, Coulomb-l'Hermine A, et al. Congenital mesoblastic nephroma 50 years after its recognition: a narrative review. Pediatr Blood Cancer. 2017;64 https://doi.org/10.1002/pbc.26437.
117. Marsden L, Jennings LJ, Gadd S, Yu M, Perlman EJ, Cajaiba MM. BRAF exon 15 mutations in pediatric renal stromal tumors: prevalence in metanephric stromal tumors. Hum Pathol. 2017;60:32–6.
118. Beckwith JB, Kiviat NB, Bonadio JF. Nephrogenic rests, nephroblastomatosis, and the pathogenesis of Wilms' tumor. Pediatr Pathol. 1990;10:1–36.
119. Doros LA, Rossi CT, Yang J, Field A, Williams GM, Messinger Y, et al. DICER1 mutations in childhood cystic nephroma and its relationship to DICER1-renal sarcoma. Mod Pathol. 2014;27:1267–80.
120. Lee RS, Stewart C, Carter SL, Ambrogio L, Cibulskis K, Sougnez C, et al. A remarkably simple genome underlies highly malignant pediatric rhabdoid cancers. J Clin Invest. 2012;122:2983–8.
121. Isaacs H Jr. Fetal and Neonatal hepatic tumours. J Pediatr Surg. 2007;42:1797–803.
122. Thompson PA, Chintagumpala M. Renal and hepatic tumors in the neonatal period. Semin Fetal Neonatal Med. 2012;17:216–21.
123. Ng K, Mogul DB. Pediatric liver tumors. Clin Liver Dis. 2018;22:753–72.
124. Iacobas I, Phung TL, Adams DM, Trenor CC 3rd, Blei F, Fishman DS, et al. Guidance document for hepatic hemangioma (infantile and congenital) evaluation and monitoring. J Pediatr. 2018;203:294–300. e2
125. Kapur RP, Berry JE, Tsuchiya KD, Opheim KE. Activation of the chromosome 19q microRNA cluster in sporadic and androgenetic-biparental mosaicism-associated hepatic mesenchymal hamartoma. Pediatr Dev Pathol. 2014;17:75–84.
126. Isaacs H. Fetal brain tumors: a review of 154 cases. Am J Perinatol. 2009;26:453–66.
127. Isaacs H Jr. I. Perinatal brain tumors: a review of 250 cases. Pediatr Neurol. 2002;27:249–61.
128. Isaacs H Jr. II. Perinatal brain tumors: a review of 250 cases. Pediatr Neurol. 2002;27:333–42.
129. Subramaniam S, Ahmad T. Childhood brain tumors [updated 2020 Aug 10] In: StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; 2020.
130. Kumar R, Liu APY, Orr BA, Northcott PA, Robinson GW. Advances in the classification of pediatric brain tumors through DNA methylation profiling: from research tool to frontline diagnostic. Cancer. 2018;124:4168–80.
131. Isaacs H Jr. Perinatal (fetal and neonatal) astrocytoma: a review. Childs Nerv Syst. 2016;32:2085–96.
132. Gilani A, Donson A, Davies KD, Whiteway SL, Lake J, DeSisto J, et al. Targetable molecular alterations in congenital glioblastoma. J Neuro-Oncol. 2020;146:247–52.
133. de Kock L, Sabbaghian N, Plourde F, Srivastava A, Weber E, Bouron-Dal Soglio D, et al. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. Acta Neuropathol. 2014;128:111–22.
134. Crawford JR, Isaacs H Jr. Perinatal (fetal and neonatal) choroid plexus tumors: a review. Childs Nerv Syst. 2019;35:937–44.
135. Chung EM, Murphey MD, Specht CS, Cube R, Smirniotopoulos JG. From the Archives of the AFIP. Pediatric orbit tumors and tumorlike lesions: osseous lesions of the orbit. Radiographics. 2008;28:1193–214.
136. Price HN. Congenital melanocytic nevi: update in genetics and management. Curr Opin Pediatr. 2016;28:476–82.
137. Kinsler VA, O'Hare P, Bulstrode N, Calonje JE, Chong WK, Hargrave D, et al. Melanoma in congenital melanocytic naevi. Br J Dermatol. 2017;176:1131–43.
138. Hill DA, Jarzembowski JA, Priest JR, Williams G, Schoettler P, Dehner LP. Type I pleuropulmonary blastoma: pathology and biology study of 51 cases from the international pleuropulmonary blastoma registry. Am J Surg Pathol. 2008;32:282–95.
139. Foulkes WD, Priest JR, Duchaine TF. DICER1: mutations, microRNAs and mechanisms. Nat Rev Cancer. 2014;14:662–72.
140. Fakler F, Aykutlu U, Brcic L, Eidenhammer S, Thueringer A, Kashofer K, et al. Atypical goblet cell hyperplasia occurs in CPAM 1, 2, and 3, and is a probable precursor lesion for childhood adenocarcinoma. Virchows Arch. 2020;476:843–54.
141. Brock KE, Wall J, Esquivel M, Newman B, Marina N, Albanese C, et al. Congenital peribronchial myofibroblastic tumor: case report of an asymptomatic infant with a rapidly enlarging pulmonary mass and review of the literature. Ann Clin Lab Sci. 2015;45:83–9.
142. Dishop MK, McKay EM, Kreiger PA, Priest JR, Williams GM, Langston C, et al. Fetal lung interstitial tumor (FLIT): a proposed newly recognized lung tumor of infancy to be differentiated from cystic pleuropulmonary blastoma and other developmental pulmonary lesions. Am J Surg Pathol. 2010;34:1762–72.