Undifferentiated Sarcoma of the Liver

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Undifferentiated (embryonal) sarcoma of the liver (USL) is a rare primary hepatic malignancy principally affecting patients of pediatric age. It is believed to be a primitive mesenchymal neoplasm, which usually behaves in a highly malignant fashion. The median survival has been less than a year. The only chance for cure appears to be radical excision of the tumor. However, some patients may develop recurrent disease despite complete surgical resection of the tumor. Recently, long-term disease-free survival has been achieved in cases which underwent aggressive multimodal treatment. Herein we report on a 12-year-old girl who underwent surgical excision of USL. Histologically, it was composed of pleomorphic stellate or spindle-shaped cells in a myxoid stroma. Characteristic periodic acid Schiff-positive, diastase-resistant intracytoplasmic hyaline globules were seen. Immunohistochemically, the tumor cells were positive for vimentin, α1-antitrypsin, and α1-antichymotrypsin. In addition, p53 protein was expressed in 40% of tumor cells, and Ki-67 was demonstrated in 45% of tumor cells. Postoperative chemotherapy was recommended, but was refused by the patient's family. A recurrent liver mass was found 171 days after the operation. Chemotherapy was refused once again by the patient's family, and she was lost to follow-up for 5 months. The patient was brought to the outpatient clinic again because of abdominal fullness and back pain. The recurrent tumor was 20 cm in size with compression of the inferior vena cava. She was admitted and received chemotherapy with vincristine, ifosfamide, and cisplatin. (Chang Gung Med J 2002;25:399-404)

Key words: undifferentiated (embryonal) sarcoma, liver, p53 protein, Ki-67.

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Undifferentiated (embryonal) sarcoma of the liver (USL) is a rare hepatic neoplasm found predominantly in the first 2 decades of life.1) It was first recognized as a clinicopathologic entity by Stocker and Ishak in 1978.1) Before their report, this tumor had been described under different names such as embryonal sarcoma,2) mesenchymoma,3) primary sarcoma,4) or fibromyxosarcoma.5) The median survival has been less than a year1) because its biological behavior is highly malignant.6) However, long-term disease-free survival has recently been achieved in some cases undergoing aggressive multimodal treatment.6,7) Herein, we report on a case of USL in a child and discuss the clinical, pathologic, and immunohistochemical features of this rare malignancy.

CASE REPORT

A 12-year-old girl suffering from right upper quadrant pain for a week was first seen at a local hospital. Abdominal computed tomography (CT) performed there revealed a liver tumor of 15 cm in the right lobe. She was subsequently transferred to our hospital. A right upper quadrant mass with tenderness was palpable. Laboratory tests showed

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leukocytosis (WBC count: 12.2 \times 10^9/l), elevated aspartate aminotransferase (75 U/l), alanine aminotransferase (55 U/l), and alkaline phosphatase (121 U/l). Direct hyperbilirubinemia (direct/total bilirubin: 14/32 \mu mol/l) was also detected. Alpha-fetoprotein (1.45 \mu g/l) was within normal limits. Hepatitis B virus surface antigen and anti-hepatitis C virus antibody were negative. Abdominal ultrasonography revealed a huge heterogeneous mass with cystic components in the right lobe of the liver (Fig. 1). A right hepatectomy was performed. Postoperative chemotherapy was recommended, but was refused by the patient's family. She was discharged 11 days after the operation, and received follow-up in the outpatient clinic. Abdominal ultrasonography performed 3 months later showed no evidence of tumor recurrence. However, on postoperative day 171, a follow-up abdominal CT showed a large heterogeneous mass with heterogeneous enhancement in the medial segment of the left lobe of the liver. It was compatible with a recurrent tumor. Chemotherapy was once again refused by the patient's family, and she was lost follow-up for 5 months. The patient was brought to the outpatient clinic again because of abdominal fullness and back pain. The recurrent tumor was 20 cm in size with compression of the inferior vena cava. She was admitted and received chemotherapy with vincristine, ifosfamide, and cisplatin.

The resected specimen consisted of a piece of liver measuring 20 \times 18 \times 8.5 cm and weighing 1800 g. Upon cutting, a white and soft tumor measuring 18 \times 16 \times 8 cm was seen 0.2 cm away from the nearest resection margin. Cystic spaces and hemorrhagic foci were observed (Fig. 2). Histologically, the tumor was composed of pleomorphic spindle-shaped and stellate cells in a myxoid stroma with hemorrhage, necrosis, and entrapped dilated bile ducts (Fig. 3). Tumor cells were either closely packed or loosely scattered with marked nuclear pleomor-

![Fig. 1](#) Abdominal ultrasonography showing a heterogeneous mass (arrowheads) with cystic components in the right lobe of the liver.

![Fig. 2](#) A well-demarcated white and soft tumor with cystic spaces and focal hemorrhage.

![Fig. 3](#) Tumor composition of pleomorphic spindle-shaped and stellate cells in a myxoid stroma. Entrapped bile ducts can be seen at the periphery. (H & E stain, 100×)
phism. Brisk mitosis and atypical mitotic figures were present. Bizarre and multinucleated giant tumor cells were also seen. Periodic acid Schiff (PAS)-positive, diastase-resistant hyaline globules were found in the cytoplasm of the tumor cells (Fig. 4).

Immunohistochemically, the tumor cells were positive for vimentin, α-antithrombin, and α-antichymotrypsin. Immunostainings for cytokeratin, α-fetoprotein, desmin, muscle-specific actin, smooth muscle actin, S-100 protein, and factor VIII-related antigen were all negative. P53 protein was expressed in 40% of tumor cells, and Ki-67 was demonstrated in 45% of tumor cells.

Ultrastructurally, the tumor was composed of primitive mesenchymal cells. Membrane-bound electron-dense inclusions were seen in some tumor cells. Because the tissue was retrieved from a paraffin block, most of the ultrastructural details were indiscernible.

**DISCUSSION**

USL is an uncommon liver malignancy seen most frequently in pediatric patients. More than 90% of patients are younger than 20 years of age; there is no sexual preponderance. The most common clinical presentation is abdominal pain or a palpable mass. The tumor is well circumscribed, solid to cystic, and mostly occurs in the right lobe. Leukocytosis and elevated aspartate aminotransferase and alkaline phosphatase are not uncommon laboratory findings. The serum α-fetoprotein level is always normal. There is no correlation with hepatitis B or C virus infection.

On cross-section, the tumor is often soft and variegated, with white gelatinous areas and foci of tumor necrosis and hemorrhaging. It is typically well demarcated, but not encapsulated. Most tumors have prominent areas of cystic degeneration. Tumor rupture with massive intraperitoneal hemorrhaging may occur. Cases with hepatic vein invasion and extension up to the inferior vena cava into the right atrium and ventricle have also been reported. Under the microscope, the tumor appears to be an undifferentiated sarcoma without a specific pattern or differentiation. It is composed of pleomorphic stellate or spindle-shaped cells in a myxoid stroma. Multinucleated giant tumor cells with eosinophilic cytoplasm and frequent mitosis are usually present. PAS-positive, diastase-resistant hyaline globules, which are believed to be lysosomes or apoptotic bodies, are frequently seen within tumor cells as well as in extracellular stromata. Although such findings are considered to be characteristic of USL, they can also be observed in malignant fibrous histiocytoma as well. The presence of entrapped hepatocytes and dilated bile ducts at the periphery of the tumor is another histologic feature, which is also seen in mesenchymal hamartoma. Mesenchymal hamartoma is the most common benign hepatic tumor in children. Stromal cells in mesenchymal hamartoma are benign in appearance. Therefore, it is not difficult to distinguish between these 2 entities. Other differential diagnoses for USL include embryonal rhabdomyosarcoma, sarcomatoid variant of hepatocellular carcinoma, and hepatoblastoma of mixed epithelial and mesenchymal pattern. Embryonal rhabdomyosarcomas mainly occur in large bile ducts and contains rhabdomyoblasts with cross-striations, whereas no discernible specific differentiation of rhabdomyoblasts can be recognized by routine light microscopy in USL. Hepatocellular carcinomas with sarcomatoid areas may mimic USL, but typical areas of the carcinoma can always be found by thorough sampling. As for hepatoblastomas of mixed epithelial and mesenchymal pattern, the differences are readily identifiable. One
is the mixture of epithelial and mesenchymal tissues in the tumor, and another is the benign nature of the mesenchymal component.

Immunohistochemically, USL may express divergent differentiation, as evidenced by positive results for desmin, muscle-specific actin, S-100 protein, or cytokeratin in some cases. The tumor cells are always positive for vimentin, and are often positive for \( \alpha \)-antitrypsin and \( \alpha \)-antichymotrypsin. However, these markers are non-specific. Overexpression of p53 protein in our case may or may not have resulted from p53 gene mutation, since a case with a point mutation of the p53 gene has been reported. Our finding of a high Ki-67 score indicates high proliferative activity of the tumor. This has been seen in previous flow cytometric DNA studies in which a high growth fraction with aneuploidy was noted in 3 of 7 cases. USL is consistently negative for \( \alpha \)-fetoprotein. This is an important finding to differentiate it from hepatocellular carcinoma and hepatoblastoma. Electron microscopy reveals primitive mesenchymal cells with well-developed endoplasmic reticulum and membrane-bound electron-dense inclusions. Occasional cells with differentiation toward fibroblasts, histiocytes, myofibroblasts, leiomyoblasts, and rhabdomyoblasts have been reported. It has been postulated by most workers that USL is a primitive mesenchymal neoplasm, possibly derived from a primitive multipotential precursor cell that may have foci of differentiated sarcoma. The histogenesis of USL remains uncertain, but histologic, ultrastructural, and immunohistochemical features point to a possible correlation with malignant fibrous histiocytoma. One reported case of USL with cytogenetic analysis showed near triploid and near hexaploid clones with extensive chromosomal rearrangements, which is similar to that seen in some soft tissue sarcomas, including malignant fibrous histiocytomas, leiomyosarcomas, and osteosarcomas. As previously mentioned, a mesenchymal hamartoma is similar to USL histologically except for the benign stromal component. Interestingly, a case of USL arising in a mesenchymal hamartoma has been reported. Flow cytometric analysis showed that the mesenchymal hamartoma part was diploid, while the USL part displayed a prominent aneuploid peak (DNA index=1.62). Cytogenetic analysis of the USL part showed structural alterations of chromo-

some 19 which had been identified in cases of mesenchymal hamartoma as well. It has been suggested that USL might be the malignant counterpart of mesenchymal hamartoma.

USL behaves in a highly malignant fashion, and the median survival has been less than a year. Complete surgical resection is the key to a favorable outcome. However, despite apparent complete resectability in some cases, local recurrence and distant metastases have been major impediments to achieving long-term disease-free survival. Recent studies have shown that the best results with more cases of long-term disease-free survival can be achieved by aggressive multimodal treatment, including surgery and adjuvant chemotherapy. Preoperative chemotherapy may provide sufficient tumor shrinkage to enable surgical resection, while postoperative chemotherapy plays an important role in preventing recurrence.

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肝未分化肉瘤

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肝未分化肉瘤是一種主要發生於兒童的罕見原發性肝臟惡性腫瘤。它被認為是一種原始間葉腫瘤，並有高恶性度的表現，過去平均存活不到一年。完全切除腫瘤是治療的唯一希望，但即使完全切除，仍有多數病人會有腫瘤再發。近年來利用積極性多模式治療，併用外科切除和化學治療，已有更多長期存活病例。我們在此報告一例接受切除肝未分化肉瘤的12歲女性病患。組織學上，腫瘤由多形性呈現或梭狀細胞和黏液樣間質所組成，並有典型的過碘酸Schiff陽性，澱粉樣質抗性的透明小球。免疫組織化學方面，腫瘤細胞是vimentin，αv-抗雌蛋白酵素，和αv-抗雌凝乳蛋白酵素陽性。另外，有40%的腫瘤細胞表現p53蛋白，Ki-67則在45%的腫瘤細胞染出。手術後建議病患接受化學治療，但家屬拒絕。術後第171天發現再發性肝腫瘤，家屬再度拒絕化學治療，並不再回診追蹤。5個月後，病人因腹胀及背痛回到門診，此時再發性腫瘤已達到20公分並壓迫下腔靜脈。病人於住院後接受vincristine，ifosfamide，及cisplatin化學治療。(長庚醫誌 2002;25:399-404)

關鍵字：未分化肉瘤，肝，p53蛋白，Ki-67。