Case Report
An undifferentiated embryonal sarcoma of the liver containing adipophilin-positive vesicles in an adult with massive sinusoidal invasion

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Received July 4, 2012; Accepted August 23, 2012; Epub October 1, 2012; Published October 15, 2012

Abstract: Undifferentiated embryonal sarcoma of the liver (UESL) is a malignant mesenchymal tumor that occurs typically in children and rarely in adults. Here we describe a case of UESL in a 51-year-old woman who presented with a cystic lesion in the liver. Because it grew slowly, the anterior segment of the liver was resected to check the lesion. Histologically, the lesion looked like a telangiectatic hepatic adenoma. Two years after resection, the tumor recurred, and she died 3 years later due to liver failure. The autopsy revealed that these lesions were UESL with massive sinusoidal invasion, and a review of the case indicated the primary lesion was also UESL. We also confirmed these tumor cells by staining with CD56, alpha-smooth muscle actin (SMA), and adipophilin, suggesting that they have a character similar to that of stellate cells in the space of Disse. The histological result of our patient revealed atypical UESL. Therefore, UESL should be considered when a hepatic lesion with degeneration is seen, even in an adult. In addition, the immunohistochemical appearance of this case implies that UESL is perhaps derived from stellate cells or stellate cells with myofibroblast differentiation in the space of Disse.

Keywords: Adipophilin, adult, hepatic adenoma, liver, stellate cell, undifferentiated embryonal sarcoma

Introduction

Undifferentiated embryonal sarcoma of the liver (UESL) is a malignant mesenchymal tumor first characterized by Stocker and Ishak in 1978 [1]. It is very aggressive and prognosis is poor. UESL typically occurs before the second decade of life and is rare in adults. To the best of our knowledge, only 14 cases of UESL have been reported in patients over 50 years of age [1-3]. Typically, UESL is a solid tumor composed of bizarre spindle cells and polygonal cells loosely arranged in a myxoid matrix. Tumor cells sometimes infiltrate slightly into the adjacent liver parenchyma with entrapped hepatocytes in the invasion front of UESL. Because of the rarity of UESL in adults, it may be misdiagnosed as another type of neoplasm, including some kinds of sarcoma and hepatocellular carcinoma [1, 4-6]. Furthermore, due to its primitive-ness and the diversity of histological appearance, the origin of UESL remains unknown.

In this paper, we describe a case of UESL in an adult that mimicked hepatic adenoma. The tumor showed massive intrasinusoidal invasion with sinusoid dilatation, and its appearance was similar to that of a hepatocytic lesion. Such histological appearance and immunohistochemical features suggest that UESL has a character resembling that of stellate cells in the liver.

Clinical summary and pathological appearance of the primary lesion

The patient was a 51-year-old Japanese woman who had suffered from multiple sclerosis for 20 years. Liver function tests were slightly abnormal when she was admitted to our hospital for
UESL with adipophilin-positive vesicles in adult

an exacerbation of multiple sclerosis, and her liver was checked by computed tomography (CT). On CT, there was a small cystic lesion (approximately 1 cm diameter) in the right lobe of the liver. Laboratory data indicated no hepatitis viral infection. At the age of 53 years, the cystic lesion had grown to 10 cm in diameter (Figure 1A). Because it was very difficult to determine whether or not it was malignant by CT, the anterior segment of the liver was resected and pathological analysis was performed.

The hepatic lesion was a soft, hemorrhagic mass with degeneration, measuring 12 × 11 × 7 cm (Figure 1B). Histologically, the lesion looked as if hepatocytes had proliferated with sinusoidal dilatation and congestion (Figure 1C and 1D). Because there were few atypical cells, the lesion was diagnosed as telangiectatic hepatic adenoma (THA) at that time.

However, when the patient was 55 years old, she developed multiple cystic lesions in the liver and metastatic lesions in the left lung (0.5 cm in diameter) and thoracic spine (5 × 3.5 cm). At 56 years old, she died of liver failure due to tumor occupation. An autopsy was performed on the liver.

Pathological findings on autopsy

The liver weighed 2440 g. In gross morphology, there were many round, well-circumscribed, but incompletely encapsulated lesions (9 cm maximum diameter) containing gelatinous or coagulated blood (Figure 2A). The periphery of these tumors had a solid but soft component demonstrating gray-white, reddish, or green bile.

Histologically, most parts of the tumor were degenerated. In the solid component, spindle

Figure 1. A: Computed tomography scan at 53 years old. There is a cystic lesion (approximately 10 cm in diameter) with septa in the right lobe of the liver. B: Gross features of the primary lesion. The cut surface is reddish and soft, with degeneration. C and D: Microscopic features of the primary lesion. Low power and medium power views showing a fibrous capsule containing hepatocyte cords with sinusoidal dilatation, congestion and hemorrhage.
shaped, polygonal, and multi-nucleated cells were arranged in sheets between hepatocyte cords and bile ducts (Figure 2B). In some lesions, congestion and hemorrhage with dilation of sinusoidal spaces was seen, similar to the primary lesion (Figure 2C). In other lesions, bizarre cells (Figure 2D) or hemangiopericytoma-like structures were also present (Figure 2E). The background liver tissue showed neither hepatitis nor fibrosis.
The metastatic lesion in the thoracic spine was gray-white and solid, and the cut surface exhibited hemorrhage. Histologically, the metastatic lesion contained no hepatocytic cells, but spindle, polygonal, and bizarre cells were seen in an edematous matrix (Figure 2F), suggesting that...
UESL with adipophilin-positive vesicles in adult hepatocytic cells in the primary and recurrent lesions were not tumor cells but pre-existing hepatocytes.

Immunohistochemical analysis revealed that the spindle cells expressed vimentin diffusely (Figure 3A). They also expressed CD56 (neural cell adhesion molecule) at the cell membrane (Figure 3B). Some spindle cells were positive for alpha-smooth muscle actin (SMA) (Figure 3C), muscle-specific actin (HHF-35), and desmin. A few tumor cells were also CD68 positive. In addition, some bizarre cells contained small vesicles stained positively with adipophilin (adipose differentiation-related protein) in the cytoplasm (Figure 3D, arrows). Staining for cytokeratin CAM5.2, cytokeratin AE1/AE3, EMA, hepatocyte-1, S100, CD10, HMB-45, glypican-3, CD31 (Figure 3E), and CD34 was negative.

Diastase-treated periodic acid-Schiff (PAS) staining revealed giant cells containing PAS-positive spherical globules, commonly seen in UESL [1, 7]. On the basis of these findings, we diagnosed the hepatic lesion on autopsy as UESL with massive sinusoidal invasion and hepatocyte entrapment.

On review of the primary lesion, a few atypical cells with diastase resistant PAS-positive globules were seen between hepatocyte cords (Figure 3F), and CD56 positive cells were seen in dilated sinusoidal spaces. We also compared the immunohistochemical profiles, including adipophilin, of the primary lesion, the recurrent hepatic lesion and the metastatic lesion. The results indicated that these tumors were of the same origin (data not shown).

Discussion

In children in the first and second decades of life, UESL is the third most common malignant tumor in the liver. However, UESL is extremely rare in adulthood [1-3]. Moreover, UESL shows an enormous variety of histological features; for example, epithelioid appearance, spindle cells with herringbone arrangement, hemangio-pericytoma-like structure, rhabdomyosarcomatoid or liposarcoma-like appearance. Due to such scarcity and diversity of histological features, UESL in adults tends to be misdiagnosed [1].

In the present case, autopsy revealed that the recurrent lesions contained mainly two types of cells—atyypical spindle cells and hepatocytic cells. Both types of cells were also seen in the primary lesion. In this case, the most important point to diagnose was whether or not the hepatocytic cells in these lesions were a tumor component. If only the hepatocytic cells had been tumor cells, the primary lesion would have been a hepatic adenoma because the hepatocytic cells were only slightly atypical and did not invade adjacent parenchyma. Indeed, we initially diagnosed the primary lesion as THA because there were many hepatocytes with sinusoidal dilatation and few atypical cells. However, the tumor had recurrent and metastatic lesions, indicating malignancy, and the metastatic lesions outside the liver did not contain hepatocytic cells. Moreover, there were some portal areas with bile ducts between hepatocytic cells in the primary and recurrent lesions (Figure 2B). Therefore, we concluded that these hepatocytic cells were not tumor cells but pre-existing hepatocytes. It was also suggested that only spindle cells infiltrating into sinusoids were tumor components.

Although UESL exhibits aggressive behavior, UESL usually shows expansive growth with an incomplete, fibrous capsule, or only slight invasion [4, 8, 9]. Levy et al. reported a series of UESL, in which only 3 of 24 cases showed entrapment of hepatocytes in the tumor periphery [9]. UESL with both massive sinusoidal invasion and hepatocyte entrapment, as in the present case, has not been reported yet. This is why THA is an uncommon candidate for differential diagnose of UESL.

The origin and the direction of differentiation of UESL remain unclear. Recently, two groups reported CD56 expression in UESL. Pérez-Gómez et al. reported that UESL expressed CD56 diffusely in eight cases in children [6], and Li et al. reported diffuse immunostaining for CD56 in UESLs in four adults [5]. In both reports, membranous staining for CD56 was observed in every examined UESL case. On the other hand, Nishio et al. showed that UESL showed myofibroblastic differentiation by immunohistochemistry and electron microscopy [8]. In the present case, tumor cells express CD56 (Figure 3B), desmin, and alpha-SMA (Figure 3C), which is consistent with other
reports. Moreover, adipophilin expression was detected in some tumor cells (Figure 3D), showing that UESL in this case contains intracytoplasmic fat droplets, as reported by Agaram et al [10]. In liver tissue, it is known that adipophilin is expressed in not only hepatocytes with steatosis but also stellate cells [11, 12]. Hepatic stellate cells are known as vitamin A storage cells located in the space of Disse, and they are sometimes differentiated into myofibroblasts. In the present case, tumor cells are located mainly in the subendothelial space, a similar situation to stellate cells. It is also known that hepatic stellate cells express CD56 [13] and alpha-SMA [11] to some degree. These findings suggest that parts of the tumor cells exhibited a character similar to that of stellate cells in the space of Disse. This insight is consistent with the tumor cell behavior in the present case, where for example, tumor cells showed massive sinusoidal invasion. Although there are no other reports on adipophilin staining in UESL, we consider it a valuable means of verifying adipophilin expression in cases of UESL. Presently UESL is a diagnosis of exclusion. However, such immunohistochemical profiling including CD56 and adipophilin will be useful for UESL.

In conclusion, when a hepatic lesion with sinusoidal dilation is found, not only hepatocytic neoplasm like THA, but also the invasion of UESL should be considered. To prevent misdiagnosis, careful analysis is required and immunohistochemical profiling including CD56 and adipophilin may be helpful.

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