Neuroblastoma is the most common extracranial solid tumor in children and the most common tumor in infants. The etiology of neuroblastomas is not clearly understood. They arise in tissues which have sympathetic nerves, such as the adrenal glands, and paramedian sympathetic chain. A neuroblastoma arising in solid organs other than the sympathetic nervous system is extremely rare, and only a few cases of primary pancreatic neuroblastoma have been reported. Here, we report a case of 29-year-old woman who presented with a solitary hepatic mass. Grossly, the mass was large, creamy, rubbery firm, and showed focal hemorrhage and central cavitation. Microscopically, the tumor cells were arranged in small nests of spindle to ovoid cells with abundant neuropil. The neuroblastic nature of the tumor was confirmed by immunohistochemistry and electron microscopy. No extrahepatic mass was found, despite a thorough systemic survey such as chest and abdominopelvic computed tomography (CT) scans and a whole body positron emission tomography-CT study. To the best of our knowledge, this is the first report of a bona fide primary hepatic neuroblastoma.

**Key Words:** Neuroblastoma; Liver neoplasms; Microscopy, electron; Adult
the combination chemotherapy. Subsequently, she underwent a trisegmentectomy (segments 4, 5, and 8) to remove the residual hepatic mass. Neither enlarged lymph nodes nor peritoneal dissemination was detected intraoperatively.

The resected liver specimen showed a huge (15 × 8.5 × 7.3 cm), solid mass with central cavitation. The cut surface was creamy white, rubbery firm, and focally hemorrhagic (Fig. 2A). The mass abutted the capsule and resection margin. The non-neoplastic hepatic parenchyma adjacent to the mass was not cirrhotic. Microscopically, the tumor cells formed nests of variable sizes that dissected the hepatic sinusoids and connective tissue (Fig. 2B). The tumor replacing hepatic parenchyma left the multifocally entrapped hepatic parenchyma intact, and tissue destruction was unremarkable. Individual tumor cells were small and relatively monotonous in their appearance and had hyperchromatic nuclei and indistinct nucleoli (Fig. 2C). Notably, the tumor cells had abundant fibrillary cytoplasm, which was intermingled with neuropil-like stroma (Fig. 2D). Although the neuronal differentiation of this tumor was reflected by the abundant neuropil, no typical ganglion cells were found. Additionally, no typical tumor cell rosette was found. Immunohistochemical staining was performed to confirm the neuroblastic nature of the tumor. Tumor cells were strongly reactive to synaptophysin (Fig. 2E), CD56, and neurofilament protein (Fig. 2F), supporting the notion of neuronal differentiation. CD99 was stained weakly in fibrillary material. Cytokeratin expression was not detected. A transmission electron microscopic examination revealed several dense core granules and relatively well-defined microtubules, further supporting the neuronal differentiation (Fig. 3). Considering tumor morphology and the results of ancillary studies together, we diagnosed this tumor as a neuroblastoma. Her initial liver biopsy slide was reviewed, and the histological features of the biopsy specimen were identical to those of the resected specimen. Therefore, we corrected the diagnosis of the biopsy specimen. Because a primitive neuroectodermal tumor (PNET) can show histological features similar to the present case and has been reported in the liver, we performed a reverse transcription-polymerase chain reaction (PCR) study to detect EWS-FLI1 and EWS-ERG1 fusion transcripts, but the results were negative (data not shown). In addition, MYCN gene amplification was not found in the PCR-based study (data not shown).

The post-operative follow-up period was uneventful and no recurrent tumor was detected on a follow-up CT examination taken 4 months after surgery. Serum and urine catecholamine levels were in the normal range. Because the diagnosis of neuroblastoma was not made before resection, it is unknown whether the preoperative serum or urine catecholamine levels were elevated or not.

**DISCUSSION**

In the present report, we described a hepatic neuroblastoma that was presumably of primary liver origin. This case is extraordinary and interesting because the tumor was present only in the liver and because it developed in a previously healthy patient of relatively old age. To the best of our knowledge, our case is the first primary hepatic neuroblastoma. Although spontaneous regression or delayed recurrence of a neuroblastoma has been reported as not uncommon, we could not find any evidence of neoplastic lesions outside of the liver or any previous history of neuroblastoma.

A neuroblastoma usually occurs in organs with sympathetic nervous tissue. The adrenal gland is the most common organ, followed by the neck, mediastinum, and pelvis. Neuroblastoma of the liver is detected as metastatic disease along with a primary adrenal tumor almost exclusively. A case of solitary hepatic neuroblastoma has been reported, but that case was a delayed metastasis after complete remission of an adrenal neuroblastoma. However, we could not detect any evidence of neuroblastoma throughout the body in the present case.

An alternative explanation is that the solitary hepatic neuroblastoma formed by spontaneous regression of a primary neuroblastoma, which occurred in other organs with subsequent late hepatic metastasis. Indeed, neuroblastomas sometimes regress spontaneously. In a large-scale study investigating the natural
Fig. 2. (A) Gross appearance of the resected liver specimen. A well demarcated creamy white solid mass is replacing the resected liver. In the center is a large cavity that is filled with yellow serous fluid on arrival (removed during cutting). Some hemorrhagic spots and entrapped non-neoplastic hepatic parenchyma are evident within the tumor. (B) Microscopically, the tumor consists of nests of small blue round cells and neuropil-like stroma (H&E, × 40). (C) The tumor cells are relatively monotonous and have a round, mildly hyperchromatic nuclei and a moderate amount of clear or fibrillary cytoplasm (H&E, × 100). (D) Notably, the tumor cells have abundant fibrillary cytoplasm that is intermingled with neuropil-like stroma (H&E, × 200). (E) Immunohistochemical staining for synaptophysin is strongly positive in the tumor cells (Synaptophysin, × 200). (F) The fibrillary matrix is stained with neurofilament protein immunostaining (Neurofilament protein, × 200).

A course of a subset of patients with a neuroblastoma (stage I or II, < 5 cm in diameter) without any treatment, 13 out of 22 cases (55%) showed spontaneous regression. The mechanism of spontaneous regression is reportedly a type of programmed cell


death associated with the accumulation of autophagic vacuoles due to lysosomal-associated protein multispanning transmembrane 5 mediated lysosomal destabilization.\(^7\) Spontaneous regression is more common in infants than children and is more frequent in MYCN-non-amplified stage 4S neuroblastoma.\(^8\) However, this “spontaneous regression and late hepatic metastasis” hypothesis cannot be demonstrated in the present case because there was no evidence of a previous neuroblastoma.

The pathological diagnosis of the present case was relatively straightforward. A possible differential diagnosis was PNET, not only because a case of primary hepatic PNET has been reported but also because a PNET can show similar histological features to the present case. However, the absence of the EWS-FLI1 and EWS-ERG1 fusion transcripts along with the typical neuroblastic nature of the present case excluded the possibility of PNET.

The histogenesis of a primary hepatic neuroblastoma is unknown. However, it is plausible that a primary hepatic neuroblastoma may arise from intrahepatic sympathetic nervous tissue, because sympathetic nervous system innervates the liver and plays important roles such as tissue repair and glucose metabolism.\(^9,10\) In agreement with this idea, a few cases of primary hepatic parangglioma have been reported.\(^11-14\) Because neuroblastomas and paranggliomas share a common histogenesis and there are several examples of hybrid or transitional tumors between the two,\(^15\) the present case may represent one end of the “sympathetic nervous tumor” spectrum that shows predominant neuroblastic features.

In this report, we described the first primary hepatic neuroblastoma with detailed clinicopathological features. Morphologically evident neuronal differentiation and the absence of MYCN gene amplification in our case suggested a less aggressive clinical course but the exact biological behavior of the present case remains to be determined. We suggest that neuroblastoma should be considered in the differential diagnosis when a solitary hepatic tumor histologically resembles a neuroendocrine tumor. Furthermore, cases similar to the present one should be collected and followed up further to define the nature of this intriguing tumor.

REFERENCES

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