


Neonatal neuroblastoma 4s with diffuse liver metastases (Pepper syndrome) without an adrenal/extraadrenal primary identified on imaging

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ABSTRACT

We report the imaging appearances of a case of pathologically proven, neonatal neuroblastoma 4S with diffuse hepatic metastatic involvement at presentation. Patient had an abnormal appearing liver both by ultrasound and MR. There was no evidence for associated adrenal tumor by imaging. Lack of an associated adrenal mass led to initial misinterpretation of diffuse hepatic accumulation of MIBG seen with radionuclide scintigraphy. To the best of our knowledge, this is the first report of metastatic neonatal 4S neuroblastoma without an adrenal (or extra-adrenal) primary identified either on pre- or post-natal imaging.

CASE REPORT

CASE REPORT

A one-day old female, born at 39 weeks to a healthy mother did not have any abnormalities found on pre-natal imaging. Shortly after delivery, she was tachypneic and had an enlarged abdomen. This prompted lab work, which was significant for thrombocytopenia and coagulopathy. At this point, she was transferred to our institution.

Lab work on arrival to our hospital was significant for total bilirubin 5.7 mg/dL (normal range 0.3 – 1.9 mg/dL), indirect bilirubin 4.9 mg/dL (normal range 0 – 1.9 mg/dL), INR 2.0 (normal range 0.9-1.2), WBC 21,500 /micro liter (normal range in a newborn 9,000-30,000/micro liter), platelets 69,000/micro liter (normal range 140,000 – 450,000/micro liter). Tumor markers were as follows: Alpha fetoprotein (AFP) 97,873 IU/mL (normal range below 10 IU/mL), Urine Vanillyl mandelic acid/Creatinine 540 mg/g and peaked at 809 mg/g, Urine homovanillic acid/Creatinine 554 mg/g and peaked at 723 mg/g.

On imaging, ultrasound revealed a diffusely enlarged, markedly heterogeneous liver with patent vasculature [Figure 1]. Ultrasound appearances were interpreted as being most consistent with a hepatic primary neoplasm such as a diffuse hepatoblastoma. Given her elevated tumor markers, hepatic metastatic neuroblastoma was also offered as a differential diagnosis, although the confounding factor was her normal adrenals.

Follow-up abdominal MR images revealed a markedly enlarged and diffusely heterogeneous liver, with few T2 hyperintense foci interspersed through a background of an overall abnormal hepatic signal. On contrast-enhanced T1-weighted MR images [Figure 2], patchy heterogeneous contrast-enhancement was present. Further work up for malignancy ensued, and bone marrow biopsy was negative. The presence of abnormal tumor markers prompted an MIBG scintigraphy [Figures 3, 4], which showed diffuse hepatic accumulation of MIBG. No additional foci of abnormal uptake were identified. Adrenals were normal sized.

Ultimately, a liver biopsy was performed [Figure 5], which was consistent with poorly differentiated neuroblastoma, low MKI, favorable histology per Shimada classification. No n-myc amplification was identified in the tumor by FISH analysis. She was diagnosed with neuroblastoma stage 4s.

Initial hospital course was complicated by increase in abdominal girth, inability to tolerate oral intake requiring a J-Tube, tachypnea and coagulopathy. Given the progressive increase in abdominal girth and poor feeding, the decision was made to proceed with chemotherapy. Three weeks after initial presentation she was started on chemotherapy, which she received Carboplatin (18.6 mg/kg/dose x 1 dose) and etoposide (4mg/kg/dose x 3 doses). Neupogen was administered for expected neutropenia. She did well with chemotherapy. Tumor markers remained low and follow-up sonography of the liver revealed definite improvement [figure 6]. Eventually her Broviac line, which was placed for chemotherapy and her J – tube were removed. Currently, she is off chemotherapy and meeting appropriate developmental milestones.

DISCUSSION

Etiology & Demographics:

The etiology of neuroblastoma is not completely known. It is thought to be a failure of the neuroblasts to mature. The disease is sporadic, probably results from unknown gene changes. There are genetic markers that can predict prognosis and guide treatment.

Neuroblastoma is the most common extracranial solid tumor of childhood. It accounts for approximately 7.8% of childhood cancer. Over one-half of patients present with metastatic disease at diagnosis. The International (INSS/INRC) staging of neuroblastoma includes 5 stages according to the localization of the lesions at the time of admission [1, 2]:

Stage 1: Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph node negative for tumor microscopically (lymph nodes attached to and removed with the primary tumor may be positive)

Stage 2A: Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically

Stage 2B: Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically

Stage 3: Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral region lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement

Stage 4: Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined in stage 4S)

Stage 4S: Localized primary tumor (as defined in Stage 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow (limited to infants age <1 year). In previous staging of neuroblastoma it was stated that stage 4S manifests without radiographic evidence of bone metastases on complete skeletal survey [3].

Age distribution of neuroblastoma is as follows: 40% of patients are younger than 1 year when diagnosed, 35% are aged 1-2 years, and 25% are older than 2 years when diagnosed [4]. According to Surveillance, Epidemiology, and End Report (SEER), incidence decreases every consecutive year up to age 10 years, after which the disease is rare. The male-to female ratio is 1.2:1 and the incidence of neuroblastoma is slightly higher in white children than in black children.

Stage 4s neuroblastoma represents approximately 7–10% of all neuroblastoma cases [5]. Its hallmark is the possibility of spontaneous regression despite a large tumor burden, and an overall good prognosis [6].

Shimada classification of histopathologic features was developed for patients with neuroblastoma [7]. Important features of the classification include (1) the degree of neuroblast differentiation, (2) the presence or absence of Schwannian stromal development (stroma-rich, stroma-poor), (3) the index of cellular proliferation, (4) nodular pattern, and (5) age. Using these components, patients can be classified into favorable and unfavorable histology groups.

Clinical & Imaging findings:

Clinical manifestations can vary according to the organ involved. At presentation, the infants can be tachypneic, pale, and lethargic. The abdomen is usually distended and hepatomegaly may be the sole clinical finding. Associated skin findings of stage 4S disease include non-tender, bluish ‘blueberry muffin’ subcutaneous nodules [8]. Urinary catecholamines vanillylmandelic acid (VMA) and homovanillic acid (HVA) are usually elevated. If the liver is involved, serum lactate dehydrogenase (LDH) and liver enzymes may be elevated.

I-123-metaiodobenzylguanidine (MIBG) was developed in the early 1980s to visualize tumors of the adrenal medulla.

MIBG enters the neuroendocrine cells by an active uptake mechanism via the epinephrine transporter and is stored in the neurosecretory granules, resulting in a specific concentration in contrast to cells of other tissues. MIBG scintigraphy is used to image tumors of neuroendocrine origin, particularly pheochromocytomas, paragangliomas and neuroblastomas, although other neuroendocrine tumors such as carcinoids and medullary thyroid carcinoma can be visualized.

I-123-metaiodobenzylguanidine (MIBG) is an indispensable tool in evaluating neuroblastoma, both at initial staging and in assessment of subsequent tumor response to therapy [9]. There is a physiologic MIBG uptake by the liver. Here, we present a case in which lack of a clearly identifiable adrenal mass on imaging led to misinterpretation of diffuse

MIBG accumulation within the liver. Also, the suspicion for neuroblastoma on her ultrasound and MR was low given the normal size and appearance of her adrenals. Majority of reported cases of the 4S subtype of neuroblastoma are newborns with an associated small, localized primary adrenal mass, mostly solid, and rarely (<2% cases) cystic [10]. In this context, our patient presented an interesting dilemma. Diffuse hepatic uptake of MIBG in context of absence of an associated adrenal lesion led to this being interpreted as a false-negative finding related to normal tracer biodistribution, since liver is a site of catecholamine degradation. However, the subsequent biopsy did confirm metastatic liver involvement by neuroblastic cells. Hepatic metastatic involvement by neuroblastoma on MR presents either as a diffusely infiltrative pattern (seen in infants with stage 4S disease), or focal masses [11]. Sonographic involvement of the liver present as coarse diffuse increased echogenicity or nodular echogenic appearance. This case presented these typical findings.

Our patient presented with a variant of Stage 4s subtype of neuroblastoma, in whom manifestations of the disease included a diffusely involved liver (Pepper syndrome), with associated respiratory compromise and coagulopathy [12]. Also, there was no identifiable adrenal mass, either on prenatal or postnatal evaluation. She had favorable histology by the Shimada classification, and no evidence of bone marrow infiltration by neuroblastic cells. 4S neuroblastoma tumors are generally considered low risk and have an excellent prognosis. These may spontaneously regress.

Differential Diagnoses:

In case of an adrenal mass the differential diagnosis may include neuroblastoma and other masses that originate from the adrenal gland or the surroundings, such as Mesoblastic nephroma, Wilms' tumor, Rhabdomyosarcoma, Rhabdoid tumor, adrenal cortical carcinoma, adrenal hemorrhage, and adrenal infection such as an abscess. In our case of neuroblastoma 4s with an absence of an adrenal mass, the differential diagnosis is more intriguing as one needs to consider the disease and evaluate the case with I-123-MIBG scintigraphy and urinary VMA and HVA. The differential diagnosis of our case with liver involvement includes any infiltrative or focal primary or metastatic liver disease, such as hepatoblastoma, leukemia, lymphoma, hemangioblastomatosis, teratoma, and infections.

Neuroblastoma can be differentiated from other tumors with I-123-MIBG scintigraphy and urinary VMA and HVA. Cross sectional images are nonspecific and the differential diagnosis based on imaging is difficult. However, epicenter of a tumor based on imaging and different tumor markers may help in narrowing the differential. Tissue samples are essential in establishing the final diagnosis.

Treatment & Prognosis:

Treatment for neuroblastoma varies and depends on the stage of the disease. It may include surgery, radiation therapy, chemotherapy or any combination of these. The outcome observed with the different successive treatment approaches suggests that if infants with stage 4s neuroblastoma do require therapy, a more intensive chemotherapy may be more

beneficial [5]. In one study a more intensive treatment by CE regimen (carboplatin and etoposide), only two chemotherapy courses were required. Results of studies suggest that a prompt initiation of a more intensive treatment may be necessary in order to push the neuroblastic cells towards the regression pathway [5]. The CE regimen proved to be associated with a high response rate and good clinical tolerance when used as second-line or as first-line therapy, a schedule which has also shown good response rates and clinical tolerance in infants with localized, unresectable neuroblastoma [13]. The CE regimen is now being proposed as first-line therapy in the NB99 Infant SIOP study for patients with stage 4s neuroblastoma who do require medical intervention. Stage 4s neuroblastoma is associated with an excellent survival rate and with overall survival of 88% [5, 14].

The presented case is unique in a sense that a neuroblastoma 4s was diagnosed and confirmed pathologically without any evidence for associated adrenal tumor by imaging.

TEACHING POINT

A case of pathologically proven, neonatal neuroblastoma 4s with diffuse hepatic metastatic involvement at presentation and without adrenal mass is extremely rare. The initial evaluation may lead to erroneous interpretation. Diffuse hepatic uptake of MIBG in context of absence of an associated adrenal lesion may be interpreted as a false-negative finding related to normal tracer biodistribution, since liver is a site of catecholamine degradation.

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FIGURES

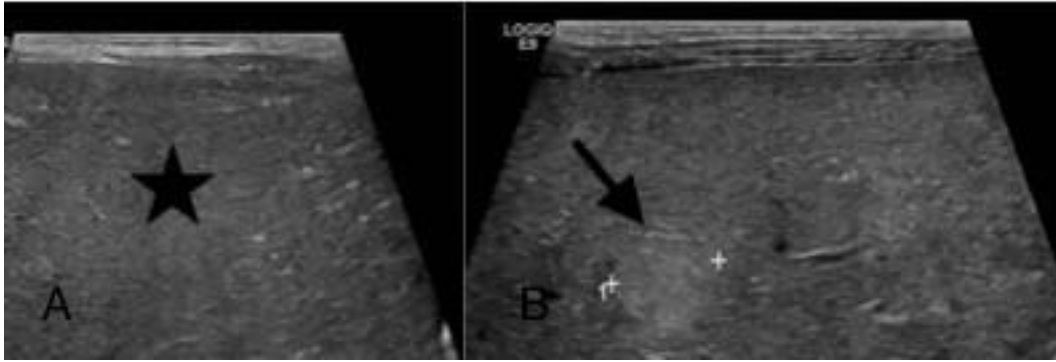


Figure 1: A one-day-old female with neuroblastoma stage 4s. Sonogram findings: Gray scale sonogram of the liver (performed with a convex transducer, 3.5 MHz) in transverse view (A) shows a diffusely coarse liver (star) and (B) reveals an echogenic nodule (arrow) against the background of diffusely abnormal hepatic echogenicity.

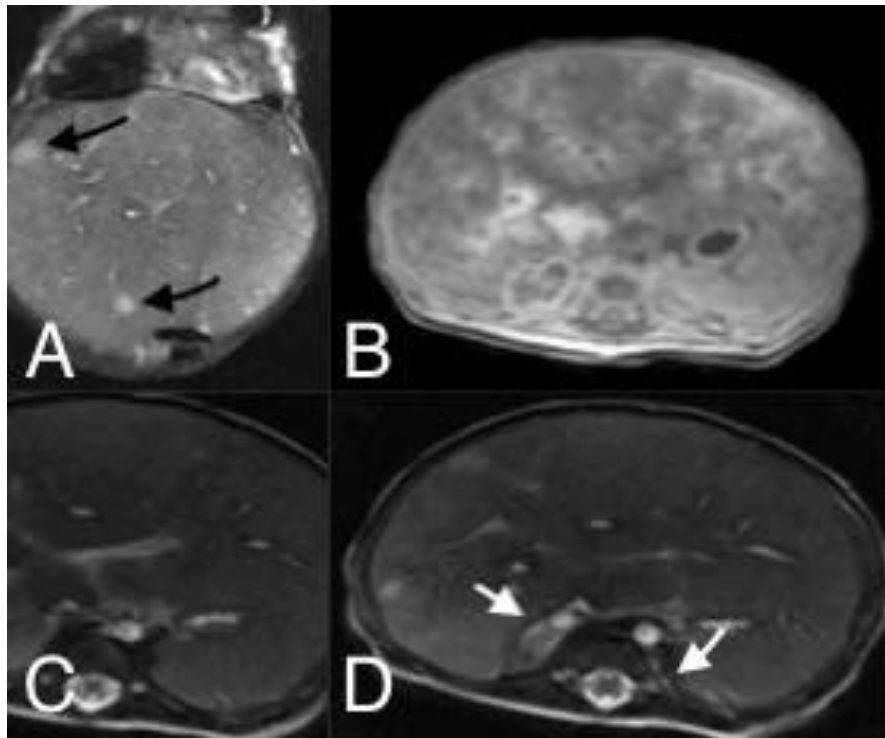


Figure 2: A one-day-old female with neuroblastoma stage 4s. MRI findings: (A) Coronal FIESTA (1.5T, TR - 5.292, TE - 2.088) shows diffusely enlarged, heterogeneous appearing liver with at least two distinctly nodular foci of hyper-intensity (arrows). (B) Axial T1 post intravenous administration of Gadolinium based contrast agent (0.16 cc of gadoversetamide, 1.5 T, TR - 4.104, TE - 1.284) taken through the mid liver shows patchy, heterogeneous contrast enhancement through the liver. (C) and (D) are SSFSE (1.5T, TR - 1106.87, TE - 202.24) in axial views that show normal appearing, thin normal adrenal glands bilaterally (arrows).

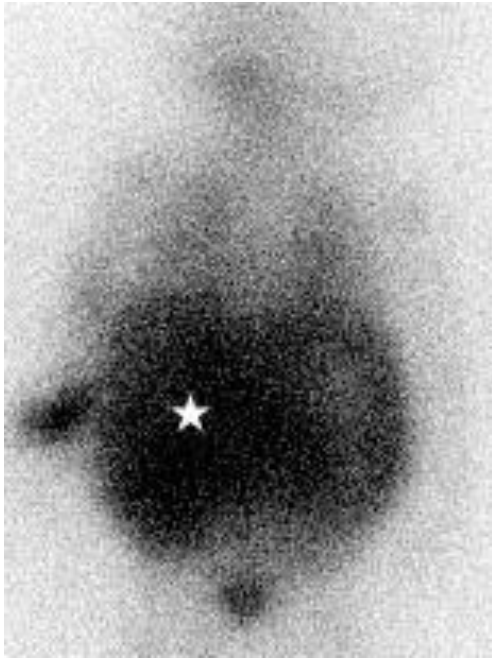


Figure 3 (left): A one-day-old female with neuroblastoma stage 4s. Planar anterior scintigraphic image acquired at 48 hours following the intravenous administration of 1.6 mCi of I-123-MIBG reveals marked diffuse hepatic accumulation of the radiopharmaceutical (white star). No additional MIBG-avid masses were noted on this study. Also, there was no bone marrow uptake of the radiotracer (marrow aspirate and biopsy were negative).

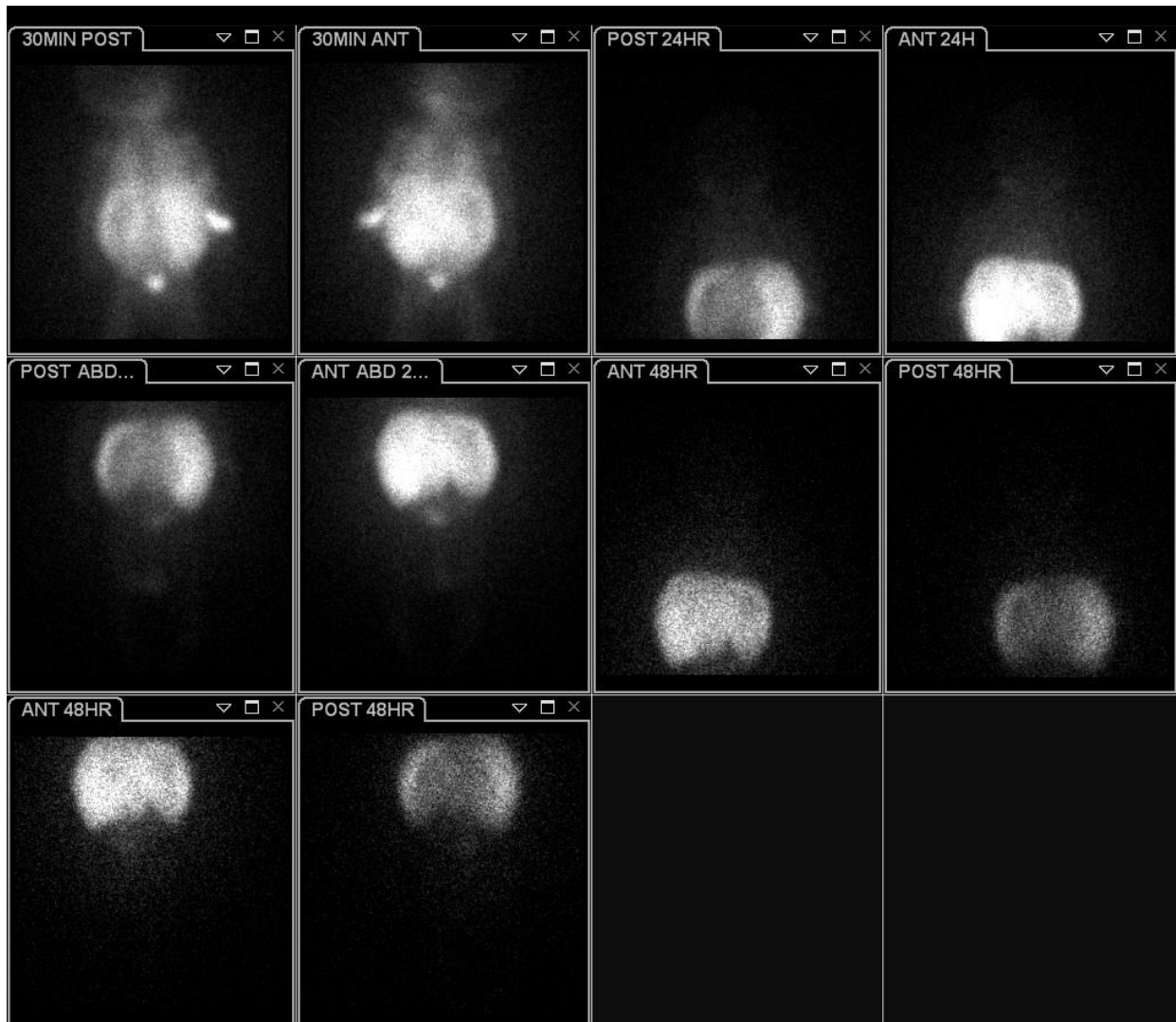


Figure 4: A one-day-old female with neuroblastoma stage 4s. Planar and sequential single photon emission computed tomography (SPECT) images acquired at 30 minutes, 24 hours, and 48 hours after the intravenous administration of 1.6 mCi of I-123-MIBG demonstrate diffuse hepatic uptake with no additional radiotracer uptake.

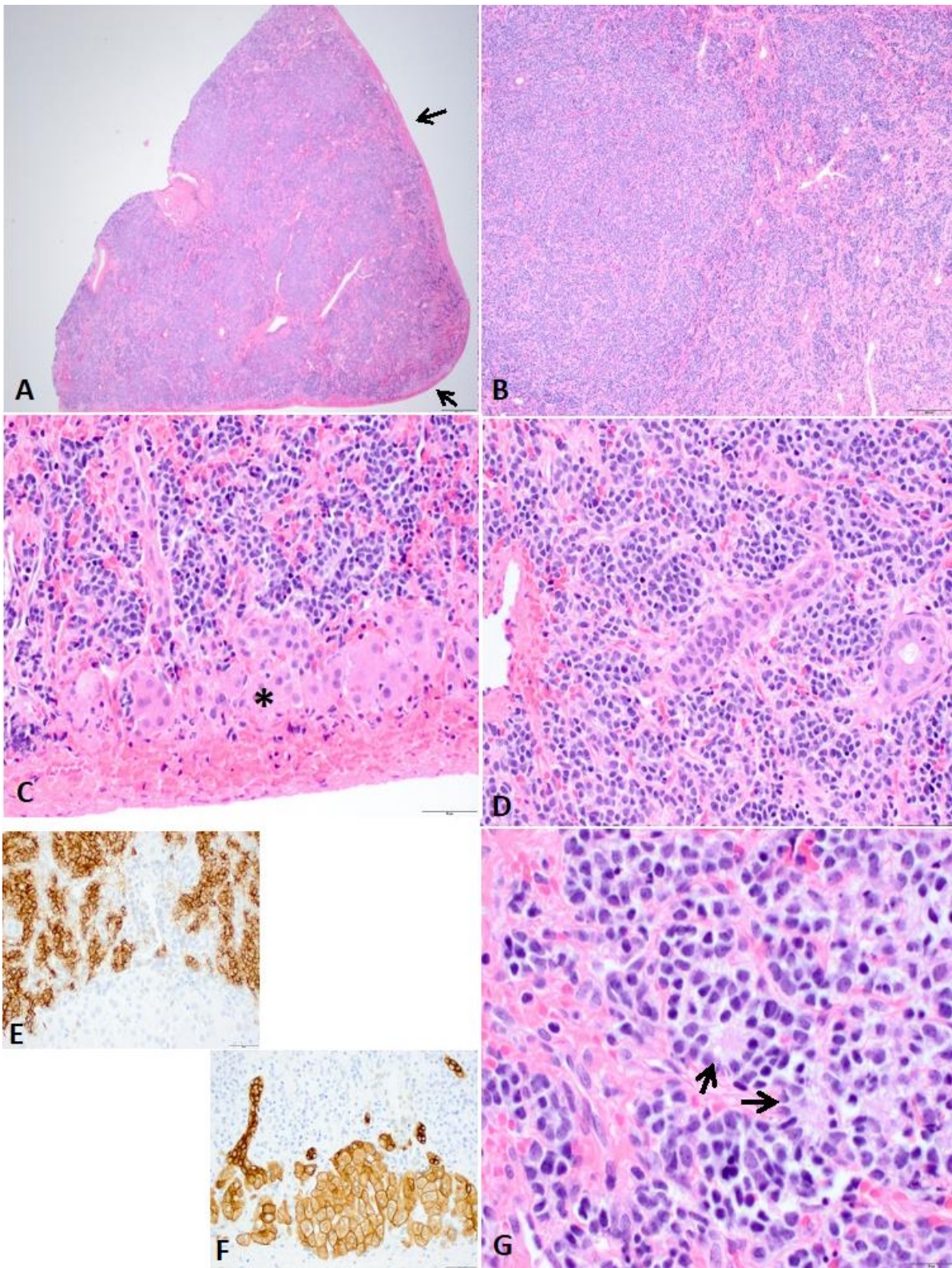


Figure 5: A one-day-old female with neuroblastoma stage 4s. Pathologic findings: (A) Two wedge biopsies (one shown here, with capsule present - arrows) and two core biopsies were performed. (B) The tumor has sheets (left) and nests (right) of tumor cells. Tumor cells are seen adjacent to hepatocytes (asterisk) under the capsule (C) and surrounding bile ductules (D, center and right). Tumor is highlighted by a CD56 immunostain (E). Adjacent liver parenchyma and bile ductules are positive for a cytokeratin immunostain while tumor is negative (F). (G) There are occasional Homer-Wright rosettes scattered in the tumor (arrows). The rosetting, the presence of a low mitotic-karyorrhectic index and the patient's young age (3 weeks) were consistent with a favorable histology of this poorly differentiated neuroblastoma (Original magnifications: A - 12.5; B - 40x; C-F - 200x; E - 400x).

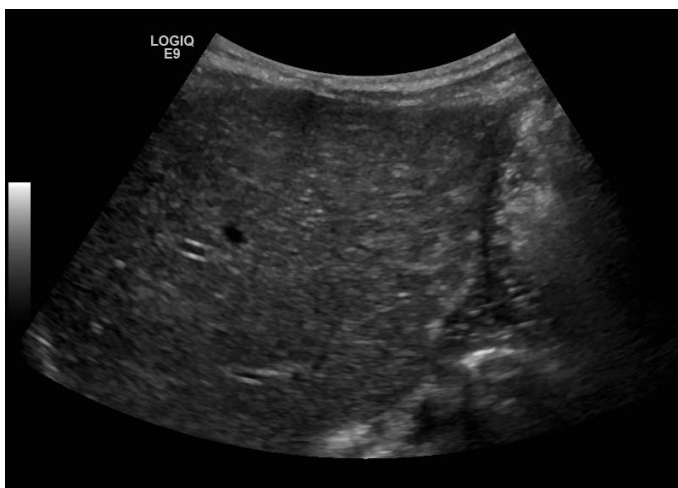


Figure 6 (left): Same patient at six-month of age; status post treatment for neuroblastoma stage 4s.^[1] Sonogram findings: Gray scale sonogram of the liver (performed with a convex transducer, 3.5 MHz) in transverse view shows normal echotexture of the liver with no evidence of nodularity.

Etiology	Unknown. Thought to be a failure of neuroblasts to mature. Neuroblasts continue to grow and divide.
Incidence	Neuroblastoma – 7.8% of childhood cancers. For neuroblastoma 4s – 7 to 10% of all neuroblastomas,
Gender Ratio	Male to female ratio of 1.2:1
Age Predilection	Neuroblastoma – below 5 years; For Neuroblastoma 4s – below 1 year.
Risk factors	Sporadic. Probably unknown gene changes. There are genetic markers that can predict prognosis and guide treatment.
Treatment	Vary according to stage and presentation. Most preferably for stage 4s is chemotherapy with CE regimen.
Prognosis	Excellent. Overall survival rate of 88%

Table 1: Summary table for neuroblastoma stage 4s.

Diagnosis	Ultrasound	CT	MRI	Scintigraphy
Neuroblastoma	Heterogeneous solid lesion, mostly echogenic.	Large, heterogeneous, lobulated soft-tissue masses. Encasing vessels. 90% calcified. Heterogeneous or little enhancement.	T1-Hypointense. T2-Hyperintense. DWI-restricted diffusion.	I-123-MIBG avid. I-123-MIBG is superior to Tc99m-MDP.
Wilms' Tumor	Heterogeneous soft tissue echotexture.	Heterogeneous soft-tissue density masses with infrequent areas of calcification. Displacing vessels. Patchy enhancement and allows for better delineation of the relationship between the mass and kidney.	T1-Hypointense. T2-Hyperintense. DWI-restricted diffusion.	Tc-99m DMSA to assess the volume of functioning renal tissue.
Mesoblastic Nephroma	Well-defined mass with low-level homogeneous echoes.	Solid hypoattenuating renal lesion. Variable enhancement.	T1-Hypointense. T2-Variable. DWI-Restricted diffusion.	Does not play a role in diagnosis.
Rhabdoid tumor	Heterogeneous echotexture.	Lobulated with individual lobules separated by intervening areas of decreased attenuation, relating to either previous hemorrhage or necrosis. Calcifications may be seen. Heterogeneous enhancement.	T1-Variable. T2-Variable.	Does not play a role in diagnosis.
Adrenal Hemorrhage	At early stage -diffuse or inhomogeneous echogenicity. Later liquefies and becomes heterogeneously anechoic.	Round or oval, often with surrounding stranding of the perirenal fat. Early stage – hyperattenuating. Later liquefies with variable attenuation. Calcifications may be seen. Thin and somewhat uniform or heterogeneous and irregular enhancement.	Acute stage: T1-isointense or slightly hypointense. T2- markedly hypointense. Subacute stage: Hyperintense on T1 and T2. Chronic stage: hypointense rim is present on T1 and T2.	Photon deficient.
Rhabdomyosarcoma	Heterogeneous well-defined irregular mass of low to medium echogenicity.	Soft tissue density. Some enhancement.	T1-Low to intermediate intensity. T2-Hyperintensity DWI-restricted diffusion.	Tc99m-MDP and Gallium-67 may be useful for diagnosis.
Hepatoblastoma	Variable echogenicity is common.	Heterogeneous mass, which is usually hypoattenuating compared to surrounding liver. Heterogeneous enhancement.	T1-Hypointense. T2-Hyperintense.	Photopenic regions following either Tc-99m SC or IDA agents.
Leukemia	Heterogeneous echogenicity.	Hepatosplenomegaly. Lymphadenopathy. Heterogeneous enhancement.	T1-Hypointense. T2-Hyperintense.	Does not play a role in diagnosis.
Lymphoma	Heterogeneous soft tissue masses.	Lymphadenopathy in different sites. Heterogeneous enhancement.	T1-Hypointense. T2-Hyperintense.	Does not play a role in diagnosis.
Hemangioma	Increased echogenicity.	Variable attenuation. Centripetal enhancement.	T1-Hypointense T2-Heterogeneous.	Does not play a role in diagnosis.
Teratoma	Echogenicity due to fat and calcifications.	Mass that contains fat and calcifications. Heterogeneous enhancement.	Fat and/or calcifications in different sequences.	Does not play a role in diagnosis.
Abscess	Heterogeneous mass.	Heterogeneous mass containing air. Heterogeneous rim enhancement.	T1-Hypointense. T2-Hyperintense.	Scintigraphy with labeled leukocytes.

Table 2: Differential diagnosis table for neuroblastoma.

ABBREVIATIONS

CE = Carboplatin and etoposide
DMSA = Dimercaptosuccinic acid
DTPA = Diethylene-triamine-pentacetic acid
FDG = Fluorodeoxyglucose
FIESTA = Fast Imaging Employing Steady-state Acquisition
INSS = International Neuroblastoma Staging System
INRC = International Neuroblastoma Response Criteria
MDP = Methylene diphosphonate.
MIBG = Metaiodobenzylguanidine
MRI = Magnetic Resonance Imaging
SFOP = French Society of Pediatric Oncology
SIOP = International Collaboration for Neuroblastoma Research
SSFSE = Single Shot Fast Spin Echo

KEYWORDS

Adrenal gland; Neuroblastoma; Liver; Neonatal; Stage 4s

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