Hepatic Angiosarcoma with Dyskeratosis Congenita

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Abstract

Nail dystrophy, oral leukoplakia and abnormal skin pigmentation are the defining features of dyskeratosis congenita. Dyskeratosis congenita is a disorder of poor telomere maintenance and is known to increase the risk of developing multiple types of malignancy. However, there are few reports of liver tumors arising in dyskeratosis congenita patients. We herein report the second case of hepatic angiosarcoma arising from dyskeratosis congenita: a 23-year-old man was introduced to our hospital due to the detection of multiple tumors in the liver. A histological analysis showed angiosarcoma that stained positive for antibodies to both CD31 and blood coagulation factor VIII.

Key words: hepatic angiosarcoma, dyskeratosis congenita

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Introduction

Dyskeratosis congenita is an inherited bone marrow failure syndrome characterized by abnormal skin pigmentation, nail dystrophy and oral leukoplakia (1-4). The disease is associated with a predisposition to cancer, with an increased risk for squamous cell carcinoma and hematolymphoid neoplasms (1-4). Dyskeratosis congenita, which was first described by Zinsser in 1906 (5) and recognized as a clinical entity by Engman (6) and Cole (7), is also known as Zinsser-Cole-Engman syndrome. Bone marrow failure is the principal cause of premature mortality in patients with this condition, followed by pulmonary fibrosis and cancer (1).

Dyskeratosis congenita carries an increased risk of developing multiple types of malignancy, including epithelial cancers, especially head and neck squamous cell carcinoma and gastrointestinal cancers (8). However, there are few reports of liver tumors arising in dyskeratosis congenita patients (8, 9). We herein report the second case of hepatic angiosarcoma arising from dyskeratosis congenita (9).

Case Report

A 23-year-old man was found to have a liver tumor and subsequently visited our hospital. He had a past history of mental retardation and was found to exhibit color changes of the tongue at 3 years of age. Pigmentation of the auricles appeared at 7 years of age, after which the pigmentation spread to the neck and limbs. Thereafter, nail dystrophy of the toes appeared at 13 years of age, and finger nail dystrophy appeared at 16 years of age. The patient was referred to a dermatologist and was finally diagnosed with dyskeratosis congenita based on the triad of 1) nail dystrophy, 2) oral leukoplakia and 3) abnormal skin pigmentation (Fig. 1). At 19 years of age, hepatosplenomegaly and liver dysfunction were noted. Although no hepatic tumors were observed in a routine checkup with abdominal ultrasound at 22 years of age, a hepatic tumor measuring 10 cm in diameter was detected during a routine checkup using abdominal ultrasound at 23 years of age. Furthermore, abdominal computed tomography (CT) revealed multiple hepatic tumors, which led the patient to consult our hospital. The patient had no past history of alcohol consumption or smoking, and no reported...
The patient showed the triad of dyskeratosis congenita. A: Oral leukoplakia, B: Abnormal skin pigmentation, C: Nail dystrophy (arrows).

Figure 1.

Table. Laboratory Data on Admission.

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Serological test</th>
</tr>
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<tbody>
<tr>
<td>RBC 345×10^6/mm³</td>
<td>TP 8.0 g/dL</td>
<td>HBsAg (-)</td>
</tr>
<tr>
<td>Hb 11.8 g/dL</td>
<td>γ-globulin 30.1%</td>
<td>HCVAb (-)</td>
</tr>
<tr>
<td>Ht 36.7 %</td>
<td>Alb 3.5 g/dL</td>
<td>ANA (-)</td>
</tr>
<tr>
<td>WBC 4,400/mm³</td>
<td>T-bil 1.9 mg/dL</td>
<td>AMA (-)</td>
</tr>
<tr>
<td>Plt 6.4×10^4/mm³</td>
<td>D-bil 0.2 mg/dL</td>
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<table>
<thead>
<tr>
<th>Coagulation</th>
<th></th>
<th>Tumor marker</th>
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<tbody>
<tr>
<td>AST 74 IU/L</td>
<td></td>
<td>AFP 2.7 ng/mL</td>
</tr>
<tr>
<td>ALT 50 IU/L</td>
<td></td>
<td>DCP 22 mAU/mL</td>
</tr>
<tr>
<td>LDH 511 IU/L</td>
<td></td>
<td>CEA 1.1 ng/mL</td>
</tr>
<tr>
<td>ALP 472 IU/L</td>
<td></td>
<td>CA19-9 8 U/mL</td>
</tr>
<tr>
<td>γ-GTP 274 IU/L</td>
<td></td>
<td>SCC 1.0 ng/mL</td>
</tr>
<tr>
<td>ChE 255 IU/L</td>
<td></td>
<td></td>
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<tr>
<td>CPK 414 IU/L</td>
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</tr>
<tr>
<td>AMY 46 IU/L</td>
<td></td>
<td></td>
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<tr>
<td>BUN 8.0 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr 0.7 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTT 5.25 KU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZTT 20.2 KU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP 1.04 mg/dL</td>
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</table>


exposure to thorotrast, vinyl chloride or arsenic. He did not have a history of taking medication.

The laboratory data on admission (Table) showed elevated levels of aspartate aminotransferase (AST) 74 IU/L (normal range, 10-40 IU/L), alanine aminotransferase (ALT) 50 IU/L (5-40 IU/L), total bilirubin (T-Bil) 1.9 mg/dL (0.2-1.0 mg/dL) and alkaline phosphatase (ALP) 472 IU/L (115-359 IU/L). Other laboratory tests showed an erythrocyte count of 345×10^6/mm³ (normal: 427-570×10^6/mm³), a hemoglobin level of 11.8 g/dL (13.5-17.6 g/dL), a platelet count of 6.4×10^4/mm³ (13.1-36.2×10^4/mm³), a total protein (TP) level of 8.0 g/dL (6.5-8.0 g/dL), a serum albumin level of 3.5 g/dL (3.9-4.9 g/dL), an amylase level of 46 IU/L (60-200 IU/L), a gamma-glutamyltransferase level of 274 IU/L (<70 IU/L), a blood urea nitrogen (BUN) level of 8.0 mg/dL (6.0-20.0 mg/dL) and a creatine (Cr) level of 0.7 mg/dL (0.61-1.04 mg/dL). The patient was negative for hepatitis B surface antigens, hepatitis C virus antibodies, anti-nuclear antibodies (ANA) and anti-mitochondrial antibodies (AMA), Alpha-fetoprotein (AFP), des-γ-carboxy-prothrombin (DCP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and squamous cell carcinoma antigen (SCC) were within the normal ranges.

Abdominal CT (Fig. 2) and magnetic resonance imaging
(MRI, Fig. 3) revealed multiple hypervascular tumors, mainly in the hepatic right lobe. The main tumor was 10 cm in diameter. The T1-weighted image of the tumor showed an irregular low-intensity signal and contained high-intensity cystic areas. The T2-weighted image also contained low- and high-intensity areas. A CT dynamic study and an MRI dynamic study each revealed faint staining in the arterial phase and increased staining in the portal and venous phases (Fig. 2, 3). The hepatocyte phase showed a low-intensity area on the MRI. 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) showed an increased uptake with a maximum standardized uptake value (SUV) of 7.8 in the hepatic tumors (Fig. 4A) and vertebral metastases (Fig. 4B). Moreover, a needle liver biopsy disclosed atypical cell infiltration with spindle- and oval-shaped nuclei (Fig. 5A), and an immunohistochemistry analysis showed positive results for vimentin, CD31, CD34 (Fig. 5B) and negative results for alpha-smooth muscle antigen (α-SMA). The hepatocytes, which were atrophied due to tumor cell growth, and the hepatic cell cords were narrowed. Irregularly-sized cavities lined with tumor cells were filled with blood and vascular invasion of the tumor was observed. Necrosis or bleeding was observed in the tumor tissues. Finally, the liver tumor was diagnosed to be an angiosarcoma with metastasis to the lung, left adrenal gland, spleen and vertebrae.

Discussion

Dyskeratosis congenita is a disease of defective telomere maintenance. Dyskeratosis congenita patients display premature telomere shortening and subsequent replicative senescence, which lead to premature stem cell exhaustion and tissue failure (1-4). Genetic analyses have revealed eight genes (DKC1, TERC, TERT, NOP10, NHP2, TIN2, C16orf57 and TCAB1) related to dyskeratosis congenita (4). Seven of these genes are important for telomere maintenance because they encode components of either the telomerase enzyme complex (DKC1, TERC, TERT, NOP10, NHP2 and TCAB1) or the shelterin complex (TINF2) (4).

Alter et al. (8) reviewed 52 studies of dyskeratosis con-
Figure 3. Gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI). T1: T1-weighted image, T2: T2-weighted image, A: Arterial phase, B: Portal phase, C: Venous phase, D: Hepatocyte phase. The main tumor was 10 cm in diameter. The T1-weighted image of the tumor showed an irregular low-intensity signal and contained high-intensity cystic areas. The T2-weighted image also contained high and low intensity areas. The dynamic study revealed faint staining in the arterial phase and increased staining in portal or venous phases. The hepatocyte phase showed a low intensity.

Figure 4. 18F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) findings. A: Hepatic tumor with a maximum standardized uptake value (SUV) of 7.8, B: Vertebral metastasis. 18F-FDG PET/CT showed an increased uptake with a maximum SUV of 8.6 in the hepatic tumor and vertebral metastases (arrow).
genita published from 1910 to 2008 and identified 52 patients (9.4%) with 61 malignancies among 552 dyskeratosis congenita cases (8). A total of 60 solid tumors were reported in 51 cases; one patient had acute myeloid leukemia. The median age at the diagnosis of malignancy was 29 (range 1.5-68) years, the median age at death was 29 (range 19-70) years and the median survival, based on the Kaplan-Meier method, was 39 (95% CI, 35-44) years. Among the 60 solid tumors, there were 24 head and neck squamous cell carcinomas in 22 patients. The next most frequently diagnosed cancers were skin squamous cell carcinoma in eight patients, followed by anorectal cancer in six patients, stomach and lung cancer in four patients each, and esophageal squamous cell carcinoma and Hodgkin’s disease in three patients each (8). Only one case of liver adenoma was reported in the study of 552 dyskeratosis congenita cases (8), and only one previous case of hepatic angiosarcoma in a patient with dyskeratosis congenita has been reported (9). The relation-
ship between angiosarcoma and defective telomere maintenance is unknown. There have been few reports concerning telomeres and angiosarcoma. The telomerase activity in dog angiosarcoma was reported to be low in one case (10). However, because there are only two reported cases of hepatic angiosarcoma in patients with dyskeratosis congenita (including the present case), further information is needed to better understand this disease.

Angiosarcoma is a rare soft-tissue sarcoma of endothelial cell origin with a poor prognosis. These lesions can arise anywhere in the body, most commonly presenting as cutaneous disease involving the head and neck. Primary hepatic angiosarcomas are significantly rare tumors, with a worse prognosis than other angiosarcomas (11). Hepatic angiosarcoma is reported to be associated with vinyl chloride; however, the majority of cases involve an unknown etiology (11). Zheng et al. reviewed 25 articles including 64 cases of hepatic angiosarcomas with detailed information (11). In that report, the median survival time was five months, and local excision alone or in combination with adjuvant therapy was the optimal treatment, with a median survival time of 17 months (11).

Contrary to the washout seen in hepatocellular carcinoma, hepatic angiosarcoma usually shows an early arterial enhancement followed by the progressive filling in of contrast within the lesion (12). However, the differential diagnosis of this tumor from other hepatic tumors by imaging may be difficult. In the present case, 18F-FDG PET showed an increased uptake, which was helpful in its diagnosis as a malignant tumor. PET is also useful for the detection of distant metastases (13).

There are no established chemotherapy regimens and there have been few clinical trials of chemotherapy for hepatic angiosarcoma (11). Some clinical studies of angiosarcoma have recently shown that single-agent doxorubicin and weekly paclitaxel-, gemcitabine- and doxorubicin-based regimens deserve consideration (11, 14), while bevacizumab, sorafenib and pazopanib are potential target drugs (10, 15, 16). However, angiosarcomas are heterogeneous. Hence, the efficacy of therapy may vary in different types of angiosarcoma (11).

We herein reported the second case of hepatic angiosarcoma arising from dyskeratosis congenita. Dyskeratosis congenita is a disorder of poor telomere maintenance and is known to increase the risk of developing multiple types of malignancy. Although most malignant tumors complicated with dyskeratosis congenita are head and neck squamous cell carcinomas, hepatic tumors should be considered in patients with dyskeratosis congenita.

The authors state that they have no Conflict of Interest (COI).

References


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