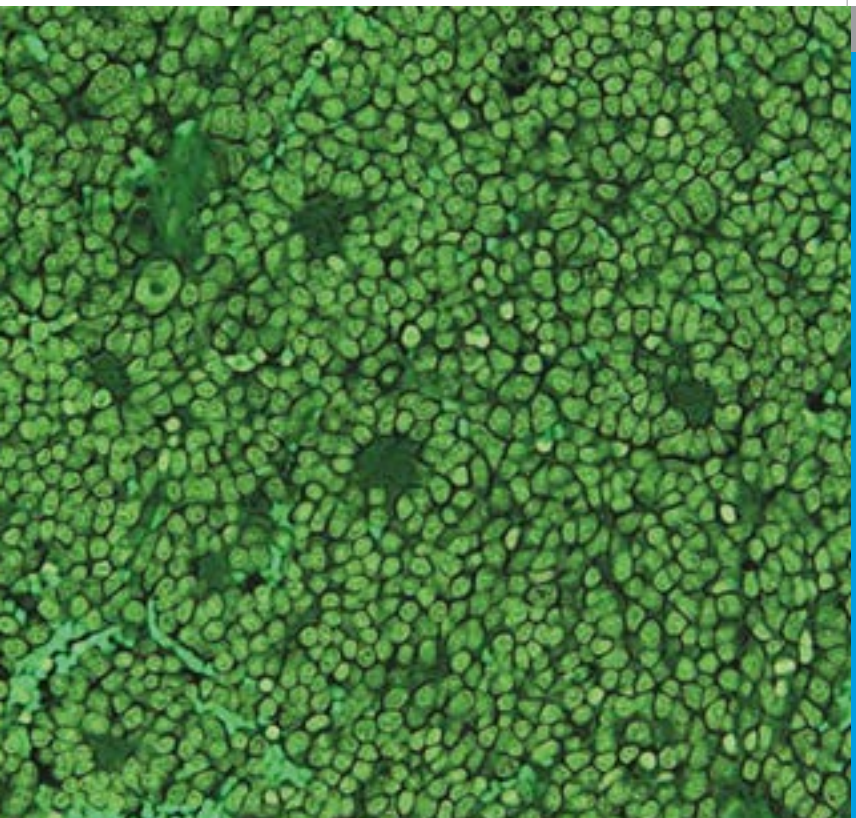
SWISS SOCIETY OF NEONATOLOGY

Diagnostic and therapeutic challenges of congenital neuroblastoma



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This female infant was born by cesarean section at another institution because of non-reassuring fetal monitoring at 39 weeks of gestation. During pregnancy, oligohydramnios and an unusually large placenta were noted.

The infant adapted without difficulties with Apgar scores of 9, 10 and 10 at 1, 5 and 10 minutes, respectively. The arterial umbilical cord pH was 7.33. At the age of 2 hours, the girl developed respiratory distress with retractions and a respiratory rate of 80/min and was put on CPAP. She remained hemodynamically stable with a mean blood pressure > 50 mmHg. At the age of 14 hours, blood gas analysis revealed a pH of 7.03, a pCO2 of 12 mmHg (1.6 kPa), a bicarbonate of 5 mmol/l and a base excess of -22 mmol/l. She was buffered with a continuous drip of bicarbonate. The liver enzymes were elevated with an AST of 12‘000 U/l and an ALT of 4‘000 U/l. Because a palpable mass was noted in the right upper quadrant, ultrasonography of the abdomen was performed and confirmed the presence of a large tumor. The finding was interpreted either as a neuroblastoma or a hemorrhage into the right adrenal gland. At that point, she was transferred to our center.

At 26 hours of age, she had a pH 7.32, a pCO2 25 mmHg, a bicarbonate of 12 mmol/l and a BE -12 mmol/l. A serum lactate level was 17 mmol/l. Six hours later, the girl developed severe arterial hypoten-

sion with a mean blood pressure of 20 mmHg which responded poorly to epinephrine. Echocardiography showed evidence of hypovolemia and myocardial hypertrophy. Crystalloids, fresh frozen plasma (initial INR of 10), blood and platelets as well as hemodynamic support with norepinephrine and dobutamine were administered. The babygramm is shown in Fig. 1.

At the age of 48 hours, she had hematochezia and again received packed RBCs, platelets, fresh frozen plasma and pantoprazole. In the following days, AST and ALT values decreased rapidly but her conjugated bilirubin increased up to 275 µmol/l. Hypoalbuminemia (17 g/l) and hyperammonemia (400 mmol/l) were additional signs of hepatic failure. On DOL 3, she was intubated and put on high frequency ventilation.

Over the following three weeks, she developed multisystem organ failure with cardiorespiratory failure, hepatic failure and ongoing coagulopathy, renal failure, and EEG evidence of encephalopathy. Her respiratory course was further complicated by severe pulmonary hemorrhage due to persisting coagulopathy despite frequent replacement of coagulation factors with fresh frozen plasma and twice daily platelet transfusions.

The most likely diagnosis of the mass identified on abdominal ultrasonography on DOL 2 was a neuroblastoma (Fig. 2). Hypoechogenic zones along the intrahepa-

tic vessels, however, were felt to represent areas of necrosis following hypoxic-ischemic events rather than metastatic infiltration. On DOL 3, a CT scan located the mass to the right adrenal gland and demonstrated compression of the inferior vena cava. Diffuse hepatic necrosis was confirmed and there was renal and intestinal hypoperfusion (Fig. 3). Interestingly, homovanillic acid (HVA) and vanillomandelic acid (VMA) measured on DOL 4 and DOL 10 were normal.

On DOL 14, it was decided to administer a single dose of cyclophosphamide. This drug has limited toxicity and can be used even in the presence of liver and renal failure. Given the lack of calcifications and negative HVA and VMA screening results, the findings of an MRI performed on DOL 18 (Fig. 4) were felt to be most compatible with a large adrenal hemorrhage. However, a neuroblastoma could not be excluded and MIBG-scintigraphy was recommended. When the radioactive tracer finally became available, the examination revealed a mass capturing the MIBG (Fig. 5). The activity over the right upper abdomen projected over the right adrenal gland and was compatible with a neuroblastoma. Activity over the left upper abdomen was felt to represent either an extension of the right adrenal mass, a second mass or hepatic infiltration.

The scintigraphy confirmed the diagnosis of congenital neuroblastoma, but there was no response to chemotherapy. Since there were no further treatment options, a multidisciplinary ethics committee decided to redirect care.

Autopsy confirmed the diagnosis of neuroblastoma of the right adrenal gland (Fig. 6, 7) with overwhelming metastatic involvement of the liver (Pepper Syndrome, Fig. 8, 9).

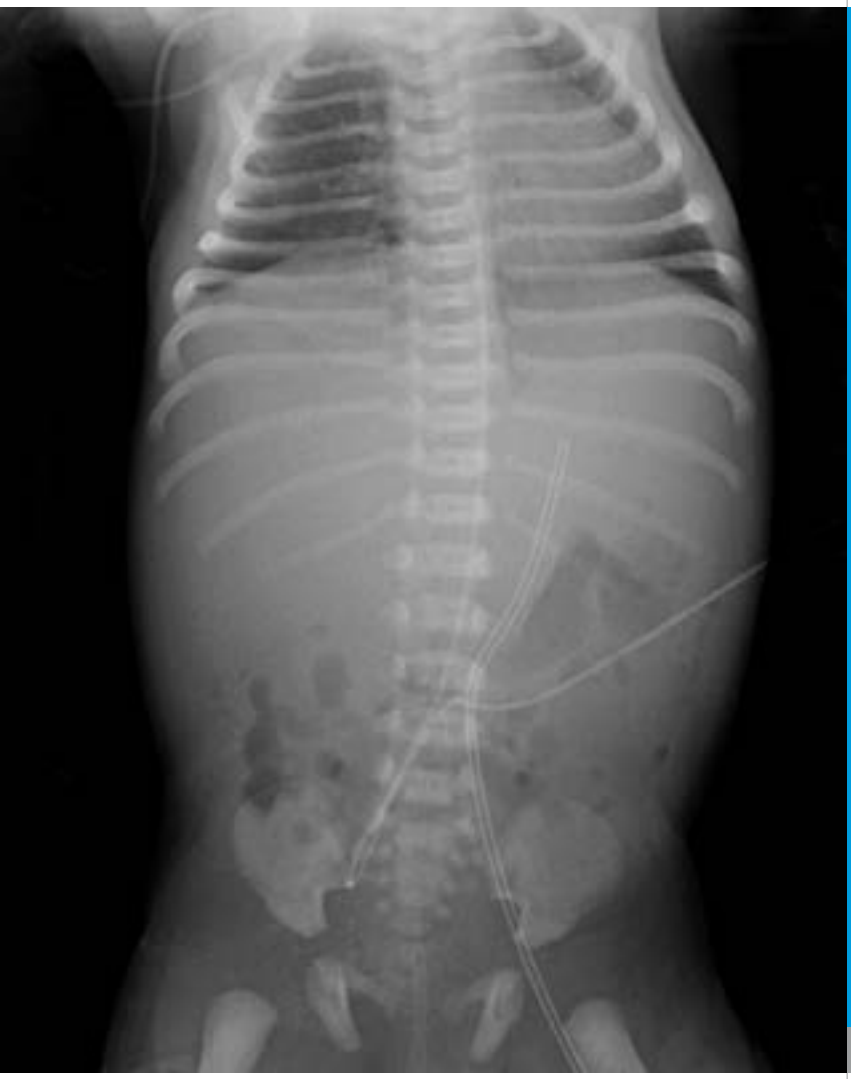

Fig. 1

Babygram showing leftward displacement of the venous and arterial umbilical catheters by the tumor of the right adrenal gland.

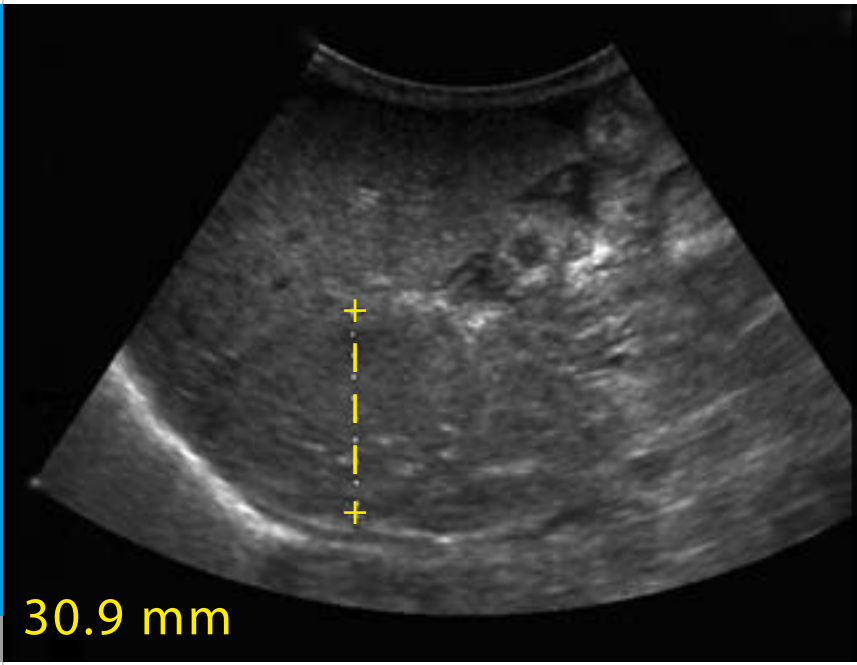

Fig. 2

Abdominal ultrasonography showing the abdominal mass.

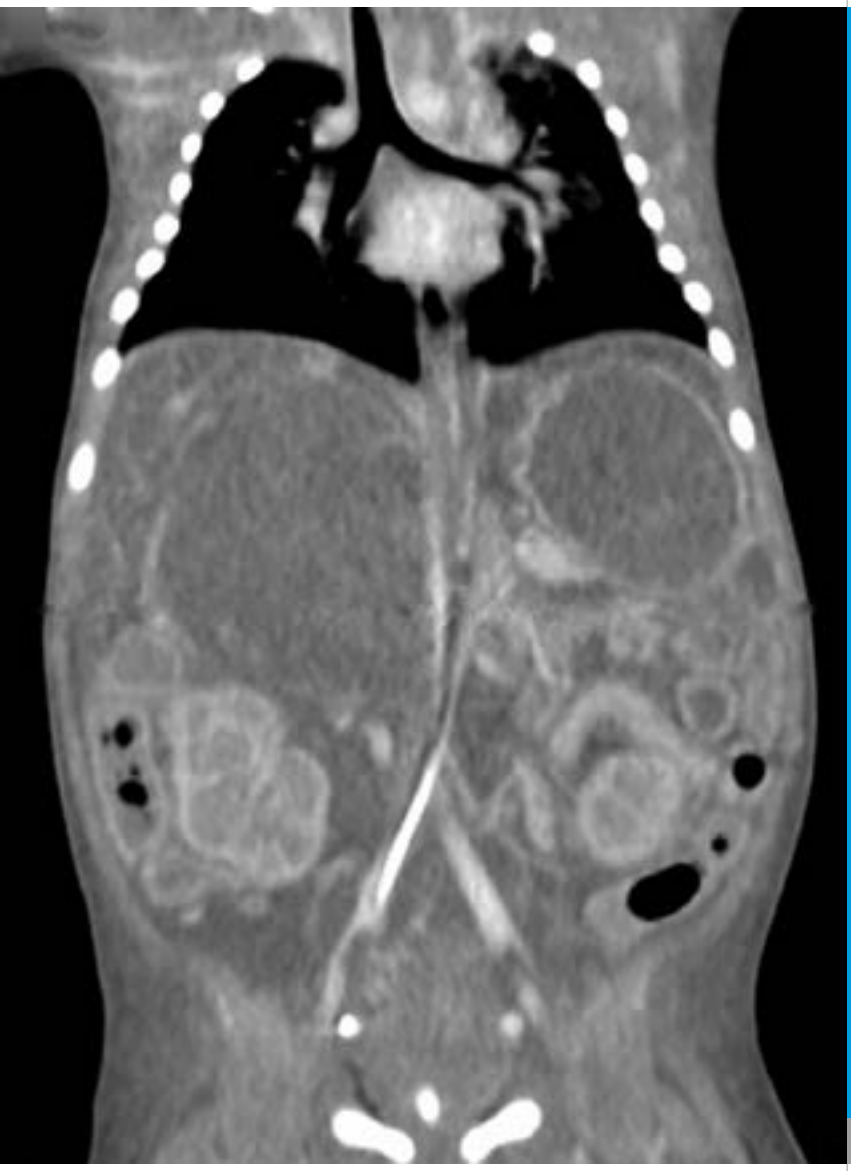

Fig. 3

CT scan showing the mass in the right adrenal gland with compression of the inferior vena cava.

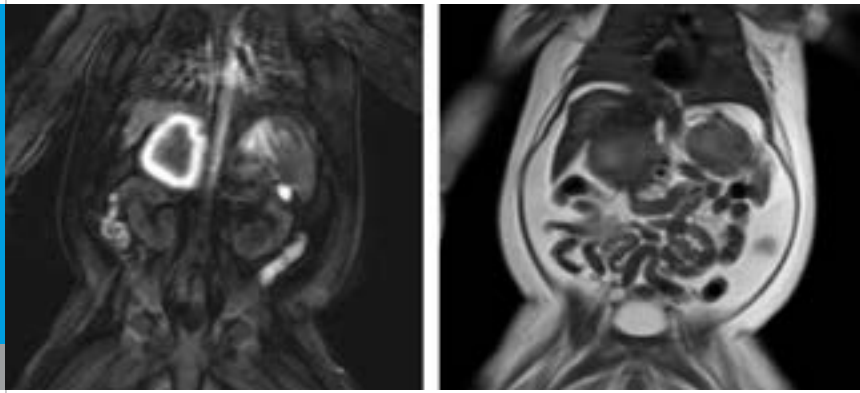

Fig. 4

MR imaging of the right adrenal gland interpreted as adrenal hemorrhage.

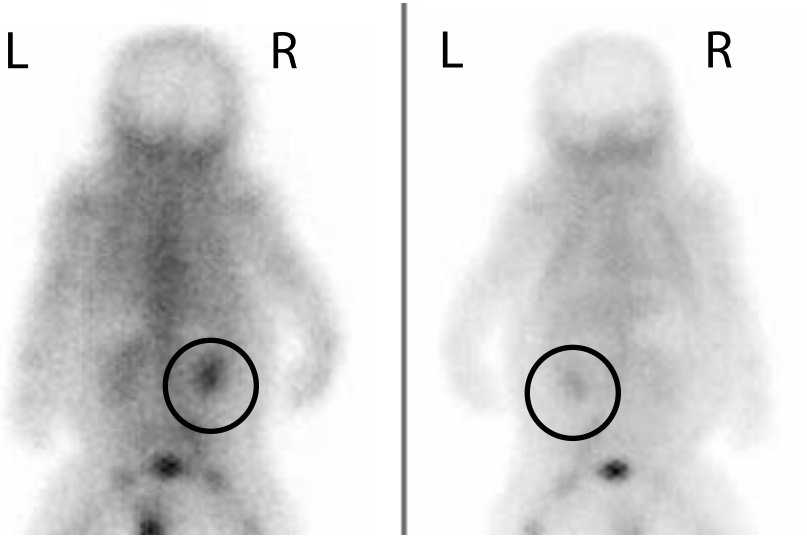

Fig. 5

MIBG scintigraphy revealing a mass capturing MIBG, compatible with a neuroblastoma.

Fig. 6

Neuroblastoma (N) of the right adrenal gland at autopsy (posterior view).

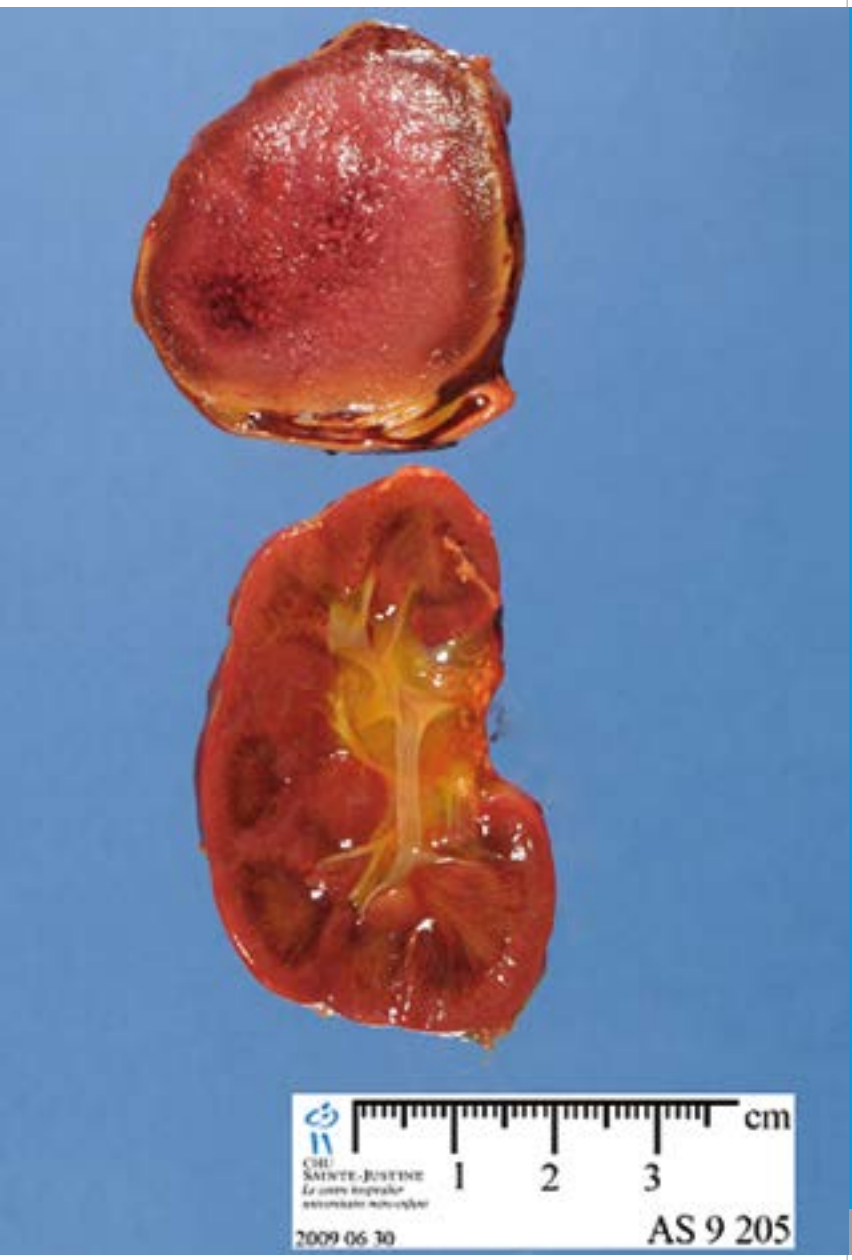

Fig. 7

Sections of the right kidney and right adrenal gland with neuroblastoma.

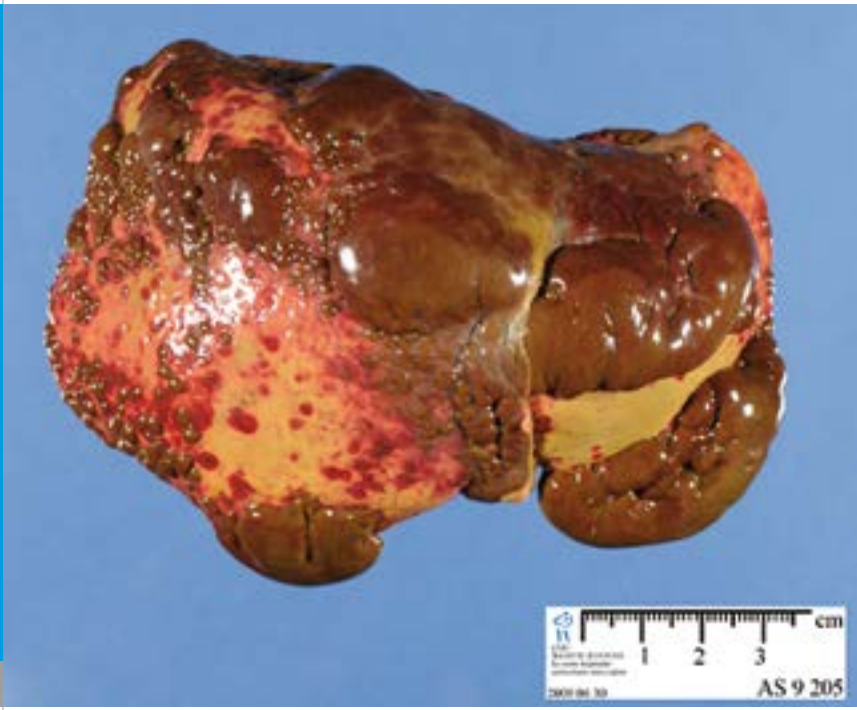

Fig. 8

Hepatic infiltration by the neuroblastoma.

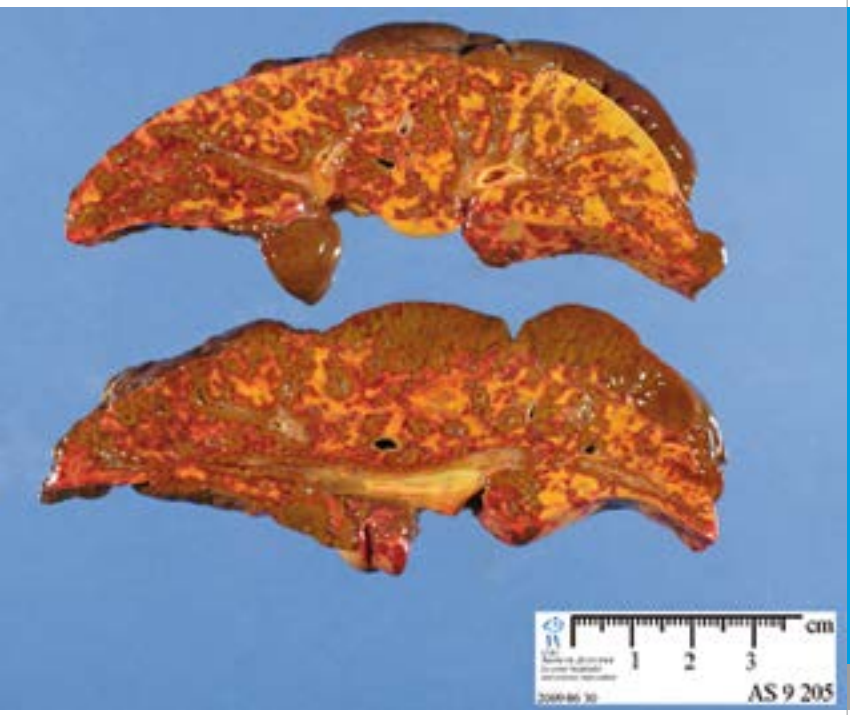

Fig. 9

Cross-section of the infiltrated liver.

DISCUSSION

Neuroblastoma is the most common malignant tumor in infancy, with approximately 20% of all cases occurring before the age of 6 months. The typical localization of neuroblastoma is abdominal (75%, and 65% of these originate from the adrenal gland) (1), presenting with a mass and compression of adjacent structures. In 20% of the cases, it is located in the chest cavity with respiratory distress as the leading symptom (2) and diagnosis is often made fortuitously. Pelvic and cervical neuroblastoma each represent 5% of cases. Stage 4S disease, with the infiltration as in our case, while having a good long-term prognosis (survival up to 90%), needs careful observation to detect potentially life-threatening complications (3, 4).

Several unusual presentations have been described, such as persistent intractable diarrhea, opsoclonus myoclonus syndrome, severe erythroblastosis, marked jaundice with hepatosplenomegaly and sepsis (5). In our case, the fact that the metabolites in the urine were negative (described in 10% of neuroblastoma cases) has led to a delay in diagnosis and in the choice of an adequate therapy. The diagnosis of infiltrative neuroblastoma was repeatedly challenged despite ultrasonographic, CT and MR imaging findings that were compatible with this diagnosis. When urinary VMA and HVA are negative but there is continuing suspicion of neuroblastoma, an MIBG scintigraphy must be obtained. As I123/131-methyliodobenzylguanidine (MIBG) accumulates in catecholaminergic cells, it pro-

vides a specific way of identifying primary and metastatic disease (6).

In the absence of a reliable diagnosis, therapy with cyclophosphamide was felt to be the only reasonable form of chemotherapy because of its limited toxicity. Unfortunately, cyclophosphamide must be activated to functional metabolites by the liver. When liver function is compromised, as in our case, cyclophosphamide metabolism may be limited with reduced biotransformation, and, consequently, reduced antitumor activity (7). Because of hemodynamic and respiratory instability of our patient, radiotherapy was not considered to be an option although neuroblastomas are sensitive to radiotherapy but not curable with radiotherapy alone. Hepatic artery embolization has been described as a treatment option in cases of stage 4S neuroblastoma with liver infiltration (8). Finally, chemoembolization with injection of cisplatinum and doxorubicin into the hepatic artery is another option that combines the cytotoxic effect of chemotherapy with the ischemic insult produced by arterial occlusion. We did not consider this treatment option for our patient because of the presence of liver failure and severe coagulopathy.

REFERENCES

1. Chandler JC and Gauderer MWL. The neonate with an abdominal mass. Pediatr Clin North Am 2004;51:979-997

2. Li AM, Chang J, Kumar A. Neonatal neuroblastoma presenting with respiratory distress. J Paediatr Child Health 2001; 37:203-205

3. Moppett J, Haddadin I, Foot ABM. Neonatal neuroblastoma. Arch Dis Child Fetal Neonatal Ed 1999;81:F134-F137

4. Brouwers FM, Eisenhofer G, Lenders JWM, et al. Emergencies caused by pheochromocytoma, neuroblastoma, or ganglioneuroma. Endocrinol Metab Clin North Am 2006; 35:699-724

5. Lindner W, Behnisch W, Kunz U, et al. Congenital neuroblastoma mimicking early onset sepsis. Eur J Pediatr 2001;160:436-438

6. Lacayo NJ, Davis KL, Neuroblastoma: Differential Diagnoses & Workup, http://emedicine.medscape.com/article/988284-overview (accessed November 22, 2010)

7. Juma FD. Effect of liver failure on the pharmacokinetics of cyclophosphamide. Eur J Clin Pharmacol 1984;26:591-593

8. Boztug K, Kiely E, Roebuck DJ, et al. Successful treatment of MYCN amplified, progressive stage 4S neuroblastoma in a neonate with hepatic artery embolization in addition to multimodality treatment. Pediatr Blood Cancer 2006;46:253-257

9. Weintraub M, Bloom AI, Gross E, et al. Successful treatment of progressive stage 4s hepatic neuroblastoma in a neonate with intra-arterial chemoembolization. Pediatr Blood Cancer 2004;43:148-151

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