Neonatal oncology: diagnostics and management

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SUMMARY

Tumors are rarely diagnosed in newborns. Natural history of such tumors, their type, and response to treatment differ from those seen in older children. The etiology is still unclear. In this paper, a retrospective study is presented of diagnostics and management of neonatal tumors from 2008 to 2012. Out of 518 neonatal admissions in that period, tumors were diagnosed in 15 patients (2.8%), in only 3 of them (20.0%) prenatally. The diagnosed tumors were teratomas (4), retroperitoneal (4), and liver tumors (7). Ten of them (66.6%) had a natural history of benign tumors. Complete surgical excision was the treatment of choice in 10 (66.6%) cases and there was no need for adjuvant chemotherapy.

Key words: *Medical Oncology; Neonatology; Neoplasms; Diagnosis*

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INTRODUCTION

Errors in embryonic development and fetal maturation may result in embryonic tumors. Antenatal sonography can indicate fetal tumor and if it is detected a multidisciplinary team of doctors are involved in addressing problems that may occur during pregnancy, labor, and immediate postnatal life.

Although real causes of congenital tumors are unknown, their association with other congenital abnormalities is well recognized (1). In some cases intrauterine environmental factors may be important (2), and even transplacental spread of maternal tumor has been reported (3). Neoplastic transformation of cells, carcinogenesis, is a dynamic, multistep and complex process that can be divided into three phases with different times of development, expression and presentation (4).

The reported incidence of neonatal tumors varies, since most reports are based on experiences of a single institution (5). Perhaps the actual incidence is even harder to evaluate regarding the difficulties related to distinction between classifying neonatal tumors as tumors or as congenital abnormalities.

Neonatal neoplasms differ in their prognosis as well as in distribution, histological type, and tumor site. Some neonatal and infantile tumors show benign behavior despite histological evidence of malignancy. Examples include some congenital neuroblastomas and hepatoblastomas in the first year of life, and sacrococcygeal teratomas in the first few months of life. The factors responsible for this "oncogenic period of grace," which starts *in utero* and extends through the first few months of extrauterine life, are uncertain (6).

This is a five-year retrospective single institution experience of tumors diagnosed in the first month of life. There were 518 neonatal admissions to Pediatric Surgery Hospital in the Institute for Children and Youth Health Care of Vojvodina of Novi Sad over the period observed. Tumors were diagnosed in 15 patients (2.8%), only 3 (20.0%) prenatally.

Teratomas

Teratomas are the most frequent perinatal neoplasms, containing tissue derived from three germinal layers. In children, they usually occur as extragonadal masses, about 40% to 50% in the sacrococcygeal region (7).

The incidence of sacrococcygeal teratomas (SCTs) is 1 in 35,000-40,000 live births, with a female predominance in a 3:1 ratio (8). Most of SCTs are benign, but about 20% are malignant (9).

They are usually large, round or lobulated, well encapsulated swellings extruding from the coccyx, although the whole tumor or a part of it may be presacral. The cut surface of teratomas can vary in appearance: it may be predominantly cystic or solid, or mixture of the two. Quite often some organs or part of organs can easily be recognized in the tumor mass. Histologically, they can be present as mature or immature teratomas.

Several classification systems for SCTs have been developed. Altman et al. classified these tumors according to the amount of pelvic and/or external tumor (10, 11):

Type I tumors (47%) are predominantly external with only a minimal presacral component, and are easily identified on prenatal ultrasound examination or at birth (Figure 1a).

Type II tumors (35%) can be both intrapelvic and external, and their intrapelvic extension is big (Figures 1b and c).

Type III tumors (8%) have mostly internal pelvic and intra-abdominal extension.

Type IV tumors (9%) tumors are completely internal, presacral with no external presentation and are usually recognized late (having already undergone malignant transformation and become symptomatic).

The great majority of tumors in newborns are benign. Solid tumors deserve greater suspicion as they are more likely to contain malignant elements.

In some tumors the histological distinction between neoplastic and poorly differentiated embryonic tissue is difficult to make. It is believed that all SCTs have malignant potential regardless of their location (12). It has been noted that presacral teratomas have a higher incidence of malignant transformation than do the sacrococcygeal ones. The reason is that these tumors do not produce symptoms until later in life. The malignant teratoma will invade the bones, the spinal canal and the rectum, and metastases especially in the lungs and liver have been described (13).

Prenatal ultrasound diagnostics of majority SCTs is possible in the weeks 22 to 24 of gestation (11, 14). These tumors appear as complex masses located at the distal end of the spine, with vascular solid components and increased echogenicity on ultrasound. Modern 3D/4D ultrasound advancements allow prenatal diagnosis even in the first trimester.

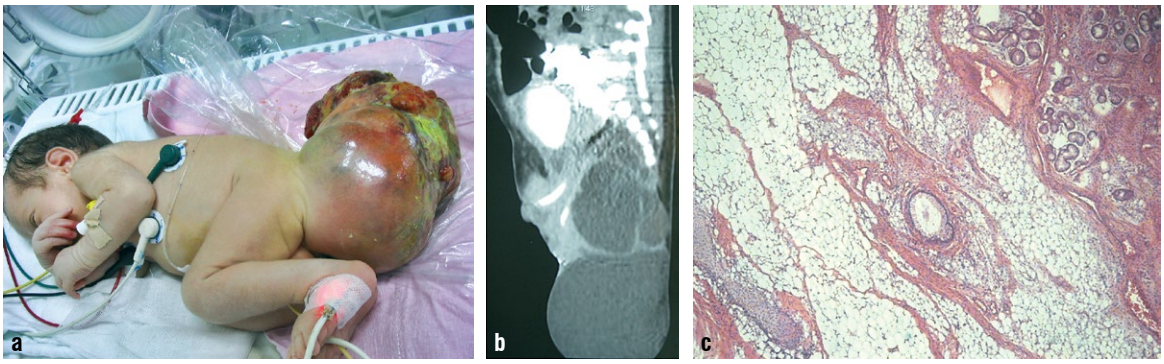


Figure 1. Sacrococcygeal teratoma. a) neonate with large sacrococcygeal mass. b) CT scan revealed tumor occupaing pelvis with large external extension. c)The mature teratoma on this microscopic field consists of mature cartilage, fibrous and adipose tissue and several seromucous glands and one mucous gland with dilated lumen (HEx100).

Magnetic resonance imaging provides additional information about intrapelvic extension and relationship to the other structures (14). If SCT is suspected, ultrafast fetal MRI is also suggested (15).

Complications of maternal condition referred to as Maternal Mirror Syndrome or Ballantines Syndrome (also referred to as pseudotoxemia, maternal hydrops Villi), and other foetal complications include: polyhydramnios, foetal cardiomegaly, nonimmune hydrops, malignant invasion, etc., (11, 16) which should be suspected for development of SCT.

The next step of diagnosing is after the birth. Anteroposterior and lateral radiographs of pelvis and spine can be routinely taken. A straight radiograph of a tumor will frequently show calcification (of either diffuse or definite structure, such as incompletely formed bones or tooth buds). The spine is usually normal, but may show developmental defects of the sacrum and coccyx. In cases with tumor extension into the pelvis and abdomen pyelogram, cystogram and barium enema may be helpful in order to demonstrate displacements of ureters, bladder, and rectum.

The differential diagnosis includes myelomeningoceles, chordoma, dermoid cysts, lipomas, etc. (17). Currarino syndrome (triad of congenital disorder of the sacrum, presacral mass, and malformations of anus and rectum) has been observed as a distinct kind of teratoma by some authors (18).

In about 18% of cases, the associated malformations are present; 15% of patients have associated congenital anomalies: spina bifida, meningomyelocele, malformations of the urinary and genital tract (duplication of uterus or vagina) the heart, the gastrointestinal tract (imperforate anus) and musculoskeletal system (sacral bone defects) appear to be the commonest (1).

The treatment of choice is primarily surgical, including removal of the coccyx. Failure to remove coccyx results in a 30% to 40% incidence of recurrence with >50% being malignant.

Prognosis depends on the time of diagnosing: in less than 2 months of age only 7% to 10% are malignant.

Over the last five years (2008-2012) four teratomas were diagnosed in four neonates at Pediatric Surgery Clinic in Novi Sad (Table 1).

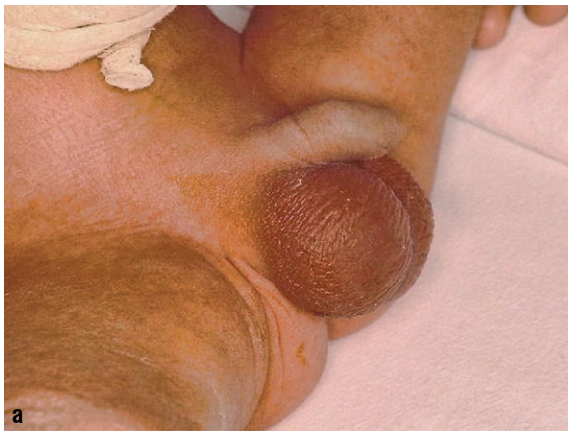
Despite the fact that SCT is clearly visible by ultrasound within the last few months of pregnancy only one was prenatally detected. It was the case with an abdominopelvic cystic mass. After the birth, it was estimated to be an intestinal duplication and was surgically removed. Histopathological finding confirmed the diagnosis. A few weeks later, the patient was readmitted for a new low abdominal mass predominantly presacral, in the pelvis. After second operation, the diagnosis was yolk sac teratoma and metastasis in bones. The child underwent radio and chemotherapy. Nowadays he is alive but with the stigmata of mental and physical retardation.

Among the four presented cases diagnoses were clear in two, confused in one (Altman type IV) and surprising in the neonate with the acute scrotum (Figures 2a and b).

We agree that when SCT is present at birth, surgery (tumor and coccyx removal) should be performed as early as possible (19, 20). Regular postoperative observation and imaging investigation are necessary to detect tumor recurrence. In patients with malignant teratoma selective chemotherapy is applied, though with complications due to therapy.

Table 1. Clinical consideration of patients with neonatal diagnosed teratoma lesions.

Gender	Time of diagnosis	Clinical findings	Imaging	Patohistology	Therapy	Ass.anomalies	Outcomes
Female	Birth	SCT	CT: SCT Type II	**Non-malignant teratoma**	–	–	Good
Female	17 days	Tumor SC regio	CT: SCT Type III	**Non-malignant teratoma**	–	–	Good
Male	Prenatal abdomino pelvic cyst	Duplication of small intestine	US: pelvic mass CT: nhomogenous pelvic mass	**Yolk sac teratoma**	Hemothepary Radiotherapy	Hypothyreosis	Phisical and mental retardation
Male	Birth	Right scrotal mass	–	**Yolk sac teratoma**	–	–	Good



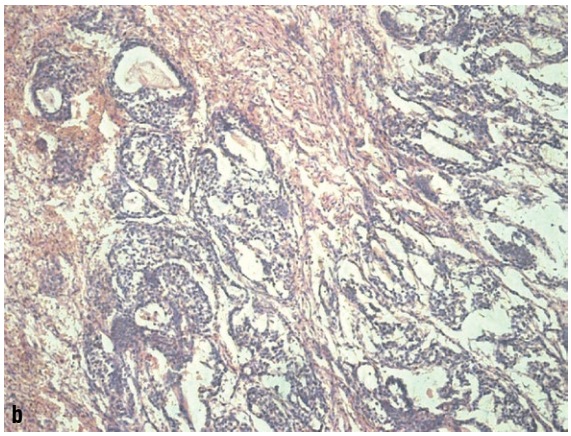


Figure 2. Gonadal teratoma. (a) A few hours after birth redness and swelling developed on the right side of the scrotum. Immediate surgical exploration excluded testicular torsion but gonad was enlarged and with unusual macroscopic appearance. (b) Tissue specimen taken during operation revealed the diagnosis: yolk sac teratoma. The anatomizing tubular and acinar architecture of small tumor cells with prominent nucleoli. This field shows solid and micro- and macrocysts growth pattern (HEx100).

Retroperitoneal tumors

Neuroblastoma

Neuroblastoma (NB) is an embryonic tumor arising from the sympathetic nervous system. The signs and symptoms reflect the tumor site and the extent of disease. Most cases arise in abdomen, either in the adrenal gland or in retroperitoneal ganglia. Clinical manifestation is a flank mass, fever, irritability, failure to thrive (21). The most common sites of metastasis are long bones, skull, liver and lymph nodes. Prenatal diagnosis is possible on maternal ultrasound scans, when tumor is usually discovered as an adrenal mass (22, 23).

Tumor markers, including elevated homovanillic acid (HVA) and elevated vanillylmandelic acid (VMA) in urine, help to confirm diagnosis. Ultrasound, CT or MRI are necessary for preoperative tumor diagnosis. Treatment of low-risk NB includes surgery, i.e. total removal of the tumor or nephrectomy, and observation. Treatment of intermediate-risk NB includes surgery, moderate dose chemotherapy, and in some cases radiation.

Treatment of high–risk NB is usually followed by high-dose chemotherapy and autologous bone marrow or stem cell transplantation (24).

The prognosis is good for many patients, since many tumors show evidence of spontaneous regression. Patients without life-threatening or organ-threatening symptoms can be safely observed for spontaneous regression. The prognosis varies depending on histological definition of the tissue pattern (Shimada classification) (25, 26).

Our experience covers two newborns with NB (Table 2.). The first one was a case of typical appearance of abdominal mass and elevated levels of HVA and VMA as tumor markers. Surgical removal was performed and no adjuvant therapy was necessary in the next five years.

The second case was with prenatally diagnosed large adrenal mass on the left, moving the kidney down. Postnatal investigation showed normal blood tests, the adrenal function also normal, so the future testings were done at regular intervals. The volume of the tumor decreased over the next three months and the structure of the adrenal gland was normalized. Periodical control over the last four years has shown normal adrenal appearance.

Renal tumors

Nephroblastoma - Wilms tumor

Wilms tumor is a complex embryonic neoplasm of the kidney, composed of blastema, epithelia, and stroma. Neonatal Wilms is very rare (21). Syndromes as the WAGR syndrome (aniridia, genitourinary abnormalities, mental retardation), Beckwith- Wiedermann syndrome (organomegaly, macroglossia, omphalocele, hemihypertrophy), etc., are reported with Wilms tumor (27).

The first notice of tumor is usually during well-child clinical examination or at home while bathing. Clinical manifestation is usually abdominal mass

Table 2. Clinical consideration of patients with neonatal retroperitoneal tumor

Gender	Time of diagnosis	Clinical findings	Imaging	Patohistology	Therapy	Ass.anomalies	Outcomes
Female	4 weeks	Abdominal tumor	US: inhomog. mass CT: kidney tumor	**Wilms' tumor**	Surgery: nephrectomy	–	Lost
Female	prenatal US: right kidney tumor	Abdominal tumor	US: inhomog.mass CT: kidney tumor	**Mesobl.nephroma**	Surgery: nephrectomy	–	Good
Male	prenatal US: adrenal cyst	Generally healthy boy	US: large adrenal partly cystic	**Neuroblastoma ?**	Observation	–	Good
Male	4 weeks	Abdominal tumor	US: right enlarged kidney tumor CT: inhomog.mass many calcifications	**Neuroblastoma**	Surgery: nephrectomy	–	Good

that may cross the midline. Physical examination should be followed by analysis as complete blood cell count, liver, kidney function studies, etc.
In the very diagnosis the difference should be stressed between this and a variety of other abdominal and pelvic tumors. Wilms tumor may be mistaken for mesoblastic nephroma (fetal renal hamartoma) (28, 29).
The staging system is used as proposed by the National Wilms Tumor Study Group. Wilms tumor has been reported with favorable and unfavorable histological variants. Neonatal diagnosis does not appear to be an adverse prognostic factor (30).
Surgical extirpation of tumor should be performed, following the preoperative chemotherapy. Wilms tumor is generally heterogeneous and malignant, and requires surgery, chemotherapy. and sometimes radiotherapy.
In our history data. there is only one case with neonatal Wilms tumor (Table 2). After a normal pregnancy a healthy female baby was born. In her fourth week, an enlargement on the right side of baby's abdomen was noticed by her mother. Ultrasound and CT revealed an ipsilateral kidney tumor. After nephrectomy and histopathology analysis the diagnosis of Wilms stage I was established. The parents refused chemotherapy and the patient was lost to follow-up.

Congenital mesoblastic nephroma (CMN)

This is a usually benign congenital neoplasm, arising from renal mesenchyma. Microscopically it is composed of mesenchymal or fibrous stroma and dysplastic glomeruli and tubuli. Histological subtypes are classic type, cellular type, and mixed type (30).
It appears as a massive, firm, solitary renal mass accompanied by hematuria, hypertension and vomiting. Sometimes clinical appearance does not help distinguish Wilms and CMN but confusion can be solved by microscopic analysis.
The sonographic picture in both tumors is that of a solitary mass replacing the normal architecture of the kidney. Cystic areas may appear. Mesoblastic nephroma is benign and nephrectomy is curative. Only recurrence and metastatic disease may complicate the postoperative period (30).
We have the experience (Table 2.) with a five-day-old baby who was admitted to our hospital for enlarged right side of the abdomen (Figure 3a). After the CT scan showed a renal tumor, (Figure 3b) nephrectomy was performed and histopathology revealed CNM (Figure 3c). No adjuvant therapy was applied and now this former patient is a healthy boy of five.

Liver tumor

Hepatic tumors in neonatal period have specific morbidity. Liver mass can be noticed as solid lesion or cystis cyst, with central necrosis. Presentation is usually as unifocal (solitary), very rarely as multifocal lesions. Microscopically, they usually present as hemangiomas, hamartomas as benign structures or rare hepatoblastoma as malignant lesion. The most frequent tumor is infantile hemangioendothelioma hepatis (IHH). Histopatohologically there are two types: Type I where multiple vascular channels with immature endothelial lining are separated from bile ductules with stroma, and Type II where the typical appearance is disorganized hypercellular tissue with no bile ductules. Hepatoblastoma is a malignant embryonic tumor and may be associated with Beckwith-Wiedemann syndrome (31).
Typically, liver tumors present as an abdominal mass and hepatomegaly. If they are very large, they may cause respiratory embarrassment. Hemangioma may be associated with anemia, progressive cardiac failure, and consumptive coagulopathy due to platelet sequestration (Kasabach-Merritt syndrome). Sometimes they may occur as an asymptomatic hepatic mass, or are incidental findings at necropsy (21).
Diagnosis is sometimes problematic because of non-specific clinical symptoms or absence of symptoms, misleading imaging and difficulties with histological appearance (32). Initial finding using antenatal sonography may be a liver mass (33). Occasionally, liver tumors are associated with arteriovenous shunting, congestive heart failure and hydrops, resulting in intrauterine or neonatal death. Both oligohydramnios and polyhydramnios have been observed. After birth all hepatic tumors may show similar sonographic features defined as a complex of heterogeneous mass, cystic, or solid lesion, with central necrosis or calcification. Laboratory investigations showed elevated liver function and high level of alpha-fetoprotein in 90% of patients with hepatoblastoma (34, 35). CT manifested well-defined mass hypoattenuating in IHH and more in heterogeneous hepatoblastoma (36). The MRI imaging finding varied depending on presence or absence of hemorrhage or infarction.
Liver masses in neonatal period are most likely to be non-malignant and patients with IHH usually have a good prognosis. In the

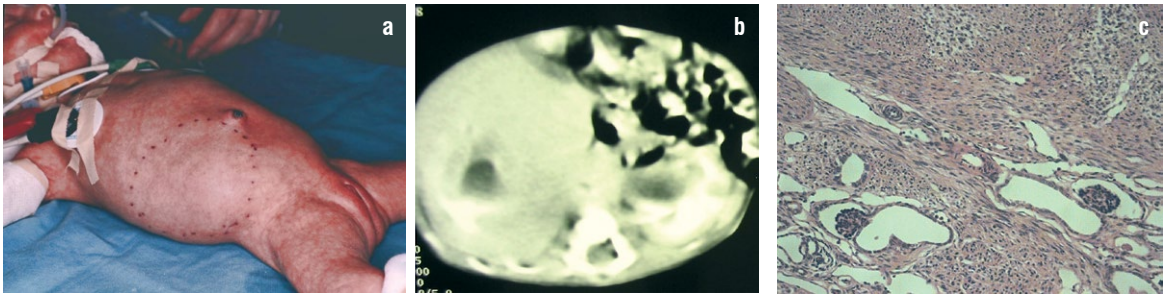


Figure 3. Retroperitoneal kidney tumor. Antenatal ultrasound of female fetus revealed a tumor mass in right kidney. (a) On the fifth day after birth tumor showed expansive growth. (b) CT scan showed enlarged right kidney with inhomogeneous mass well encapsulated. (c) Microscopical finding: congenital mesoblastic nephroma. This shows the well-differentiated, uniform spindle cells of the classic type of tumor. In the periphery of the tumor, the spindle cells interdigitate with elements of the kidney (HEx200).

Table 3. Clinical considerations of patients with neonatal liver tumor

Gender	Time of diagnosis	Clinical findings	Diagnostics	Imaging	Therapy	Ass.anomalies	Outcomes
Male	4 weeks	enlarged abdomen and liver failure to thrive	anemia hematuria liver biopsy: IHH	US: multiple nodules in liver CT: multicentric liver lesions	Corticotherapy	stenosis aorte defect. septi atrior.	Good
Male	17 days	enlarged abdomen gastroenterocolitis	anemia AFP 4066	US: well defined liver mass CT: hypoattenuating mass, calcification, necrosis	Surgery-liver resection Ph: IHH type I	–	Good
Male	5 days	enlarged abdomen small for date general hypotony	anemia tachyarrithmy	US: right liver lobe tumor CT: heteroehogenous mass occupaing right liver lobe	Surgery-liver resection Ph: Hemangioma capillare hepatis	malrotatio intestin.	Good
Male	4 weeks	enlarged abdomen	–	US: right lobe liver tumor	observation	–	Good
Female	4 weeks	enlarged abdomen	–	US: VI-VII segm. Liver tumor CT: VI-VII liver segm. inhomogenous mass	Surgery: liver resection Ph:Hepatoblastoma	–	Lost of follow-up
Male	2 weeks	by-side finding	anemia	US: right lobe liver tumor	Surgery: liver resectio Ph: IHH	–	Good
Male	2 weeks	by-side finding	anemia	US: IV segm. liver tumor CT: IV a,b segm.liver lesion	Surgery: liver resection Ph: Hemangioma capillare hepatis	palatoschisis	Good

asymptomatic child with hepatomegaly, spontaneous resolution of the IHH can be expected within a year.

Surgical resection is indicated if the mass cannot be distinguished from malignant tumor by imaging examinations, or if life-threatening symptoms are present. Malignant hepatoblastoma often has to be treated with chemotherapy to achieve resectability.

If diagnosis of IHH is completed, tumor may be treated conservatively with corticosteroids, cytotoxic agents, interferon, and/or with irradiation (37). Although IHH is usually a benign lesion, malignant transformation has been reported (38, 39).

Our experience involves 7 patients with liver tumor (Table 3): four IHH type I, two capillary hemangioma (Figures 4a, b, and c) and one hepatoblastoma. No one was prenatally diagnosed; two were noticed as by - side findings. The time of symptoms and signs onset was from five days to four weeks after delivery. Five patients underwent liver resection. Hepatoblastoma was diagnosed in one patient and adjuvant chemotherapy was applied. One patient was recommended for corticosteroid therapy. Two patients with histopathological finding of IHH showed spontaneous regression by the end of their first year of life and surgery was needed. They are under regular monitoring, ultrasound and laboratory investigation.

CONCLUSION

Neonatal tumors are rare but publications on these pathological conditions have nowadays increased, since diagnosis of congenital tumors is performed earlier due to the wide use of prenatal ultrasound screening. Prenatal diagnosis allows a planned approach and it involves a team of multidisciplinary specialists in therapy.

Some tumors are visible immediately after delivery (teratomas type I-III), some show non-typical signs, and some are diagnosed accidentally. The majority of tumors identified in the first month of life are presented with a mass. Diagnostic procedures have to be less invasive in helping identify the nature of the tumor.

Most neonatal tumors have a benign behavior despite the histological evidence of malignancy. Because the histological pattern is not the determinant of the outcome, complete surgical excision is the treatment of choice for many patients, although most cases do not need adjuvant

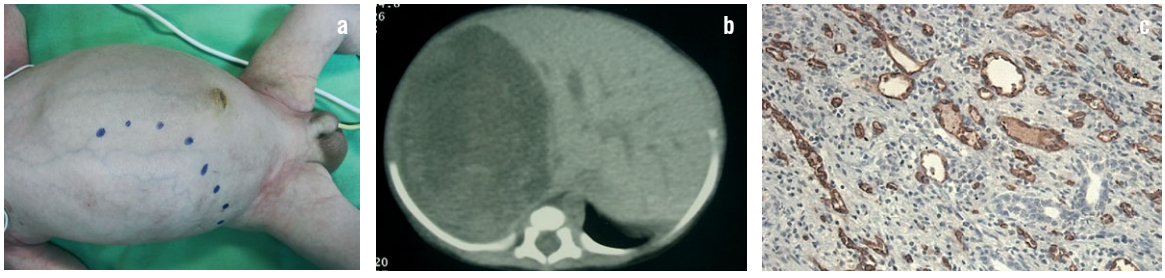


Figure 4. Liver tumor. Male neonate was admitted in hospital for gastroenterocolitis. (a) By side finding was a large tumor in the right side of the abdomen. Ultrasound and CT (b) revealed a tumor mass that fulfilled the almost all right lobe of the liver qualified as hematoma. (c) After partially liver resection histopathology finding shows liver tissue with tumor consisting of numerous capillary blood vessels and preserved biliary ducts (CD 34 x 200).

chemotherapy. A large percentage of patients can be successfully treated, with the future of well-being. Since the use of chemotherapy in neonates is associated with a high incidence of complications, and radiotherapy can lead to major handicaps in survivors, chemotherapy and especially radiation must be carefully considered on an individual basis.

Malignant tumors are rare but some benign tumors may have malignant potential, depending on their size, location, and other clinical behavior. Since some benign tumors may show malignant transformation, the patients have to be regularly examined.

Conflict of interest

We declare no conflicts of interest.

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