Perinatal Tumors

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9.1 Introduction

Most solid tumors observed in early infancy are benign. Malignant tumors diagnosed during the neonatal period are rare. They account for only 2% of all childhood cancers and have a reported incidence of 1:27,000 live births in the USA [1]. Management of affected infants is extremely challenging. Because factors such as drug absorption, metabolism, distribution, and elimination are affected by age and physiologic maturity, complications associated with the immature physiology of the neonate are common. Age-dependent maturation of the renal, hepatic, hematopoietic, and neurodevelopmental systems make the neonate particularly vulnerable to the deleterious effects of aggressive multimodal therapy involving extirpative surgery, chemotherapy, and radiotherapy [2, 3]. Over the past three decades, the long-term effects of administering anticancer therapies to neonates have become increasingly evident [2–9]. An additional complicating factor is that many neonatal malignancies differ significantly from similar tumors in older children with respect to their biological behavior [10–12]. Certain benign tumors (e.g., sacrococcygeal teratoma) may have malignant potential and undergo malignant change if untreated. Other tumors that are histologically malignant (e.g., fibrosarcoma) may exhibit benign behavior. Some benign tumors may be life threatening because of their size, anatomic location, and impact on infant physiology. Additionally, congenital neuroblastoma may have an unpredictable course, with many tumors involuting spontaneously and others progressing to a fatal outcome.

Due to the rarity of malignant neoplasms in neonates, existing treatment protocols are based on studies that predominantly comprise older children. These protocols may not consider the unique aspects of treating perinatal tumors. In an effort to shed light on this topic, I will address the distinguishing clinical features, management, and prognosis of the most common perinatal neoplasms, including teratomas, neuroblastoma, sarcomas, renal and hepatic tumors, and retinoblastoma.

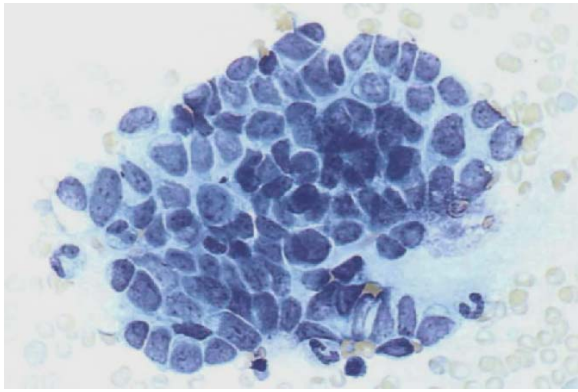

Fig. 9.1 Neuroblastoma cells in bone marrow.

9.2 Overview

9.2.1 Clinical Presentation

Nearly 50% of tumors occurring in neonates are observed at birth; another 20–29% become evident within the first week of life [13, 14]. Although there is variation in the reported frequency of specific tumor diagnoses across neonatal series [14–19], teratomas and neuroblastoma account for approximately two thirds of reported neoplasms. The most common finding on physical examination is a palpable mass. Nonspecific symptoms such as irritability, lethargy, failure to thrive, and feeding difficulties may indicate the presence of an occult neoplasm. Petechial hemorrhages and other hematologic abnormalities may indicate extensive bone marrow replacement by tumor cells such as neuroblastoma or leukemia (Fig. 9.1).

The association between congenital abnormalities and tumors is well documented, with concurrence reported in as many as 15% of neonatal tumors [17, 20, 21]. Many such associations are related to chromosomal defects, particularly trisomies 13, 18, and 21. An increased incidence of leukemia and retroperitoneal teratoma has been reported in neonates with Down syndrome [21], and teratomas are associated with regional and distal congenital anomalies including cloaca, limb hypoplasia, and spina bifida [22].

9.2.2 Oncogenesis and Genetic Risk Factors

Many neonatal malignancies are inherited or occur spontaneously as the result of a de novo mutational event. The etiology of these tumors is likely multifactorial, including both genetic and environmental factors. Both genetically determined syndromes and constitutional chromosomal defects may result in an increased risk of malignancy. This includes single-gene malignancy-related syndromes and the familial associations of tumors [22]. Particular constitutional chromosome anomalies specifically favor neoplasms occurring in the fetal and neonatal period. These anomalies have been identified in retinoblastoma (13q) and nephroblastoma (11p) [23]. In patients with Denys-Drash syndrome, there is an association with genetic mutations located at 11p13 and WT1. These patients commonly have Wilms' tumor. The specific site of the point mutation identified in most cases is located on the WT1 gene exon 9 [24]. Other examples of constitutional chromosomal anomalies associated with neoplasms include an increased risk of leukemia in patients with Down syndrome [25, 26] and a high frequency of poor-prognosis neonatal leukemia involving the 11q23 locus of the MLL gene. This specific genetic defect is rare in older children [27]. Genes that confer a higher risk of neoplasia by enhancing susceptibility to oncogenic factors are likely to exist and may play a role in certain inherited syndromes. For example, there is an increased risk of hepatoblastoma and rhabdomyosarcoma in patients with Li-Fraumeni syndrome (p53 mutation) [22].

9.2.3 Diagnostic Investigations

The selection of imaging studies is dependent upon suspected pathology, affected anatomic site, and differential diagnosis. Dramatic improvements in prenatal ultrasonography (US) and magnetic resonance imaging (MRI) have had a significant impact on prenatal diagnosis, management, and fetal outcome [28–30]. Prenatal US has been particularly useful in identifying large sacrococcygeal or cervical teratomas that may complicate vaginal delivery or be responsible for intrauterine fetal demise or postnatal complications. US can also detect adrenal or thoracic masses in the fetus, providing useful information regarding both the nature of the mass and, in most cases, its origin. Fetal MRI can better characterize and delineate specific anatomic details and the extent of tumor involvement. These complementary techniques help to facilitate the development of a comprehensive plan of action that determines the mode, timing, and location of delivery as well as the initial postnatal management strategy. Fetal surgery and the ex utero intrapartum treatment (EXIT) procedure have proven useful in treating nonimmune hydrops and congestive heart failure caused by neoplasms. The EXIT procedure has also been successfully used to salvage infants with high-grade airway obstruction caused by tumors [31].

Contrast-enhanced computed tomography (CT) provides excellent postnatal images of most neoplasms, though it has limitations in evaluating intraspinal involvement. MRI, however, is particularly

useful for evaluating tumors that involve the central nervous system or spinal canal. It is also extremely useful in the preoperative delineation of the vascular anatomy of the tumor and adjacent organs. Although limited information is available concerning the use of positron emission tomography (PET) in neonates, evidence suggests that it is helpful in determining cerebral glucose metabolism and, more importantly, holds promise in the management of selected pediatric patients with malignancy [32].

Cytogenetics is playing an increasingly important role in the diagnosis, risk stratification, and monitoring of patients with neonatal tumors. Most cancer cells are thought to have a high incidence of chromosomal changes and genetic mutations that frequently are identifiable and, in some cases, are prognostically important. For example, N-myc amplification is a specific molecular marker that characterizes a subset of aggressive neuroblastomas that usually has a poor prognosis [33].

9.2.4 Therapeutic Interventions

9.2.4.1 Surgical Management

Surgical extirpation remains the definitive treatment modality in most neonates with solid tumors. The timing of the surgical procedure and the surgical strategies employed must take into account the physiologic and metabolic needs of the neonate. Avoidance of hypoglycemia and hypothermia, especially if significant fluid or blood replacement is required or prolonged exposure occurs are important considerations.

The impact of surgery on the subsequent growth and development of the neonate can be profound, especially when major tumor extirpations are extensive or resection of unaffected tissues integral for normal structure and function has occurred. In some patients, appropriate surgical management may result in impairment of gastrointestinal or bladder function, ambulation, or future sexual function, thereby creating life-long physical and emotional burdens for patients. Interrupting or traversing normal growth centers in order to resect tumors can have a profound effect on structural symmetry and function. For example, intrathecal tumor removal extending over several vertebral segments often results in some degree of postlaminectomy scoliosis later in childhood. Preserving function and structure without compromising survival is thus the paramount principle guiding contemporary surgical and multimodal treatment strategies. For many patients in whom a tumor is initially unresectable (e.g., those with stage 3 neuroblastoma) or involves important structures that should be preserved, the administration of several courses of preoperative chemotherapy has been extremely beneficial. This approach has allowed delayed complete primary resection with preservation of vital structures, thus improving surgical outcomes and quality of life.

9.2.5 Radiotherapy

Because many malignant tumors in childhood are radiosensitive, radiotherapy plays an important role in the management of advanced-stage tumors. In light of the scarcity of neonatal data, however, treatment parameters such as dosing schedules have been extrapolated largely from data in older children. Because the neonate experiences rapid growth of organs and structures, radiotherapy has a profound impact on subsequent development. The sensitivity and detrimental effects of radiation therapy on the central nervous system, skeletal growth, and visceral organs appear to be inversely related to the child's age and directly related to the radiation dose [6].

In a seminal study of children younger than age 2 years, Meadows, et al. [6] found that growth disturbances and musculoskeletal abnormalities were the most common late effects of radiation therapy. Approximately 85% of patients had some degree of bone or soft tissue abnormality; this problem was most severe in children who had received thoracic or spinal irradiation. Other authors have documented a wide spectrum of significant late radiation effects, including scoliosis and severe bony deformities (70%) and delayed physical development [14, 34]. Children receiving radiation to the cerebrospinal axis for leukemia or brain tumors reportedly experience major delays in cognitive development, and infants treated with cranial irradiation have a high incidence of learning disabilities and mental retardation [35, 36]. The severity of these disabilities is strongly correlated with radiation dose. As in older children, other significant late effects of radiation therapy in neonates include breast agenesis, aortic arch dysgenesis, second malignancies (particularly leukemias and breast and thyroid cancer), and chronic renal and hepatic insufficiency [36–40].

9.2.6 Chemotherapy

The lack of substantial pharmacologic data on newborns significantly complicates the administration of chemotherapeutic agents. Knowledge of drug interactions, metabolism and clearance, and toxicity are all areas of notable deficiency. They remain the focus of intense ongoing discussion and contemporary investigation. In an overview of a recent (2003) workshop concerning cancer pharmacology in infants and young children, a significantly greater incidence of neurotox-

icity for vincristine, hepatic toxicity for actinomycin D, and ototoxicity for cisplatin [41] was observed in infants and young children For virtually all of these older agents and the newer camptothecin agents, the limited available data indicate that weight-based dosing in young children normalizes the drug clearance profiles and may improve the toxicity profiles, bringing them in line with that of older children [41].

During the course of the second National Wilms' Tumor Study, the prescribed doses of actinomycin D, vincristine, and doxorubicin were reduced by 50% due to observed excessive myelodepression in infants younger than 1 year of age. Interestingly, reduction of dose did not compromise therapeutic effectiveness [42]. A similar dose reduction approach was followed in the Intergroup Rhabdomyosarcoma Study protocols [43]. Excessive drug-related toxicity has not been observed in infants with leukemia. Moreover, reduced dosage protocols have had a detrimental effect on clinical response and outcome [44].

9.3 Teratomas

Teratomas are embryonal neoplasms that contain tissues from at least two of the three germ layers (ectoderm, endoderm, and mesoderm). These neoplasms arise in both gonadal and extragonadal sites, with location thought to correspond to the embryonic resting sites of primordial totipotential germ cells. Tumor location correlates with the age of the patient. Teratomas occurring in infancy and early childhood are generally extragonadal, whereas those presenting in older children more commonly occur in the ovary or testis [45]. More than 50% of teratomas are evident at birth and are most commonly seen in the sacrococcygeal area. Although more than one third of teratomas of the testis are recognized in the first year of life, these lesions are rarely diagnosed in the neonatal period. The sacrococcyx is also the most common extragonadal location irrespective of age (45–65%) [46]. Cervicofacial and central nervous system tumors and tumors of the retroperitoneum are seen less frequently. Teratomas presenting in the mediastinum, heart, and liver are rarely seen. Excluding testicular teratomas, 75–80% of teratomas occur in females. Approximately 20% of tumors contain malignant components, the most common being endodermal sinus tumor [46].

A wide range of congenital anomalies is seen in association with teratomas, and the type of anomaly frequently depends on the tumor site and size. Single or combined malformations of the genitourinary tract, rectum, anus, vertebrae, and caudal spinal cord are sometimes found in patients with extensive sacrococcygeal teratomas [16, 47–49]. Disfiguring cleft palate defects are found in newborns with massive cranial and nasopharyngeal teratomas [50].

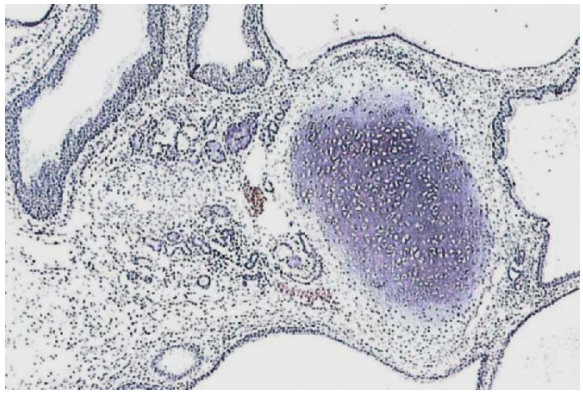

Fig. 9.2 Microphotograph of a benign teratoma showing differentiated cartilage, respiratory epithelium, mucinous epithelium, and salivary gland acini.

Teratomas can present as solid, cystic, or mixed solid and cystic lesions. Most teratomas that are present at birth consist of ectodermal and mesodermal components. Epidermal and dermal structures such as hair, sebaceous glands, sweat glands, and teeth are frequently present. Virtually all teratomas have mesodermal components, including fat, cartilage, bone, and muscle. Endodermal components commonly include intestinal epithelium and cystic structures lined by squamous, cuboidal, or flattened epithelium [51]. Pancreatic, adrenal, and thyroid tissue, as well as mature and immature neuroepithelial and glial tissue is also frequently seen (Fig. 9.2).

Tumors are histologically classified as either mature or immature, with most pediatric teratomas classified as mature. These tumors exhibit an absence of coexisting malignant cells and little or no tendency to malignant degeneration. They nevertheless may be fatal if the airway is compromised or if vital structures such as the brain or heart are involved. Moreover, depending on location and size, even benign tumors may be inoperable and incompatible with extrauterine life.

Although useful tumor grading systems have been developed [52, 53], these systems are of limited use in regard to the fetus or newborn in that embryonic or immature elements may be appropriate for the stage of development [54, 55]. Regardless of tumor grade in these patients, immature teratomas are associated with a favorable prognosis, and only in rare cases does immature neuroglial tissue metastasize to adjacent lymph nodes, lungs, and other distant organs from an immature primary site [56, 57]. (For additional information on germ cell tumor staging and grading systems, refer to Chap. 13.)

The most important predictor of recurrence in pediatric immature teratomas appears to be the presence

of microscopic foci of yolk sac tumor [58]. Because of their small size, these tumors may be missed by the pathologic sampling process. Such oversights may account for metachronous metastases after resection of the immature teratoma metastasis.

In general, the prognosis of neonates depends upon the resectability of the tumor and the presence of metastases or metastatic potential.

9.3.1 Sacrococcygeal Teratoma (SCT)

9.3.1.1 Clinical Presentation and Diagnosis

SCT is the predominant teratoma as well as the most common neoplasm of the fetus and newborn. The tumor has an estimated incidence of 1:20 000 to 1:40 000 live births and a female predominance ranging from 2:1 to 4:1 [47, 59–61]. Ten percent to 20% of patients with SCT have coexisting congenital anomalies such as tracheoesophageal fistula, imperforate anus, anorectal stenosis, spina bifida, genitourinary malformations, meningomyelocele, and anencephaly [16, 57, 62–64]. Also, many patients have significant structural abnormalities of juxtaposed organs resulting from displacement by a large teratoma.

A classification system developed by Altman, et al. [65] divides SCTs into four distinct anatomic types that differ in the degree of intra- and extrapelvic extension (Fig. 9.3). Type I (46.7%) is predominantly external, with minimal presacral extension. Type II (34.7%) arises externally and has a significant intrapelvic component. Type III (8.8%) is primarily pelvic and abdominal but is apparent externally. Type IV (9.8%) is presacral and has no external manifestation. The incidence of malignant components not only correlated with anatomic type (8% in type I vs. 38% in type IV) but also with age at diagnosis and gender; however, the size of the tumor was unrelated. The rate of malignancy of tumors in older infants (>6 months) and children is significantly higher than that of the visible exophytic tumors seen in neonates. Malignant change appears to be more frequent in males, particularly those with solid versus complex or cystic tumors [66–67]. The most common malignant elements identified within sacrococcygeal lesions are yolk sac tumor and embryonal carcinoma (Fig. 9.4) [68].

In countries where antenatal US screening is carried out, most large SCTs are diagnosed before birth. Uterine size larger than expected for a gestational date (polyhydramnios or tumor enlargement) is the most common obstetrical indication for initiating maternal-fetal US examination. Sonography may reveal an external mass arising from the sacral area of the fetus (Fig. 9.5). This mass is composed of solid and cystic areas, with foci of calcification sometimes apparent. Most prenatally diagnosed SCTs are extremely vascular and can be seen on color-flow Doppler studies.

Lumbosacral myelomeningocele is the most likely condition to be confused with SCT. Lumbosacral myelomeningocele and cystic SCT may show similar findings on US. Since both are associated with elevated maternal levels of alpha fetoprotein (AFP), these levels are not helpful in distinguishing between the two entities. Other critical information gained from US includes the possible presence of abdominal or pelvic extension, evidence for bowel or urinary tract obstruction, assessment of the integrity of the fetal spine, and documentation of fetal lower extremity function [69]. Imaging of the fetal brain is helpful in establishing the diagnosis in that most fetuses with lumbosacral myelomeningocele have cranial findings such as Arnold-Chiari malformation [70]. When there is doubt, performing a fetal MRI can be extremely valuable in clarifying fetal anatomy and in making a definitive diagnosis (Fig. 9.6). Other soft tissue tumors that may mimic SCT include neuroblastoma, hemangioma, leiomyoma, and lipoma [70].

Tumors can grow at an unpredictable rate to tremendous dimensions and may extend retroperitoneally displacing pelvic or abdominal structures (Fig. 9.7). Large tumors can cause placentomegaly, nonimmune fetal hydrops, and the mirror syndrome [59, 71]. These conditions are thought to result from a hyperdynamic state induced by low-resistance vessels in the teratoma. Without fetal intervention, high-output cardiac failure and hydrops resulting in fetal demise is almost certain. Thus, in a select subset of fetuses that meet specific criteria, restoring more normal fetal physiology may be achieved by surgical debulking of the SCT in utero [72].

Neonatal death may occur due to obstetric complications from tumor rupture, preterm labor, or dystocia [73–75]. Impending preterm labor from polyhydramnios or uterine distension from tumor mass may therefore require treatment by amnioreduction or cyst aspiration. Dystocia and tumor rupture can be avoided by planned cesarean section delivery for infants with tumors larger than 5 cm [45].

Antenatal diagnosis carries a significantly less favorable outcome than diagnosis at birth, and prognostic factors outlined in the current SCT classification system are not applicable to fetal cases. While the mortality rate for SCT diagnosed in neonates is 5% at most, that for fetal SCT is close to 50% [71, 73, 74]. Results of most clinical series indicate that hydrops and/or polyhydramnios and placentomegaly portend a fatal outcome. The indication for maternal-fetal US has also been shown to be a predictive factor [73]. If SCT is an incidental finding on routine prenatal US, the prognosis is favorable at any gestational age. Many of these lesions are predominantly cystic and relatively avascular

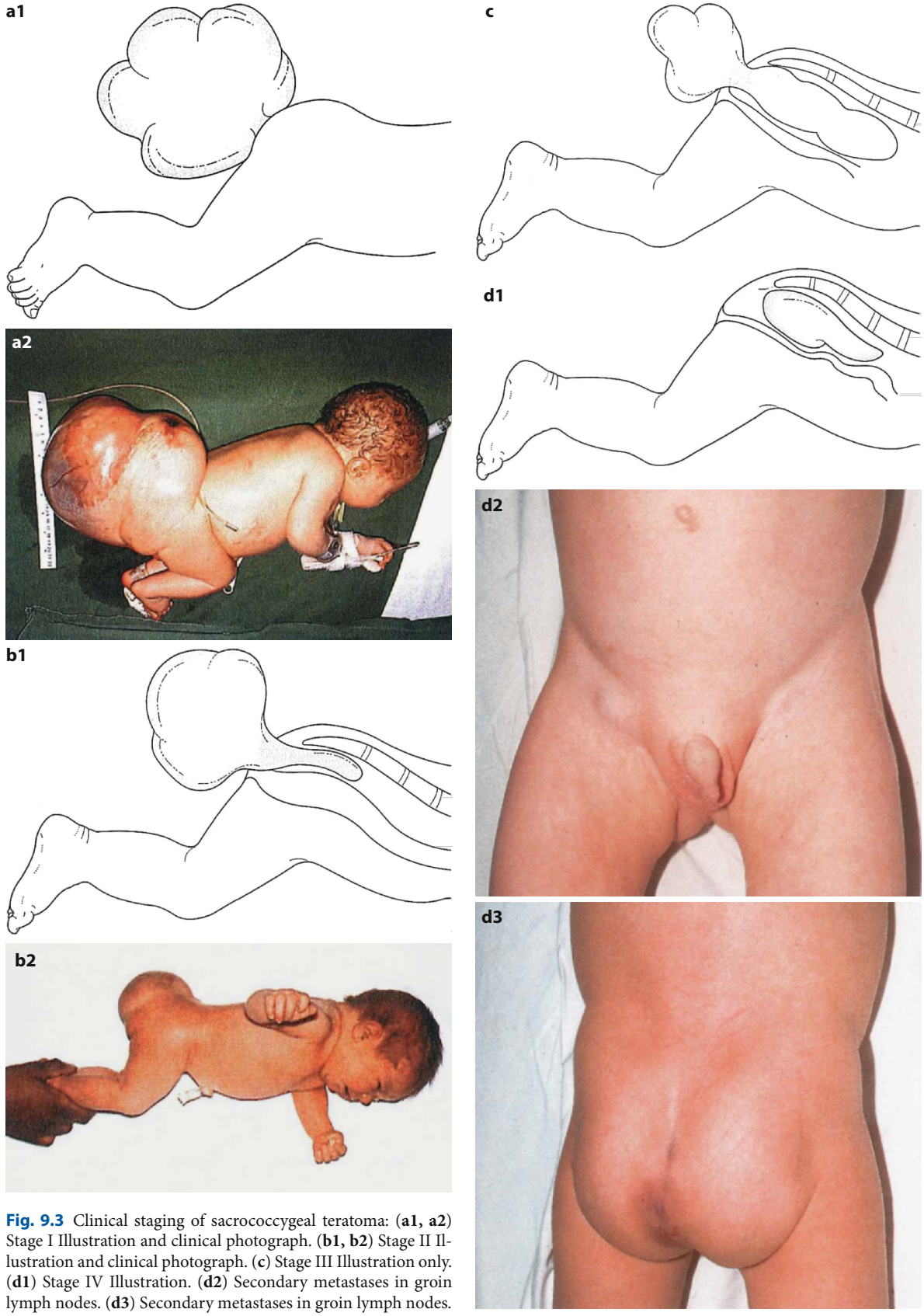

Fig. 9.3 Clinical staging of sacrococcygeal teratoma: (**a1, a2**) Stage I Illustration and clinical photograph. (**b1, b2**) Stage II Illustration and clinical photograph. (**c**) Stage III Illustration only. (**d1**) Stage IV Illustration. (**d2**) Secondary metastases in groin lymph nodes. (**d3**) Secondary metastases in groin lymph nodes.

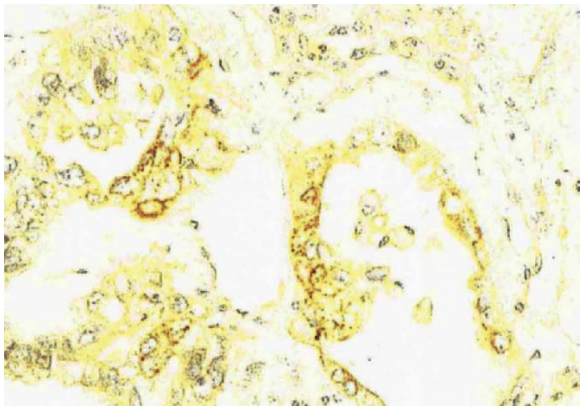

Fig. 9.4 Histology of an endodermal sinus tumor with alpha-fetoprotein stain.

and can be managed postnatally with surgical resection. If US is initiated due to maternal indications, the outcome is much less favorable. Additionally, prematurity from polyhydramnios or cesarean section performed before 30–32 weeks' gestation results in increased mortality [45]. In light of these factors, antenatal diagnosis requires referral to a high-risk obstetric center, with immediately available neonatal intensive care and qualified pediatric surgical and anesthesia expertise.

Postnatal diagnosis is determined by clinical findings on physical examination, serum levels of AFP and ß-human chorionic gonadotropin (ß-HCG), and a number of radiographic imaging studies. Ninety percent of SCTs are noted at delivery, with a protruding caudal mass extending from the coccygeal region.

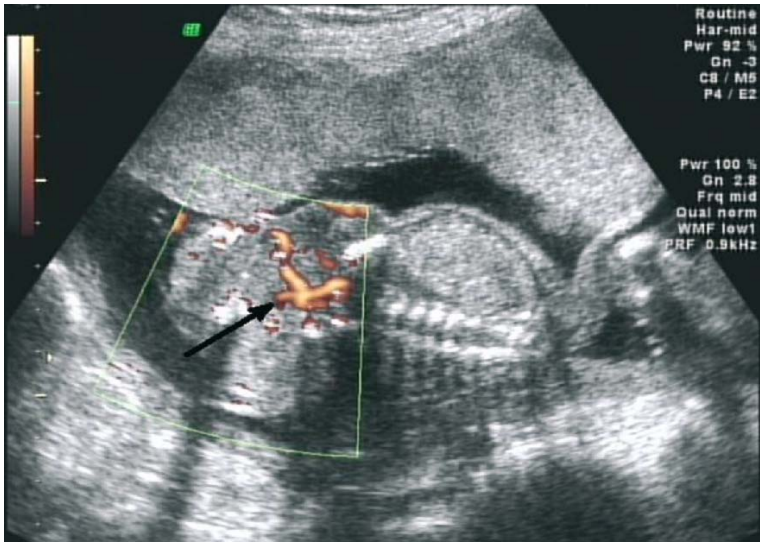

Fig. 9.5 Antenatal maternal-fetal Doppler ultrasound of a 21-week gestation fetus with a sacrococcygeal tumor showing solid and cystic components. *Black arrow* marks vessel with high blood flow within the tumor on the Doppler image. Courtesy of Dr. Timothy Crombleholme, M.D.

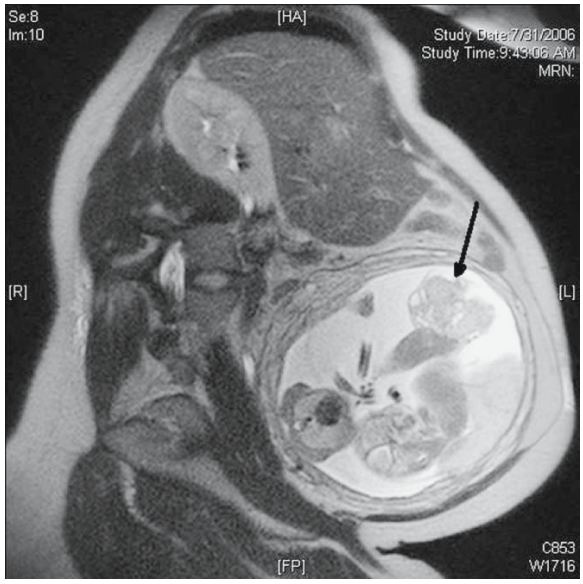

Fig. 9.6 MRI of twin gestation at 21 weeks with one twin having a large sacrococcygeal teratoma (*black arrow*) associated with hydrops and high output failure. Courtesy of Dr. Timothy Crombleholme, M.D.

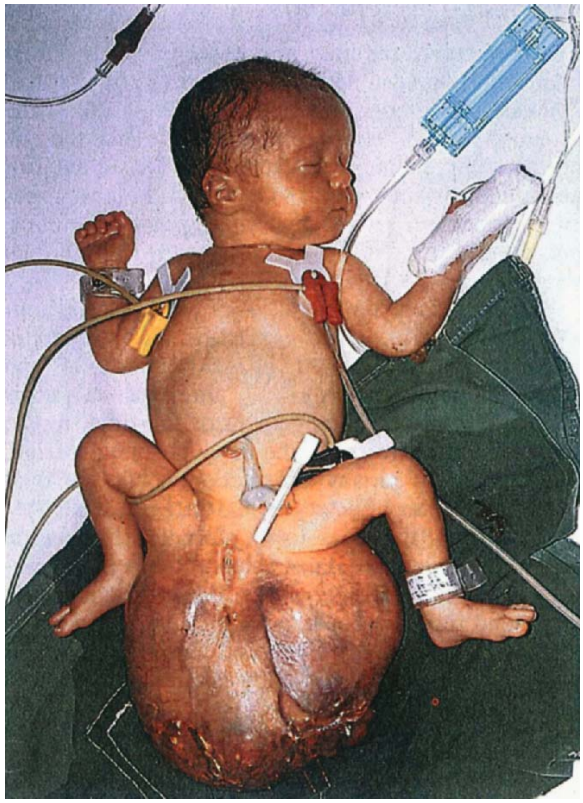

Fig. 9.7 Neonate with a large sacrococcygeal teratoma.

These tumors are easily recognized and a diagnosis can generally be made by physical examination alone. Intrapelvic components can be diagnosed by a rectal digital examination. SCTs seen at birth are predominantly benign, and many are functionally asymptomatic.

Intrapelvic variants may have a delayed postnatal presentation [59, 65, 71]. They are typically noted in infants and children from ages 4–6 months to 4 years. In contrast to the SCTs seen in neonates, these tumors are located in the pelvis and have no external component. More than one third are associated with malignancy. Clinical presentation may include constipation, anal stenosis or symptoms related to the tumor compressing the bladder or rectum and a palpable mass. Presacral tumors are associated with sacral defects and anorectal malformations (Currarino triad) [46].

Radiographs of the pelvis identify any sacral defects or tumor calcifications. CT with intravenous and rectal contrast material defines the intrapelvic extent of the tumor, identifies any nodal or distant metastases, and demonstrates possible urinary tract displacement or obstruction. CT imaging also identifies liver metastasis and periaortic lymph node enlargement. MR imaging is useful when spinal involvement is suspected or if the diagnosis is in doubt. A chest radiograph is useful in revealing obvious pulmonary metastases. Because chest CT is more reliable in identifying smaller metastatic lesions, it should be performed when there is a high index of suspicion.

9.3.1.2 Operative Treatment

9.3.1.3 Open Fetal Surgery

In a fetus with a large SCT, signs of cardiovascular compromise and early hydrops are indications for open fetal surgery. Since the first reported fetal resection of SCT in 1997 [76], this approach has had several long-term survivors. Because in utero SCT resection commonly precipitates preterm labor, meticulous monitoring and tocolytic therapy during the immediate postoperative period is essential. Hospitalized patients undergo daily US and fetal echocardiography as indicated. Although signs of hydrops generally begin to resolve within several days of tumor resection, complete resolution may take weeks [29]. Since the intrauterine procedure is not designed to completely remove the teratoma, patients often require a second operation postnatally to remove the coccyx and any residual tumor mass. At surgery, the exophytic tumor is dissected free of the anus and rectum. The tumor is then removed by dividing it near the coccyx with a thick tissue-stapling device [29].

A rapidly enlarging macrocystic SCT results in polyhydramnios and placentomegaly, with associated mirror syndrome. Because this syndrome resembles severe pre-eclampsia and is life threatening to the mother, immediate delivery of the fetus or infant is essential.

9.3.1.4 Postnatal Intervention

The treatment of choice for infants with SCT is complete surgical resection, with the exception of emergencies related to tumor rupture or hemorrhage that adversely affect the neonate's hemodynamic status. The operative procedure can be performed on an elective basis early in the newborn period. The anatomic location of the tumor determines the operative approach. Tumors with extensive intrapelvic extension or a dominant abdominal component (type III or IV) are initially approached through the abdomen. A posterior sacral approach is sufficient for most type I tumors and type II tumors.

Operative goals include: (a) complete and prompt tumor excision. A significant delay may result in serious complications, including pressure necrosis, tumor hemorrhage, and malignant degeneration; (b) resection of the coccyx to prevent tumor recurrence; (c)

reconstruction of the muscles of anorectal continence; and (d) restoration of a normal perineal and gluteal appearance [77, 78].

Initial control of the middle sacral and hypogastric arteries may be required in order to safely remove tumors in these fragile infants. The procedure is performed in a temperature-controlled environment, and infants are protected from heat loss with appropriate measures. The urinary bladder is catheterized and the operation is generally performed with the patient in a prone jackknife position, cushioned in a sterile foam ring. After skin preparation and sterile draping, a frown-shaped or inverted chevron incision is made superiorly to the tumor (Fig. 9.8a). This incision provides excellent exposure and keeps later wound closure some distance from the anal orifice. To delineate the rectum, the surgeon's finger and/or a Hegar dilator also may be inserted 3 cm into the anal canal. After raising skin flaps off the tumor, the attenuated retrorectal muscles are carefully identified and preserved. The mass is mobilized close to its capsule, and hemostasis is achieved with electrocautery or ligatures. To retard heat loss, warm gauze pads are placed over the exposed dissection and the tumor mass. The main blood supply to the tumor usually arises from a primitive middle sacral artery or from branches of the hypogastric artery. After division of the coccyx from the sacrum, the vessels can be observed exiting the presacral space ventral to the coccyx. For patients with extremely large or vascular lesions in which excessive fluid shifts or hemorrhage may result in operative mortality, surgeons occasionally use extracorporeal membrane oxygenation (ECMO) in conjunction with hypothermia and hypoperfusion to facilitate better control of bleeding during resection [79].

As failure to remove the coccyx is associated with a recurrence rate as high as 37% [80], the coccyx is excised in continuity with the tumor (Fig. 9.8b). The tumor is dissected free from the rectal wall and the anorectal muscles are reconstructed. The levator muscles are attached superiorly, providing support to the rectum and positioning the anus in the normal location. A closed-suction drain may be placed below the subcutaneous flaps. The wound is then closed in layers with interrupted absorbable sutures. A urinary catheter is left in position for several days. To maintain cleanliness of the wound, the patient is kept prone for several days after surgery.

Premature newborns with large teratomas are challenging to manage. Due to lung immaturity, increased tumor vascularity, and poor tolerance of blood loss, surgical risks are high [81]. In these patients, devascularization and staged resection may be considered to avoid excessive blood loss. The fetus with a large SCT presents an even greater management challenge. As

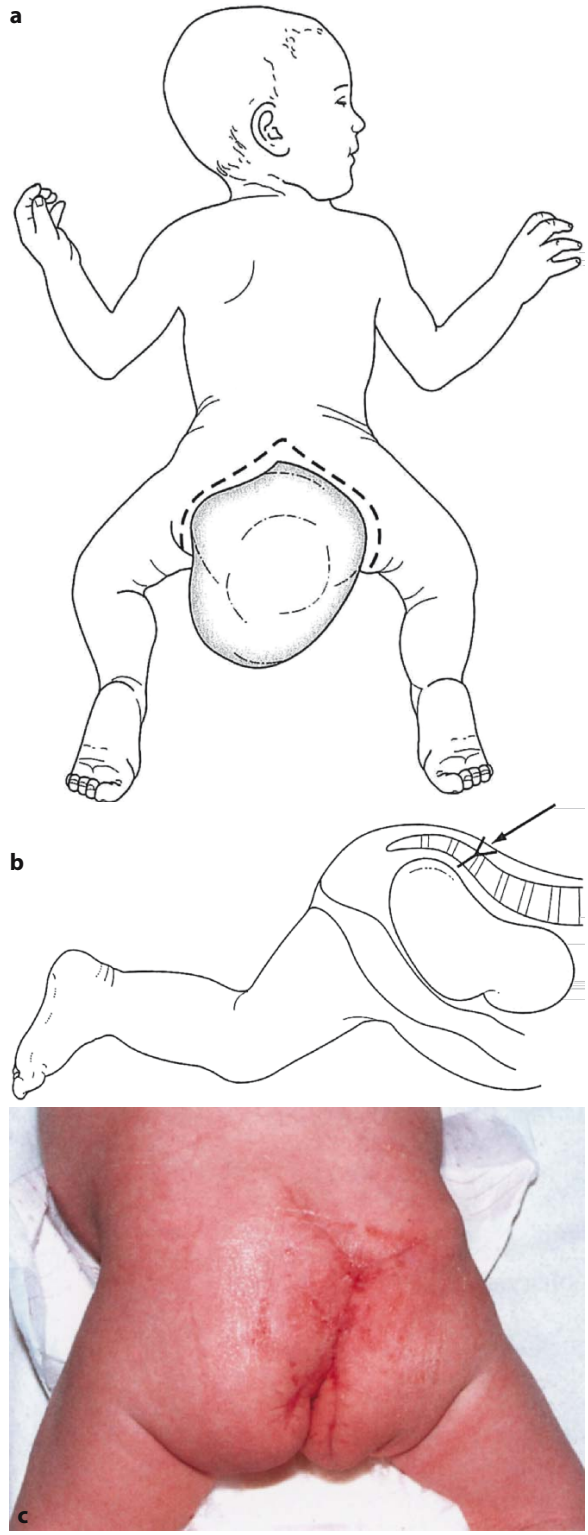

Fig. 9.8 Operative details. (**a**) Position of the patient for surgery. The chevron incision is used. (**b**) Cross-section of tumor and excision of coccygeal segment to ensure complete incision. (**c**) Postoperative cosmetic result.

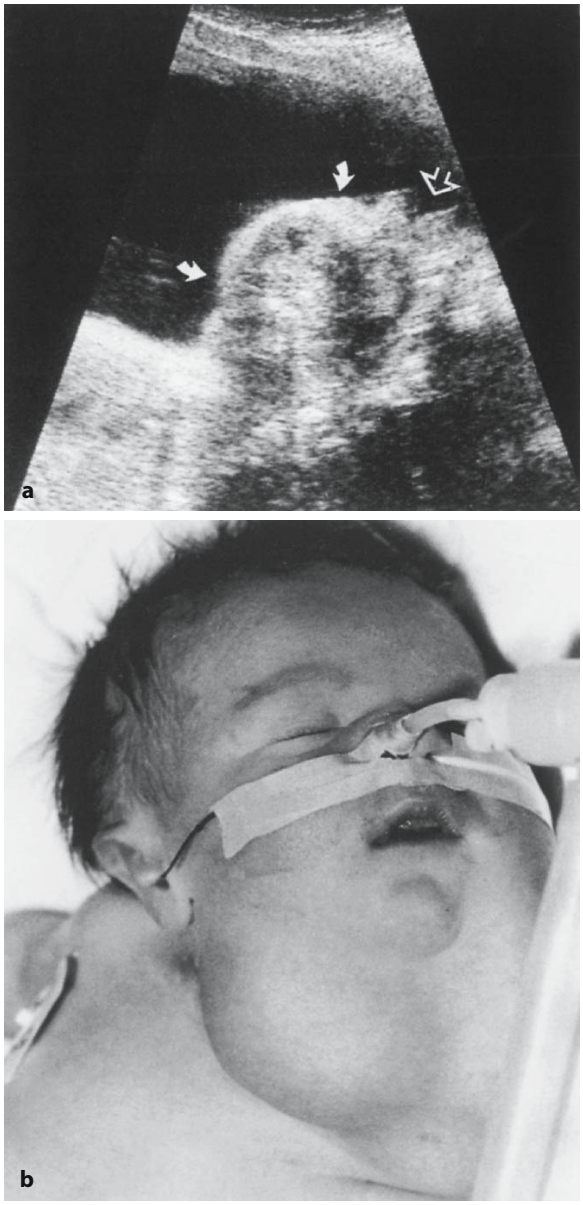

Fig. 9.9 (**a**)Antenatal ultrasound of a cervical teratoma (**b**) Infant with a cervical teratoma causing respiratory distress.

mentioned earlier, fetal hydrops and placentomegaly are associated with fetal demise.

The most serious complication of excision is intraoperative hemorrhage, and the major cause of mortality is hemorrhagic shock. One successful preoperative strategy for stabilizing patients with vascular tumors in which there is significant bleeding is to tightly wrap the teratoma with an elastic bandage. As a salvage approach for acute life-threatening hemorrhage, performing an emergent laparotomy and temporarily cross-clamping the distal abdominal aorta has been reported [82].

As with any surgical procedure, wound complications can occur. Resection of teratomas with significant intrapelvic and intraperitoneal extension may be associated with temporary or persistent urinary retention in the postoperative period, but these symptoms generally resolve. Although patients with small tumors usually have normal anorectal continence, 30–40% of premature infants with large SCTs and in whom the levator and gluteal muscles are severely attenuated, have fecal incontinence. Long-term bowel management strategies allow most patients to achieve socially manageable bowel function.

9.3.1.5 Adjuvant Chemotherapy

Detection of malignant elements necessitates adjuvant multiagent chemotherapy. The most active antineoplastic drugs include cisplatin, etoposide, and bleomycin. Reports indicate impressive survival after administration of intensive chemotherapy both in children with locally advanced disease and in those with metastatic disease [83–85]. Even with malignant transformation of SCT, reported survival is 88% with local disease and 75% with distant metastases [86]. Moreover, it appears that stage, extent of metastasis, and extension into bone have no prognostic significance when children are treated with platinum-based regimens [87].

For patients in whom the primary malignant tumor is unresectable, a course of multiagent chemotherapy is administered to facilitate subsequent resection. If a good tumor response is indicated by a diminishing serum AFP level, CT imaging, and a chest radiograph, resection is undertaken after several cycles of chemotherapy.

In patients with localized malignant recurrence, complete resection remains the cornerstone of salvage treatment. This is carried out in conjunction with adjuvant chemotherapy.

Chemotherapy also has been effective in the treatment of metastatic foci in the lungs and liver. However, to ensure removal of any malignant elements, residual lesions must be excised. Although radiation therapy is uncommon and used selectively, it may have a role in controlling unresectable disease.

9.3.1.6 Long-Term Outcomes

Research over the past several decades indicates that age at diagnosis is the dominant prognostic factor for SCT. Fetuses diagnosed with SCT after 30 weeks' gestation tend to have better outcomes than those diagnosed earlier [74, 88]. When the diagnosis is made prior to 2 months of age or excision is performed prior to 4 months of age, the malignancy rate is 5–10% [89,

90]. Additionally, cystic tumors, which are generally mature, carry a better prognosis. Complications related to hemorrhage, vascular steal, and malignancy are seen more frequently in patients with solid tumors.

The long-term survival of newborns who have undergone complete resection is generally excellent regardless of tumor histology [91]. Nevertheless, because all SCTs have a risk of local and/or distant recurrence, close follow-up at 3-month intervals for a 3- to 4-year period is essential. An 11% tumor recurrence with mature teratoma and a 4% recurrence with immature teratoma have been reported [63]. Although 43–50% of these occurrences are malignant, the chemosensitivity of yolk sac (endodermal sinus) tumor results in a high survival rate. Serum AFP levels are monitored and physical examinations are performed. Special attention is given to rectal examination in that it may detect a presacral recurrence. When serum AFP levels do not fall appropriately, abdominal US is performed. When there is an index of suspicion, an abdominopelvic CT or MR imaging and a lung CT are performed. Recurrent tumor may be benign, but should be reexcised to minimize the long-term risk of malignant transformation.

9.3.2 Head and Neck Teratomas

Head and neck teratomas account for 5% of all neonatal teratomas. These neoplasms have no sex or race predilection. They can occur in the brain, orbit, oropharynx, and neck.

9.3.2.1 Intracranial Teratomas

Intracranial teratomas account for approximately 50% of all brain tumors in early infancy [59]. These tumors occur most commonly in the pineal region but also are found in the hypothalamus, ventricles, and suprasellar and cerebellar regions. Unlike intracranial teratomas in older children, most intracranial teratomas in neonates are benign. The most common presenting symptoms and findings are related to the presence of obstructive hydrocephalus. On imaging studies, these lesions may be suspected by visualizing midline or paraxial intracranial calcifications.

Although resection is the treatment of choice, many neonatal intracranial teratomas are not resectable. Palliative shunting to alleviate intracranial pressure and hydrocephalus has little long-term benefit. Moreover, in some infants, shunting has been associated with extracranial spread of tumor. The role and effectiveness of chemotherapy remain undefined for this subgroup of patients.

Long-term survival is predicated on complete tumor removal. Outcomes are significantly worse for patients with extensive intracranial involvement that is not amenable to complete resection. Survival for these patients is reportedly between 15% and 20% [92].

9.3.2.2 Cervicofacial Teratomas

Cervical teratomas are extremely rare neoplasms. They occur with an estimated incidence of 1:40 000 to 1:80 000 live births and account for 2% of all neonatal tumors [93, 94]. Although most cervical teratomas are histologically benign, they frequently cause significant airway and esophageal obstruction in the perinatal period and are thus potentially fatal. Primary tumor sites include the tongue, nasopharynx, palate, sinus, mandible, tonsil, anterior neck, and thyroid gland. Males and females are equally affected.

Prenatal US is a reliable and essential diagnostic tool for detecting these lesions in utero, allowing for careful arrangement of the time, mode, and place of delivery (Fig. 9.9). When large cervical teratomas are prenatally detected, findings generally reveal multiloculated irregular masses with both solid and cystic components [95]. To delineate anatomy more clearly, fetal MR imaging is the diagnostic imaging study of choice. Of cases detected prenatally, lymphatic malformation (cystic hygroma) is the most likely entity to be mistaken for cervical teratoma. Similarities in size, sonographic findings, clinical characteristics, location, and gestational age at presentation can make this distinction difficult [96]. Other lesions to be considered in the differential diagnosis include large branchial cleft cyst and congenital thyroid goiter. Because fewer than 30% of cervical teratomas are associated with elevated serum AFP levels, this assay is not particularly helpful in the differential diagnosis of fetal cervical masses [70]. Approximately one third of prenatally diagnosed cases are complicated by maternal polyhydramnios, due to esophageal obstruction and/or interference with fetal swallowing. There is a high incidence of preterm labor and delivery that may be related to increased uterine size resulting from polyhydramnios and/or tumor.

Cervical teratomas are generally large and bulky, often measuring 5–12 cm in diameter (Fig. 9.9b). Tumor masses greater than the size of the fetal head have been reported [96–98], as has involvement of the oral floor, protrusion into the oral cavity (epignathus), and extension into the superior mediastinum [97]. Massive lesions may cause dystocia, requiring a cesarean section to deliver the baby. Various anomalies occurring in association with cervical teratomas have been reported. These include craniofacial and central nervous system anomalies, hypoplastic left ventricle, trisomy

13, and a case each of chondrodystrophia fetalis and imperforate anus [93]. Mandibular hypoplasia also has been seen as a direct result of mass effect on the developing mandible [70].

Up to 50% of cervicofacial teratomas have calcifications present and these are often seen more easily on postnatal plain radiographs [95]. When calcifications are present in a partially cystic and solid neck mass, they are virtually diagnostic of cervical teratoma [95]. A postnatal CT scan is particularly useful in delineating the anatomic extent and precise involvement of the neoplasm.

As shown in a number of series [93, 97–101], airway obstruction at birth is life threatening and associated with a high mortality rate. In patients with massive fetal neck masses, this is generally associated with a delay in obtaining an airway and ineffective ventilation. Delay in acquiring an adequate airway can result in hypoxia and acidosis and if longer than 5 min, can result in anoxic injury. In light of these concerns, most cervicofacial teratomas are definitively treated immediately after delivery, which preferably should take place at a tertiary care center with an expert perinatal team that includes a pediatric surgeon. Optimally, if a cesarean section is performed, maternal-fetal placental circulation should be maintained while an airway is secured. This is accomplished by employing an EXIT procedure; this allows time to perform procedures such as direct laryngoscopy, bronchoscopy, tracheostomy, surfactant administration, and cyst decompression, which may be required to secure the airway [70]. Because precipitous airway obstruction may occur due to hemorrhage into the tumor, orotracheal intubation is indicated in all patients, regardless of the presence or absence of symptoms.

In some reported series [101–103], infants have either had acute airway obstruction or lost a previously secure orotracheal airway within a few hours or days after delivery. Because early resection after stabilization is the most effective method of achieving total airway control, it is the treatment of choice. Delaying surgery can have other serious ramifications, including retention of secretions, atelectasis, and/or pneumonia due to interference with swallowing [49, 96]. Resection also removes the risk of malignant degeneration, which occurs at much higher frequencies (>90%) in cases of cervical teratomas that are not diagnosed or treated until late adolescence or adulthood [104].

To minimize operative morbidity, dissection of the teratoma should begin in areas distant to important regional nerves. Cervical teratomas often have a pseudocapsule, which facilitates gentle elevation of the tumor out of the neck. If the tumor arises from the thyroid gland, the involved thyroid lobe is excised in continuity with the teratoma. As glial metastases may be present, any enlarged lymph nodes should be excised with the tumor. After excision, a drain is left in place for 24–48 h. Because these tumors are often large, envelopment of vital anatomic structures in the neck is common. In some cases, complete tumor excision with acceptable functional and cosmetic results can be achieved only by staged procedures.

In contrast to the high incidence of malignancy (>60%) in adults, malignant cervicofacial teratomas with metastases are comparatively uncommon in neonates, with a reported incidence of 20% [93]. Despite the existence of poorly differentiated or undifferentiated tissue in the primary tumor, many infants remain free from recurrence following complete resection of a cervical teratoma. Such cases suggest that malignant biologic behavior is uncommon in this population [95, 96]. Reported findings show a number of consistent histologic patterns [93]. Neuroectodermal elements and immature neural tissue are the most commonly observed tissues in metastatic foci. In approximately one third of cases, the metastases are more differentiated but confined to regional lymph nodes. Patients with isolated regional lymph node metastases who are treated with excision of the primary tumor generally survive free of disease [46]. This supports the concept that the presence of metastases containing only differentiated tumor usually correlates with a good prognosis.

There are currently no chemotherapy guidelines for neonates with malignant cervical teratomas. Based on results in their series, however, Azizkhan, et al. [93] have recommended that this modality be reserved for infants with disseminated disease (undifferentiated lesions) and those who have invasive tumors and residual disease after resection.

Although cervical teratoma is generally a benign tumor, the possibility of malignant transformation mandates close surveillance for tumor recurrence. Serum AFP levels should be monitored at 3-month intervals in infancy and annually thereafter, with a rising level alerting the clinician to possible tumor recurrence. As previously discussed, serum AFP levels must be interpreted with caution and viewed within the framework of their natural half-life. Imaging studies twice a year for the first 3 years of life are also recommended. Since the thyroid and parathyroid glands may be removed or affected by tumor excision, the risk of temporary or permanent hypothyroidism must be considered. If encountered, these complications must be monitored and managed appropriately.

9.3.2.3 Retroperitoneal Teratomas

The retroperitoneum is the third most common extragonadal site for occurrence of teratoma, accounting for 2–5% of all pediatric cases [105, 106]. Most lesions

are observed in early infancy and 50% are identified in the first year of life [59, 92]. Females are more commonly affected (2:1) than males. Infants generally present with a palpable abdominal mass. CT or MR imaging of the abdomen helps differentiate this neoplasm from the more commonly occurring neuroblastoma or Wilms' tumor. Laparotomy or a minimally invasive laparoscopic approach is used to achieve complete tumor resection; however, larger lesions are more likely to require an open procedure. Although an overall malignancy rate of 7% has been documented in children with teratomas, approximately 24% of retroperitoneal teratomas diagnosed during the first postnatal month have been found to be malignant, based on histology or clinical course [107]. Additionally, 30–40% of tumors have histologically immature elements. Malignant recurrence has been reported in patients with benign retroperitoneal teratomas containing immature components. As such, malignant lesions and lesions containing high-grade immature elements should be treated with adjuvant cisplatin-based chemotherapy following resection [106].

9.4 Neuroblastoma

Neuroblastoma arises from neural crest cells and can present anywhere along the sympathetic chain, including the adrenal medulla and sympathetic ganglia. It is the second most common tumor diagnosed in the neonatal period, with a reported incidence of 5–8 per million live births [108, 109]. It is also the most common neonatal malignancy, accounting for nearly one third of all malignancies diagnosed in newborns [108, 109]. Autopsy series of infants who have died from unrelated causes indicate an occurrence rate (in situ neuroblastomas) far exceeding the reported incidence of neuroblastoma [110, 111]. Most of these tumors are occult and known to regress spontaneously.

Up to 80% of neuroblastomas have recognizable and abnormal chromosomal patterns. In most cases, the defect is found on chromosomes 1 and 17 [18]; however, other abnormalities have been identified at 4p, 6q, 9q, 10q, 11q, 12q, 13q, 14q, 16q, 22p, and 22q [112]. The most important of these abnormalities are N-myc amplifications, deletions of chromosome 1p, and aneuploidy [18, 113–115]. Amplification of the N-myc oncogene is associated with a more aggressive tumor type that often presents with advanced stage disease. As such, it is considered a critical prognostic factor [18, 33, 113–115].

9.4.1 Clinical Presentation

The most common presentation of neonatal neuroblastoma is an abdominal mass arising from the adrenal gland. Primary lesions also can occur in the neck, mediastinum, retroperitoneum, and pelvis. Symptoms vary, depending on the anatomic location of the tumor, its physiology, and its mass effect. Nearly half of tumors have metastases at diagnosis, most commonly to the liver [116]. Hepatomegaly or massive abdominal distention associated with respiratory compromise may be the initial findings in patients with disseminated disease. These patients also may have skin nodules and bone marrow involvement (stage 4S).

Most neuroblastomas diagnosed during the neonatal period present as solid lesions, although cystic lesions have been described; such lesions may arise from an adrenal cyst or develop as a result of hemorrhage or degeneration within a solid neuroblastoma [117].

9.4.2 Diagnostic Evaluation

9.4.3 Antenatal

The routine use of antenatal US has increasingly identified the presence of adrenal tumors and other intra-abdominal masses [118–121]. Fetal MRI may be required to help distinguish neuroblastomas from other mass lesions [122]. Unlike neuroblastomas diagnosed during the neonatal period, prenatally diagnosed lesions often have a cystic component [119]. More than 90% of these cystic tumors arise in the adrenal grand, suggesting a link between perinatal tumors and the nodular collections of neuroblasts that are part of normal adrenal development [123]. Moreover, there is evidence that cystic tumors are caused by a disturbance in the natural course of neuroblastic nodule regression [123]. Most antenatally diagnosed cystic tumors are stage 1, 2, or 4S and usually have favorable biological characteristics. Evidence indicates that these lesions have a tendency to regress spontaneously [124].

Although increased urinary excretion of catecholamine metabolites is found in most children with neuroblastoma, a significant percentage of infants in whom there is a fetal diagnosis of intra-abdominal neuroblastoma have negative markers, reflecting the presence of a nonfunctioning tumor [117, 125, 126.]. Catecholamine-secreting fetal tumors are sometimes recognized, however, by the onset of maternal hypertension or pre-eclampsia appearing in the last trimester of pregnancy [127]. These offspring usually have either stage 4 or 4S disease or multiple metastases to the placenta [118].

9.4.4 Postnatal

Imaging studies are required during the postnatal period to differentiate neuroblastomas from adrenal hemorrhage, renal masses, and intra-abdominal extralobar sequestration. Diagnosis is confirmed by biopsy of the primary or metastatic tumor foci. As most neuroblastomas secrete varying quantities of catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA), these values should be checked by random urine studies [128, 129]. Open biopsy should be avoided in neonates with massive liver involvement and in those that are high surgical risks due to impaired ventilation or concern about wound closure. In such patients, elevated urinary catecholamine levels and a positive bone marrow aspirate are sufficient to confirm the diagnosis. Tissue samples also should be analyzed for histology, amplification of the N-myc oncogene, chromosome IP, other tumor markers (e.g. TrK-A) and for ploidy, which significantly affect prognosis [113–115].

Staging requires CT or MRI scans of the primary lesion and suspected metastatic sites. A technetium or MIGB bone scan should be obtained to identify possible cortical bone metastases.

9.4.5 Stage 4S Disease

Infants younger than 1 year of age often present with a pattern of metastatic disease (stage 4S) that is unique to this age group. Stage 4S infants may have a small or undetectable primary neuroblastoma with metastases to the liver, skin, and bone marrow [130, 131]. The adrenal is the most common primary site. Skin lesions typically present as multiple bluish subcutaneous nodules. Stage 4S tumors exhibit particularly interesting biologic behavior. Most (75%) of these tumors regress spontaneously during infancy [132, 133]. Frequently, however, newborns with massive hepatic involvement are subject to a wide spectrum of significant respiratory and cardiovascular problems that may be fatal.

9.4.6 Treatment and Prognosis

Treatment strategies are based on stage and biologic features. As most oncologic studies do not segregate neonates from the broader grouping of infants younger than age 1 year, information pertaining to both treatment and prognosis in this specific age group is scant. Overall survival rates of infants younger than age 1 year, however, are known to be significantly greater than those of older children.

9.4.6.1 Stages 1 and 2

Neonates with stage 1 or 2 disease are considered to be at low risk regardless of biologic tumor features. Surgery alone is generally sufficient to control disease, and survival is nearly 100% [116]. In patients with stage 2 disease without N-myc amplification, residual microscopic disease usually regresses without additional intervention.

9.4.6.2 Cystic Neuroblastoma

Most prenatally diagnosed cystic neuroblastomas are localized and exhibit favorable biologic features. These tumors are usually associated with an almost universally favorable outcome [119, 121, 124]. As with low-stage solid tumors, cystic tumors are typically managed with resection.

Because of uniformly positive outcomes, as well as evidence that some cystic lesions regress spontaneously [124], the Children's Oncology Group (COG) has initiated a prospective study to investigate the effectiveness of observation alone as a management strategy. In the current protocol, serial sonograms are used to monitor the mass during the first few months of life to determine if tumor regression is ongoing. Surgical resection is reserved only for cystic tumors that fail to regress or increase in size [123]. To date, results of this study have not been reported.

9.4.6.3 Stages 3 and 4

The incidence of stage 3 and 4 tumors in neonates and infants younger than 1 year is lower than that in older children [131]. Infants with stage 3 disease generally undergo several cycles of combination chemotherapy followed by delayed primary resection. Those without N-myc amplification have an excellent prognosis and enjoy a 90% event-free survival [134]. Infants with stage 4 disease without N-myc amplification do not fare as well. Although studies show variable survival rates, these rates exceed 50% [135–137].

Infants with stage 3 or 4 disease and N-myc amplification are considered to be a particularly high-risk group, requiring more intensive high-dose chemotherapy and radiation therapy and possible bone marrow rescue. Despite this approach, those with more than 10 copies of the N-myc oncogene have rapidly progressive disease and frequently die [137].

9.4.6.4 Stage 4S

The survival rate of infants with stage 4S disease is greater than 80%, often without specific treatment [138, 139]. Most patients have favorable genetic and biologic factors, including high proto-oncogene Trk-A expression, absence of N-myc amplification, favorable histology, and no evidence of allelic loss of chromosome 1p [138.].

Despite the high rate of spontaneous tumor regression, progressive hepatomegaly may lead to respiratory embarrassment or inferior vena caval compression. In these patients, low-dose radiation to the liver (1–1.5 Gy per day over several days, with a total dose of 6–12 Gy) and low-dose chemotherapy (cyclophosphamide, 5 mg/kg per day) are used to accelerate tumor regression. As a measure of last resort, some surgeons have released the intra-abdominal compartment syndrome by creating a ventral hernia, using a large silastic patch to cover the surgical defect. This approach is generally not effective and therefore is no longer advocated.

A small subset of stage 4S patients with adverse genetic and biologic prognostic factors (e.g., more than 10 copies of N-myc and chromosome 1p deletion) require more aggressive therapy, including resection of the primary tumor, if identified. In cases with massive hepatic involvement, resection of the primary tumor confers no benefit in terms of survival. Most deaths in stage 4S occur in infants younger than 2 months of age with severe symptoms due to hepatomegaly. As compared to older infants, this younger group exhibits less tolerance to therapy [131, 139].

9.5 Soft Tissue Sarcomas

More than 75% of soft tissue masses in children younger than age 1 year are benign lesions of vascular or fibromuscular origin. Soft tissue sarcomas diagnosed during the neonatal period are extremely rare, accounting for approximately 10% of all neonatal malignant tumors and only 2% of all childhood sarcomas [3, 14, 140]. (Fig. 9.10) These tumors falls into three diagnostic groups, including congenital fibrosarcoma, rhabdomyosarcoma, and an exceedingly rare and diverse group of tumors sometimes collectively referred to non-rhabdomyosarcoma soft tissue sarcomas. Soft tissue sarcomas usually present as a mass on physical examination. Imaging studies are used to assess evidence of local or distant spread. In some patients, diagnostic bone marrow aspiration also may be used to rule out bone marrow involvement.

Soft tissue sarcomas differ in their natural history and their response to chemotherapy and radiotherapy. In view of the known long-term effects of radiotherapy, this should be used only as a treatment of last resort. Surgery plays a major role both in establishing the diagnosis and in tumor management, especially in neonates. Optimally, localized soft-tissues masses are treated by wide excision with a clear margin, if this can be achieved without compromising function, growth, or appearance [141].

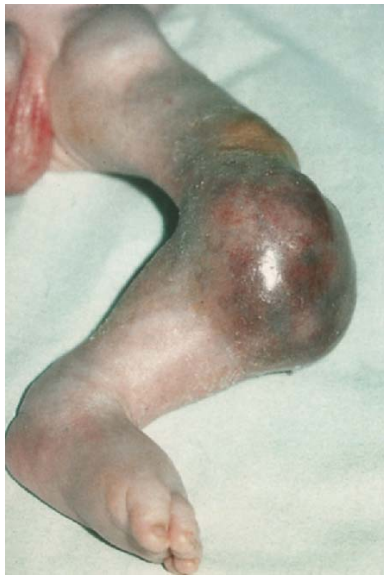

Fig. 9.10 Clinical photograph of a neonate with a sarcoma of the knee with metastatic spread to groin lymph nodes.

9.5.1 Congenital Fibrosarcoma

Congenital fibrosarcoma is a well-recognized tumor with a low metastatic rate and a five-year disease-free survival greater than 90% [142–144]. It is characterized by the t (12;15) chromosomal translocation involving the ETV6 and NTRK3 genes, which is not found in fibrosarcomas that occur later in childhood [145, 146]. Congenital fibrosarcoma most commonly occurs in the extremities, but may arise in the back, retroperitoneum, sacrococcyx, and head and neck. The incidence of this tumor is higher in the first 6 months of life, and approximately one third of tumors diagnosed before age 5 are diagnosed shortly after birth [142, 147]. Spontaneous resolution of congenital fibrosarcomas has been documented [141].

Primary excision is the first line of treatment. Large bulky neoplasms that are not amenable to limb-sparing surgical procedures can be managed with perioperative chemotherapy (vincristine, actinomycin D, and cyclophosphamide) [141, 144]. This approach allows for delayed and less extensive resection that might otherwise result in significant mutilation or morbidity.

In some cases, chemotherapy may even lead to complete remission, thus eliminating the need for excision [141]. Although metastases are uncommon, local tumor control may be exceedingly difficult, with tumor recurrence reported as high as 40% [140, 142, 143, 147, 148]. In general, prognosis is not adversely affected by local tumor recurrence or metastatic spread, although exceptions have been reported [149].

9.5.2 Rhabdomyosarcoma

Because less than 5% of all rhabdomyosarcomas present in patients younger than age 1 year, data pertaining to neonatal rhabdomyosarcoma is extremely limited. In an Intergroup Rhabdomyosarcoma Study (IRS) reported in 1994, there were only 14 neonates in a study group of 3,217 patients, an incidence of 0.4% [43].

Two histologic subtypes of rhabdomyosarcoma have been described: embryonal and alveolar. These subtypes have differing clinical behaviors and are associated with distinct chromosomal translocations. The predominant histologic subtype in rhabdomyosarcomas presenting in neonates is embryonal. These lesions are associated with allelic loss of the 11p15 region [150].

Approximately half of neonatal rhabdomyosarcomas arise in the bladder, vagina, testicular, and sacrococcygeal regions [151]. In a multi-institutional Children's Cancer Group (CCG) study reported in 1995, a common characteristic of neonatal rhabdomyosarcoma was its aggressive biologic behavior as half of the patients had widespread disease at the time of diagnosis [140]. Metastatic disease can appear in the lungs, lymph nodes, liver, bone marrow, bone, and brain [152, 153].

Treatment of rhabdomyosarcoma comprises multimodal therapy with surgery and combination chemotherapy. The most effective chemotherapy regimen is considered to be vincristine, actinomycin D, and cyclophosphamide [154, 155]. Complete resection of nonmetastatic primaries is recommended if it can be accomplished with acceptable morbidity. Radiotherapy is reserved for infants with gross or microscopic residual disease. Prognosis depends on stage at presentation, histologic characteristics of the lesion, and the location of the primary tumor. Infants with embryonal histology and complete surgical resection do well, with cure rates higher than 90% [154]. Those with primary tumors in the head and neck (except parameningeal) and genitourinary region enjoy this same favorable prognosis [154]. Infants with metastatic disease at diagnosis do not fare well, with long-term survival rates of 25% [155].

9.5.3 Non-Rhabdomyosarcoma Soft Tissue Sarcomas

Other neonatal soft tissue sarcomas are exceedingly rare, with published experiences consisting only of small series or case reports. The previously cited CCG study reported nine neonates with non-rhabdomyosarcoma soft tissue sarcomas [140]. In seven of these nine patients, tumors were diagnosed at birth. Four patients had evidence of extensive regional spread or metastatic disease at the time of diagnosis. The pathology included malignant mesenchymal sarcoma (n=4), primitive sarcoma (n=1), angiosarcoma (n=1), chondrosarcoma (n=1), rhabdoid sarcoma (n=1), and the remaining tumor was unclassified. Primary tumor sites were head and neck, extremities, and trunk. Tumor management was based on location, biology, and resectability. Five of the nine newborns in this study survived (mean follow-up, 9 years). These patients had localized disease at the time of surgery. Four infants had complete surgical resections, and one had microscopic disease at the surgical site; this patient was treated with chemotherapy. All patients with unresectable regional or metastatic disease died despite adjuvant chemotherapy.

9.6 Renal Tumors

Solid renal neoplasms are extremely rare in neonates, accounting for only 8% of neonatal tumors [15, 16]. The most common tumor of the kidney in the neonate is congenital mesoblastic nephroma (CMN), which accounts for approximately 75% of the renal neoplasms in this age group [156]. This is followed by Wilms' tumor, which has an incidence in neonates lower than 0.2% [156, 157].

9.6.1 Congenital Mesoblastic Nephroma

CMN is a benign mesenchymal renal tumor that is histologically characterized by the proliferation of spindle-shaped cells arranged in fascicles that separate normal renal parenchymal tissue. This tumor occurs more commonly in males (2:1). Most neonates with CMN present with a palpable, nontender abdominal mass but hematuria, hypertension, and vomiting can occur (Fig. 9.11a, b). Although prenatal US has enabled detection of some renal neoplasms in utero, there are no specific prenatal sonographic characteristics that reliably distinguish between CMN and Wilms' tumor [158]. Based on incidence alone, however, a renal tumor presenting during the newborn period is more likely to be a CMN. Postnatal imaging modalities such as MRI can be useful in making a more precise diag-

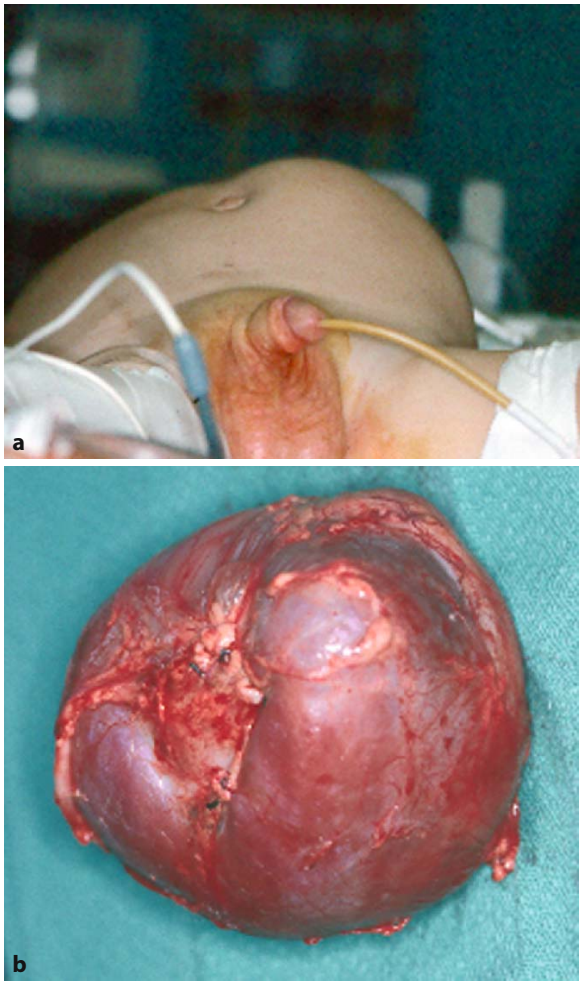

Fig. 9.11 (**a**) A 3-week-old infant with a congenital mesoblastic nephroma (**b**) Operative specimen

nosis but also are limited in distinguishing between the two tumors. Histologic assessment thus remains essential for establishing a definitive diagnosis [159].

Most cases of CMN are confined to the renal capsule, and as such, nephrectomy is curative. In some patients, however, the growth pattern is one of local invasion and extension through the renal capsule. During the course of resection, these tumors may be particularly friable and prone to intraoperative bleeding and rupture [15, 160]. Despite these possible complications, a survival rate exceeding 90% has been reported [15]. Metastases, which rarely occur, are managed with chemotherapy [161].

9.6.2 Wilms' Tumor

Wilms' tumor is thought to arise from nephrogenic rests that persist beyond 36 weeks of gestation [162]. Unlike CMN, this tumor affects both sexes equally [163, 164]. Both WAGR syndrome (Wilms, aniridia, genitourinary tract abnormalities, mental retardation) and Beckwith-Wiedemann syndrome (gigantism, omphalocele, macroglossia, hemihypertrophy) are associated with an increased risk of developing Wilms' tumor. These syndromes are associated with a loss of function of the WT1 gene at chromosome band 11p13 (WAGR) [165] or WT2 at chromosome band 11p15 (BWS) [166]. Among patients with Wilms' tumor who have no identifiable syndrome, approximately 40% have abnormalities in expression of WT1 and WT2 [167].

As with CMN, Wilms' tumor in neonates usually presents as a nontender abdominal mass. Most tumors are low stage and have favorable histology, however, metastatic disease can occur [157, 168]. The most common site of metastasis is the lungs. Primary excision of the tumor and chemotherapy are currently the mainstay of treatment, resulting in cure rates of greater than 90% [157, 168]. In light of this favorable prognosis, a recent COG protocol for infants with small (<550 g) stage I tumors compared treatment with surgery alone to treatment with surgery and a brief course of adjuvant chemotherapy [169]. Recurrence rates in the cohort who received surgery alone approached 15%, thus resulting in early closure of this arm of the study. Fortunately, most of these patients were treated successfully with salvage chemotherapy. Higher stage disease mandates more intensive chemotherapy, and in some patients, radiation therapy.

9.7 Liver Tumors

Primary liver tumors are extremely rare and account for only 2% of neonatal neoplasms [170]. They include a wide spectrum of benign and malignant neoplasms that occur with a distribution that is different from that in older children [171]. Most benign neonatal liver tumors are of vascular origin. The nosology of these tumors remains inconsistent and confusing. Many liver lesions that were formerly referred to as infantile hemangioendotheliomas are now considered to be hepatic hemangiomas. These lesions are generally asymptomatic and are incidental findings on prenatal or postnatal US. When symptomatic, however, hepatic hemangiomas are associated with serious and/or life-threatening complications. The second most common benign liver tumor of neonates and infants is mesenchymal hamartoma. The most common neonatal malignant liver tumor is hepatoblastoma; however, less than 10% of these tumors occur during the neonatal period [171].

9.7.1 Infantile Hepatic Hemangiomas

Unlike cutaneous hemangiomas of infancy, hepatic hemangiomas are rarely seen. These lesions follow a natural history similar to that of cutaneous lesions, and as with cutaneous lesions, they occur more commonly in females. Most hepatic hemangiomas are asymptomatic and incidentally discovered during imaging of the abdomen. Diffuse involvement of the liver is more often associated with severe complications during the proliferative phase, such as high output cardiac failure, hepatic dysfunction, abdominal compartment syndrome, and hypothyroidism. Significant symptoms or complications generally become evident during the first 3–4 months of life. Cutaneous hemangiomas are frequently the first indication of potential visceral involvement; however, hepatic and other visceral hemangiomas also can occur without cutaneous involvement [172].

Hepatic hemangiomas present variably, from tiny asymptomatic tumors that are detected incidentally to large (>5 cm in diameter) single, or multiple tumors that may or may not be associated with high output cardiac states. Infants are frequently seen with a triad of hepatomegaly, anemia, and high-output cardiac failure [173]. A systolic bruit may occasionally be heard over the enlarged liver. In rare cases, progressive and massive liver enlargement may cause abdominal compartment syndrome, resulting in life-threatening visceral ischemia and ventilatory failure [174].

US of the liver in infants with multiple or solitary lesions is useful both for initial screening and for following up of lesions that are well characterized. US demonstates either a single lesion or multiple lesions with draining veins and often a dilated proximal abdominal aorta. There may also be signs of significant intrahepatic shunting. US may also detect large hepatic lesions antenatally [175].

MRI is the imaging technique of choice for completely defining the extent and location of hepatic hemangiomas and their relationship to vascular structures. Although imaging features vary, most lesions appear as focal or multifocal T2-hyperintense spheres with centripetal contrast enhancement and dilated feeding and draining vessels (Fig. 9.12a). Three atypical patterns have also been found which include focal mass lesions with a large central varix with or without direct shunts, focal mass lesions with central necrosis or thrombosis, and massive hemangiomatous involvement of the liver with abdominal vascular compression [176]. The latter pattern of massive replacement of liver is associated with abdominal compartment syndrome, hypothyroidism, and a high mortality rate. Hypothyroidism is attributed to high levels of type 3 iodothyronine deiodinase activity produced by hemangiomas; this activity inactivates circulating thyroid hormone [177]. Patients with diffuse liver hemangiomatosis should undergo screening for hypothyroidism. Because an abnormal thyroid-stimulating hormone level may not develop until a hemangioma proliferates, repeat testing is indicated when lesions undergo considerable growth. For patients with diffuse hemangiomatosis, high-output cardiac failure, and compartment syndrome the mortality rate exceeds 50%.

Angiography also is performed to define lesions prior to instituting embolic therapy. Angiographic features of hepatic hemangiomas are variable, ranging from discrete hypervascular tumors to diffuse tumors with macroscopic arteriovenous, arterioportal, and portosystemic shunting [173, 178]. Because hepatic hemangioma and arteriovenous malformations are rheologically fast flow, they may be mistaken for one another; however, arteriovenous malformations are extremely rare. Large solitary lesions diagnosed antenatally or soon after birth are likely to be congenital hemangiomas that are characterized by central necrosis of the lesion, capillary proliferation in the periphery of the lesion, and indistinct lesion margins due to abnormally large vessels extending into the adjacent liver tissue (Fig. 9.12b).

When imaging features are atypical and the diagnosis is unclear, incisional or excisional biopsies are extremely helpful in determining the pathology of a lesion and the most appropriate course of treatment. Differential diagnosis includes neuroblastoma, hepatoblastoma, and mesenchymal hamartomas, as well as a number of other neoplasms.

Most infantile hepatic hemangiomas, including those detected incidentally on imaging studies, remain asymptomatic throughout their natural clinical course. Patients with focal lesions without high flow seen on Doppler US generally do not require treatment [176]. Those patients with small, asymptomatic lesions should be followed with sequential physical examinations and US studies. Treatment should be reserved for infants with enlarged lesions that cause significant symptoms or complications.

Either systemic oral or intravenous corticosteroid therapy is the initial treatment of choice, depending on the severity of symptoms. For unstable patients, intravenous corticosteroids are preferred. In the protocol currently followed at Cincinnati Children's Hospital Medical Center, high doses of methylprednisolone are administered at a daily dose of 30 mg/kg for 3 days. This is followed by a daily dose of 20 mg/kg for 4 days and then a daily dose of 10, 5, 2, and 1 mg/kg for 1 week, with each dose given once daily before 8:00 am. Patients who are relatively stable are treated with oral corticosteroid therapy. Oral prednisone or prednisolone is administered at an initial dose of at least 3 mg/kg/day for 1 month. If the lesion responds to treatment, the patient is continued on this dose for

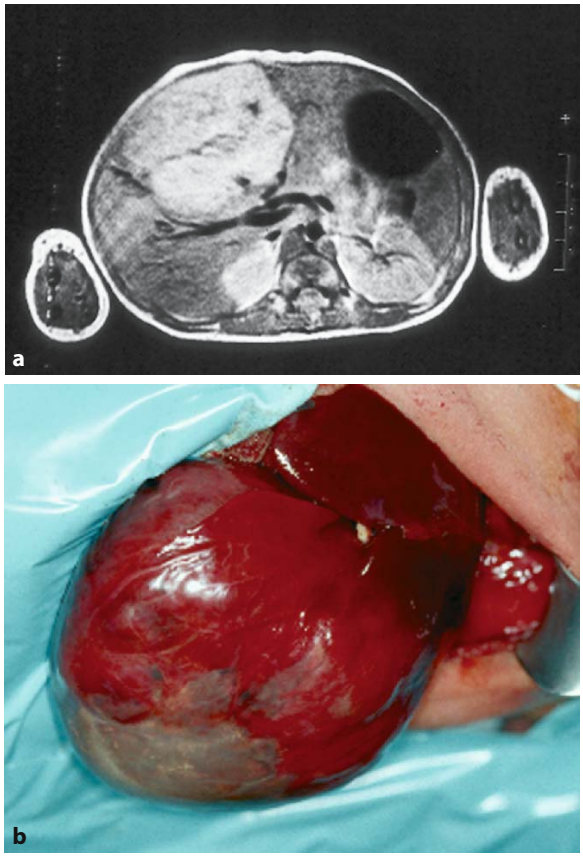

Fig. 9.12 (**a**) MRI of the liver demonstrating a large intrahepatic hemangioma (**b**) Operative photograph showing large hemangioma of the liver in a 1-month-old infant

another 4 weeks. The daily dose is then gradually lowered to 1 mg/kg/day, and is generally maintained for up to 4 months, and occasionally 6 months. If no response is seen with this dosing regimen, an attempt is made to titrate the dose to an upper limit of 5 mg/kg/day in order to effect a response. If this fails, the dose is rapidly tapered, the infant is taken off the medication, and other treatment approaches are instituted. Because rebound growth can occur if the steroids are discontinued before the end of the proliferative phase, patients should be monitored while being weaned from medication.

For lesions that are unresponsive to steroids, vincristine is the current drug of choice. Because it is a vesicant, it is best delivered through central venous access. An initial weekly dose of 0.05–1 mg/m2 is administered by intravenous injection. This dose is then tapered, increasing the interval between injections depending on the clinical response. Treatment is administered for 4–6 months.

The angiogenesis inhibitor interferon-α is also occasionally used for lesions that are refractory to corticosteroid therapy. It is typically administered as a daily subcutaneous injection at a dosage range of 1–3 million units/m2. Because of its known neurotoxicity, particularly its association with spastic diplegia [179, 180], the use of interferon-α in children younger than age 1 year should be avoided.

In patients with persistent high-output cardiac failure, angiography and embolization may be performed, with the latter being useful only if there are direct macrovascular shunts through the lesion. Because angiography and embolization are associated with risk of injury to the femoral access vessel or inadvertently embolized visceral vessels, it should be performed only by an interventional radiologist with skill and experience with these techniques in infants.

Other treatment options reserved for refractory lesions include surgical resection of large solitary lesions, hepatic artery ligation, and liver transplantation. Prior to contemporary pharmacologic therapy, resection of solitary lesions and embolization were frequently the only viable treatment options. Because they are associated with extremely high mortality, however, they are now infrequently performed. A review of the literature reported in 2003 described 35 cases treated by hepatic artery ligation with a survival rate of 80% [181]. Liver transplantation is rarely performed, and is reserved for patients in whom there is diffuse hepatic involvement and an imminent risk of death [182].

9.7.2 Mesenchymal Hamartomas

Mesenchymal hamartomas typically present as a large, palpable, nontender cystic liver mass, more common in the right lobe. Lesions are generally diagnosed during the first 2 years of life but have been reported in the newborn [171]. The mass is usually encapsulated, although occasionally it can infiltrate into the hepatic parenchyma and can cause respiratory distress or heart failure resulting from arteriovenous shunting. Although spontaneous tumor regression can occur, cases of massive local recurrence and later transformation to undifferentiated sarcoma have been reported [183–185]. Thus, when feasible, complete surgical resection is the treatment of choice.

9.7.3 Hepatoblastoma

Hepatoblastoma is an embryonal neoplasm composed of malignant epithelial tissue with variable differentiation, most often with embryonal or fetal components [171]. There is an increased incidence of this tumor among patients with Beckwith-Weidemann syndrome, Li-Fraumeni syndrome, or hemihypertrophy [186–188], and familial adenomatous polyposis [189].

There also is an increased incidence of hepatoblastoma among surviving premature infants [190, 191], with risk increasing with lower birth weight [192].

Hepatoblastomas can be detected prenatally by abdominal US and can cause polyhydramnios and stillbirth [193]. Tumor rupture and massive hemorrhage have been described following delivery [194, 195]. Postnatally, hepatoblastoma presents with abdominal enlargement and hepatomegaly. The lungs are the primary site of metastasis, though bone and brain involvement can occur. AFP levels are elevated in most patients and are especially useful in monitoring disease status following treatment.

Complete surgical resection and subsequent chemotherapy with cytotoxic agents (e.g., cisplatin and doxorubicin) is the treatment of choice [196, 197]. For neonates with lesions that initially are not resectable, preoperative chemotherapy can be beneficial. For patients with unresectable tumors confined to the liver, hepatic transplantation is an alternative [182]. Prognosis is largely dependent on resectability. Approximately two thirds of patients with tumors that are initially unresectable can be cured with chemotherapy followed by surgical resection and additional postoperative chemotherapy [198, 199].

9.8 Retinoblastoma

Retinoblastoma is a rare tumor that presents occasionally at birth. Forty percent of cases have been shown to result from inheritance of a germline mutation in the RB1 gene [200, 201]. The tumor is detected by absence of the normal red reflex when the infant's eyes are examined with an ophthalmoscope. All newborns should be screened for this reflex and any infant with a family history of retinoblastoma should undergo a comprehensive ophthalmologic examination. These patients are at risk for bilateral involvement.

When detected early, retinoblastoma usually is curable [202–204]. When disease is intraocular, laser therapy or cryotherapy are used either with or without adjuvant chemotherapy, depending on the size of the lesion. In selective cases, radiotherapy is also used to salvage vision. Extensive intraocular disease can be managed with enucleation [205]. Metastatic disease requires aggressive chemotherapy [206, 207].

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