Perivascular Sparing: an unusual pattern of disseminated liver metastasis in an infant with stage 4S neuroblastoma

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ABSTRACT

We report a case of stage 4S neuroblastoma of the left adrenal gland in a 2-month-old female infant with imaging appearance of diffuse infiltrative liver metastasis showing perivascular sparing. Multiple imaging modalities including Computed tomography (CT), Magnetic resonance (MR), and Positron emission tomography (PET/CT) demonstrated similar distribution of the tumor involvement. The histopathologic results from liver biopsy confirmed the diagnosis of liver metastases. Follow-up MR Image at 4 months later showed marked improvement following surgical removal of the primary tumor and chemotherapy. Reviewing the literature, this is the first case with this unusual appearance of infiltrative liver metastases with perivascular sparing.

Neuroblastoma is the most common malignant abdominal tumor of infants and children. In the “International Neuroblastoma Staging System” (INSS), liver involvement is shown in stage 4 and 4S neuroblastoma. The stage 4S neuroblastoma is limited to infants <1 year of age with localized primary tumor and disseminated tumor restricted to skin, liver and/or bone marrow [1]. We here report a 2-month-old female infant with stage 4S neuroblastoma showing an unusual pattern of diffuse infiltrative liver dissemination with perivascular sparing on multi-modalities.

CASE PRESENTATION

A 2-month-old female full-term infant had no significant abnormality at birth. In the “International Neuroblastoma Staging System” (INSS), liver involvement is shown in stage 4 and 4S neuroblastoma. The stage 4S neuroblastoma is limited to infants <1 year of age with localized primary tumor and disseminated tumor restricted to skin, liver and/or bone marrow [1]. We here report a 2-month-old female infant with stage 4S neuroblastoma showing an unusual pattern of diffuse infiltrative liver dissemination with perivascular sparing on multi-modalities.
contrast administration, the perivascular branching appearance persisted (Fig. 1b). Left adrenal neuroblastoma was considered, with uneven fatty liver, or liver metastases of neuroblastoma.

Pre-enhanced Magnetic resonance imaging (MRI) revealed left adrenal gland tumor, hepatosplenomegaly and again heterogeneous liver parenchyma. The perivascular areas showed relatively normal signal intensity, while other peripheral areas showed increased T2-weighted and decreased T1-weighted signal intensity (Fig. 1c, 1d). There was no evidence of hepatic steatosis on T1-weighted dual gradient-echo in-phase and opposed-phase MR imaging. In the enhanced MR study, heterogeneity with relatively low enhancement was demonstrated at perivascular areas. Infiltrative type metastasis of neuroblastoma of the liver was considered.

PET/CT and bone scintigraphy were arranged for whole-body staging. PET/CT (Fig. 1f) showed increased uptake in the left adrenal gland and liver. An inhomogeneous, infiltrative appearance of increased glucose uptake

![Figure 1](image)

**Figure 1.** CT, MRI and PET-CT scan at different levels. a. pre-enhanced CT axial image; b. contrast-enhanced CT axial image; The CT scan shows a 2.4–cm left adrenal gland tumor (arrow in a.) with calcification, and infiltrative decreased density in the enlarged liver with an unusual perivascular sparing pattern. c. T2-weighted fat-saturated axial image (TR/TE = 2000/100ms); d. T1-weighted axial image (TR/TE = 15.049/4.7283ms); e. Post-enhanced T1-weighted axial image. On MRI, the perivascular areas show relatively normal signal intensity, while peripheral areas show increased T2-weighted and decreased T1-weighted signal intensities. Following contrast administration, heterogeneous enhancement with relatively low enhancement at perivascular areas is depicted. Note the left adrenal tumor in d. f. PET-CT scan reveals high FDG uptake in the left adrenal gland (arrow), and inhomogeneous infiltrative glucose uptake in the liver with reverse peripheral enhancement and perivascular sparing. These imaging findings suggest infiltrative tumor dissemination in the liver with perivascular sparing.
was noted in the liver on PET/CT scan with reverse peripheral enhancement and perivascular sparing. There was no other regional or distant metastasis or bone marrow involvement delineated on PET/CT and bone scintigraphy. Bone marrow biopsy showed no definite evidence of neuroblastoma involvement.

This patient was classified as stage 4S neuroblastoma with low to intermediate risk according to clinical staging, pathologic results, and gene study. Surgery for left adrenal gland and intraoperative liver biopsy were performed after general survey and staging. The histopathological results of the adrenal gland and liver both revealed neuroblastoma (Fig. 2). After surgery, she received 8 cycles of chemotherapy with Carboplatin, Etoposide, Cyclophosphamide and Doxorubicin. Four months later, follow-up MRI showed nearly total resolution of the infiltrative liver metastases (Fig. 3), reduction of the liver size, and no imaging evidence of recurrence.

DISCUSSION

Neuroblastoma is the most common malignant abdominal tumor of infants and children. According to INSS, tumor involvement and age are important prognostic factors. There is a special category, Stage 4S, defined as localized, resectable, primary tumor occurring in children younger than 1 year of age, and dissemination is limited to liver, skin, or bone marrow. In stage 4S neuroblastoma, more than 80% of patients have liver involvement [2]. In the literature, liver metastases in the neuroblastoma are either nodular or diffuse infiltrative in morphology [2, 3]. Hepatomegaly is the usual finding [3]. In our case, an unusual pattern of perivascular sparing of diffuse neuroblastoma dissemination in the liver was depicted on CT, MR and PET/CT. Reviewing the literature, this perivascular sparing pattern of liver metastasis from neuroblastoma has not been reported. Tazoe J et al. reported a case with unusual periportal fatty metamorphosis observed in diffuse liver metastases of stage 4S neuroblastoma [4]. In our patient, no overt fatty infiltration was shown on CT or MRI in the perivascular areas. An unusual “tree-and-branch” appearance of the perivascular sparing was observed on multi-modalities. The histopathological results of liver biopsy proved the diagnosis of tumor dissemination.

123I-metaiodobenzylguanidine (MIBG) is helpful in staging of neuroblastoma, showing uptake in the primary and secondary diseases [5]. The MIBG scan was not performed in this patient because the 123I-MIBG radioisotope was not commercially available in Taiwan. The

Figure 2

2a Figure 2. Photomicrographs of left adrenal tumor (a. hematoxylin and eosin; original magnification, 100X) and liver biopsy (b. hematoxylin & eosin, original magnification, 100X,) both compatible with neuroblastoma. Sections of adrenal gland and liver biopsy show small-sized neoplastic cells with round hyperchromatic nuclei arranged in multiple vague nodules separated by delicate fibrous septa.
role of PET scan is still under evaluation. Sharp SE et al. reviewed 60 patients with neuroblastoma and found that 
$^{18}$F-FDG PET scan was superior to $^{123}$I-MIBG scan in 
detecting stage 1 and 2 neuroblastoma, with disease extent 
in the chest, abdomen, and pelvis [6]. However, PET is 
inferior to $^{123}$I-MIBG scan in the evaluation of high grade 
(such as stage 4) neuroblastoma. [6, 7]. In normal cases, 
the liver parenchyma shows relatively perivascular high 
FDG uptake on PET-CT scan. In our patient, the PET scan 
showed reverse peripheral enhancement and perivascular 
sparing. The results could support the diagnosis of tumor 
dissemination in the liver with perivascular sparing.

Other diffuse liver diseases should be listed in the 
differential diagnoses. Diffuse liver diseases can be 
categorized as storage, vascular, and inflammatory causes, 
depending on the predominant pathophysiologies [8]. In the 
storage group, a list of diseases has been reported, such as 
fatty liver, Wilson disease, glycogen, lipid storage disease, 
and mucopolysaccharidoses. Hepatic steatosis, hepato-
splenomegaly, and chronic cirrhosis may be demonstrated. 
In some inflammatory disease, such as acute viral hepatitis, 
the CT or MR findings may show hepatomegaly, peripheral 
edema, heterogeneous density and enhancement of the 
liver, which are similar to those of our patient. Regarding 
the vascular group, in early stage of Budd-Chiari disease, 
diffuse heterogeneous density and “mosaic” enhancement 
of liver parenchyma will be depicted, mimicking the 
imaging appearances of our patient. In our patient, the 
T1-weighted dual gradient-echo in-phase and opposed-
phase MR imaging showed no evidence of steatosis. There 
were no symptoms or signs supporting the diagnosis of 
storage abnormalities or infection. There was no evidence 
of hepatic or caval venous occlusion found in our patient on 
dynamic MR study with contrast. Furthermore, the unusual 
distribution of hepatic lesion disappeared on follow-up MR 
study after chemotherapy.

This unusual pattern of liver dissemination of neurob-
lastoma with perivascular sparing has not been reported in 
the literature. The liver metastases from other organs may 
occur via hematogenous, lymphangitic spreading, or direct 
invasion. The etiology of this unusual perivascular sparing 
patterns of neuroblastoma dissemination in the liver is 
unknown. The possible pathophysiology may be caused by 
the hematogenous tumor spreading, seeding from periphery 
of liver, and growing centripetally, finally causing perivas-
cular sparing. In this patient, the histopathology results 
of liver biopsy proved neuroblastoma dissemination. The 
perivascular sparing of the tumor was suggested by the 
findings of multiple imaging modalities.

To our knowledge, this is the first case with perivas-
cular sparing appearance of the liver dissemination in the 
neuroblastoma. Ultrasound, CT or MR studies can well

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**Figure 3.** MR images at 4 months later following chemotherapy. **a.** T2-weighted axial image (TR/TE = 2100/100ms); **b.** Non-enhanced T1-weighted axial image (TR/TE = 15.049/5.5985ms). Significant improvement of the tumor infiltration and reduction of the liver size are demonstrated.
Perivascular sparing of liver metastases in neuroblastoma. If the diagnosis is uncertain, the PET or MIBG scans may be helpful to support the diagnosis and for staging.

REFERENCES