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Case Report

Epithelioid Hemangioendothelioma of the Liver Showing Spontaneous Complete Regression after the Cessation of Methotrexate Intake

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Keywords
Epithelioid hemangioendothelioma · Liver · Methotrexate · Spontaneous regression

Abstract
A 71-year-old man with slight fever and dull abdominal pain was referred to our hospital. He had been receiving methotrexate (MTX) to treat his rheumatoid arthritis for more than 6 years but stopped taking MTX after admission due to the rapid aggravation of his liver function. Computed tomography (CT) showed multiple liver lesions with late enhancement, highly suggesting them to be cholangiocarcinomas. Tumor marker levels were normal except for a slightly elevated PIVKA-II level, i.e., 45 mAU/mL (range 0–40 mAU/mL). We did a biopsy to the largest lesion and endoscopic biliary drainage to make a definitive diagnosis of the hepatic lesions and treat jaundice, respectively. Pathological study showed round, polygonal, and spindle-shaped epithelial atypical cells growing in a sarcomatoid fashion. Atypical cells were positive for CD31, CD34, vimentin, and TFE3, and some of them had intracellular vacuoles, leading to the diagnosis of epithelioid hemangioendothelioma (EHE) of the liver. The patient got well 4 weeks after the endoscopic biliary drainage. CTs showed marked regression of the EHE lesions 3 months after biliary drainage and complete regression in 12 months. The patient further developed Hodgkin lymphoma in the para-aortic lymph nodes 23 months after the biliary drainage and is now under chemotherapy for the malignant lymphoma. We, however, have not detected any EHE lesions in the liver or distant organs for at least 16 months after the confirmation of complete regression of the EHE lesions. Oncologists should note the spontaneous regression of the EHE and investigate the correlation between MTX cessation and EHE regression.

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Introduction

Epithelioid hemangioendothelioma (EHE) is an extremely rare, i.e., one per one million, vascular neoplasm composed of epithelioid cells with endothelial characteristics [1–4]. EHE arises in the liver, lung, bone, skin, soft tissue, thyroid, spleen, stomach, prostate, ovary, and brain. EHE can cause various symptoms such as anorexia, weight loss, fatigue, nausea, abdominal pain, and jaundice in patients with liver EHE; dyspnea, cough, hemoptysis, and clubbing in those with pulmonary EHE; and pain and pathologic fracture in those with bone EHE.

Approximately half of EHE cases are pathologically proven to be of blood vessel origin. However, neither risk factors nor key molecules have been established for the development of EHE. EHE, therefore, needs earlier and accurate diagnosis for better clinical outcome due to the lack of effective disease-specific therapies for this disorder.

Like other solid malignancies, treatment of EHE is markedly affected by the disease spread. Localized EHEs are good candidates for some kinds of surgical interventions [5]. Meanwhile, extensive EHEs are often treated with antiangiogenic agents, chemotherapeutic agents, tyrosine kinase inhibitors, and immunomodulators. It, however, is well known that some EHEs regress spontaneously without any anti-tumor therapies. We herein report a case of spontaneous complete regression of liver EHEs after the cessation of methotrexate (MTX) therapy for rheumatoid arthritis.

Case Report

A 71-year-old man with slight fever and dull abdominal pain was referred to our hospital. He had undergone drug-eluting stent grafting to the coronary arteries for angina pectoris 4 years before and had been receiving MTX (12 mg p.o. once a week) to treat his rheumatoid arthritis for more than 6 years. Ultrasonography on annual medical checkups had showed no abnormalities in the abdomen, including the liver, at least for the past 2 years. Abdominal ultrasonography, however, showed multiple oval lesions, up to 35 mm in size, with mixed high and low internal echoes in the liver on this admission (Fig. 1). Although follow-up computed tomography (CT) after coronary artery stent grafting taken 2 years before showed no marked findings in the liver, enhanced CT showed multiple low-intensity lesions in the liver (Fig. 2a). Blood tests showed inflammatory findings, total bilirubin of 6.4 mg/dL, normal tumor marker levels except for a slightly elevated PIVKA-II level of 45 mAU/mL (range 0–40 mAU/mL), and no hepatitis B and C infection. Taken together with the images and laboratory findings, we highly suspected the lesions to be either metastatic liver tumors or cholangiocarcinomas. In order to rule out the metastatic tumors, upper and lower endoscopic examinations were done on the patient, leading to the confirmation of no abnormalities in the esophagus, stomach, proximal duodenum, rectum, and colon. The rapid aggravation of his liver function made us stop the MTX therapy and place an endoscopic biliary drainage tube into his bile duct. In addition, we performed a biopsy of the largest liver lesion for further systemic therapies. Histopathological examination of the biopsy specimen showed round, polygonal, and spindle-shaped epithelial atypical cells growing in a sarcomatoid fashion. Some atypical cells had an intracellular vacuole within the eosinophilic cytoplasm. Atypical cells were positive for CD31, CD34, vimentin, and TFE3, leading to the diagnosis of EHE of the liver (Fig. 3). The patient was discharged on hospital day 31 due to the full recovery from the jaundice with the biliary drainage. Enhanced CT 2 months after discharge showed complete disappearance of small EHE lesions and marked shrinkage of large EHE lesions (Fig. 2b). We, therefore, proposed surgical resection of the remaining and resectable few lesions to the patient. The patient,

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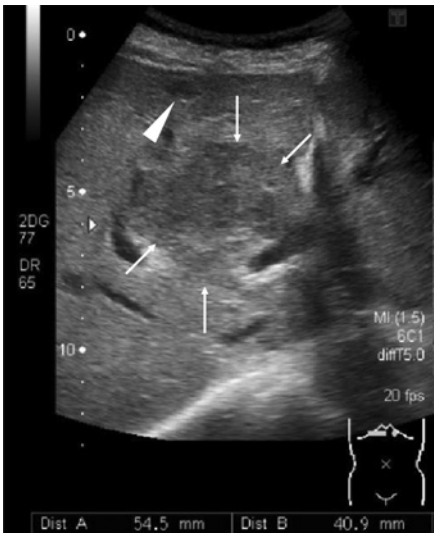

Fig. 1. Ultrasonography at his first visit to our hospital. Ultrasonography showed ill-defined mass (arrows) and small lesions (arrowhead) in the liver.

however, opted not to have surgery due both to his improved general condition and to the spontaneous regression of the EHE lesions. Follow-up CT taken 12 months after the biliary drainage showed complete regression of the liver EHE lesions (Fig. 2c). After that, the patient had been well without any EHE regrowth/recurrence for 16 months but further developed Hodgkin lymphoma in the para-aortic lymph nodes during the complete regression period. The patient is now under chemotherapy for the malignant lymphoma.

Discussion

In the differential diagnosis of intrahepatic masses, hepatocellular carcinomas often have a (pseudo)capsule composed of inflamed and fibrotic tissue, making them well-circumscribed tumors on images. Whereas extensive desmoplastic stroma generally makes the cholangiocarcinomas unencapsulated tumors with obscured tumor margins. Liver EHEs also lack a fibrotic capsule and directly face the normal hepatic cells, showing similar acoustic impedance to that of EHEs, making them indistinct tumors at least on images without contrast agents. These image similarities make it difficult for diagnostic physicians to differentiate EHEs from cholangiocarcinomas. We, therefore, initially suspected the liver lesions to be cholangiocarcinomas due to their high incidence among liver tumors.

Localized EHEs are good candidates for surgical interventions such as wedge resection of the affected lung, wide resection of the bone lesion(s), and hepatic partial resection of the liver lesion(s). Radiotherapy seems to be another feasible therapeutic option for localized lung, liver, and bone EHEs [1]. Some kinds of ablations seem promising in the treatment of EHEs, especially liver EHEs, but have not yet shown their efficacy against this disorder.

Many reports pointed out the indolent biology of EHE. Onishi et al. [5] reported no change (33%) and some regression (40%) of the largest lesion in the 15 liver EHE patients, respectively. Kitaichi et al. [6] also reported spontaneous tumor regression in three of the 21 EHE patients (14.3%) in the lung. Mechanisms of spontaneous EHE regression remain unknown but should be derived from inherent anti-tumor activities, probably immune response to some event. Female predominance of this disorder suggests the possible involvement of immune mechanisms in both the development and regression of this disease [1, 2].

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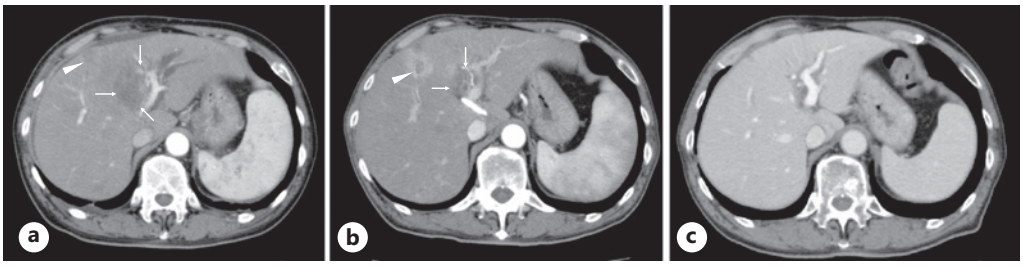

Fig. 2. Computed tomography (CT) findings over time. CT on admission showed an ill-defined large tumor (arrows) adjacent to the umbilical portion of the portal vein and a small lesion (arrowhead) near the liver surface (**a**). CT 3 (**b**) and 12 months (**c**) after biliary drainage showed marked and complete regression of the tumors, respectively.

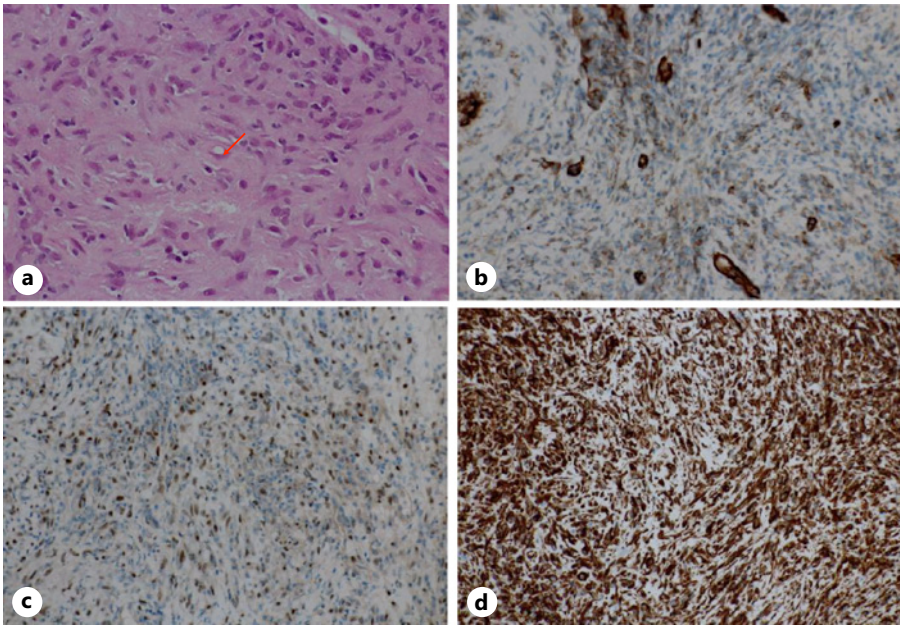

Fig. 3. Pathological findings. **a** Hematoxylin and eosin staining showed atypical epithelioid endothelial cells arranged in hyalinized stroma. Some cells exhibited intracellular vacuole (**a**, arrow). Immunohistochemical staining showed positive cells of CD31 (**b**), TFE3 (**c**), and vimentin (**d**).

In this case, endoscopic biliary drainage was also done on the patient. Anti-icteric therapy might have contributed to the spontaneous regression of the multiple liver EHEs through biliary decompression. This patient, however, had developed multiple EHEs during the no icteric period of 2 years from the prior CT evaluation to the present event. Biliary drainage, therefore, might have somewhat contributed to augment the immune response due to MTX withdrawal but should not have induced spontaneous EHE regression.

Conflicting data exist about the efficacy of chemotherapy using various agents against unresectable or metastatic EHEs [7–9]. In addition, spontaneous regression has been observed not only in the resectable EHEs but also in the multiple and unresectable EHEs like this case [5, 6]. Observation, therefore, is recommended as the first option for unresectable EHEs as long as they remain asymptomatic without accelerated growth or onset of new lesions.

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Various studies have reported that approximately 90% of EHE tumors contain rearrangement of WWTR1 and CAMTA1 genes. Some cases without rearrangement of CAMTA1 show positive YAP1-TFE3 fusion [10]. Dermawan et al. [11] reported that YAP1-TFE3-fused EHEs presented favorable biology compared to that of conventional EHEs. Positive TFE3 immunostaining does not directly imply the YAP1-TFE3-fused phenotype but suggests the strong correlation to this phenotype. However, no reports have described the relationship between spontaneous regression and genetic phenotype of EHEs. To treat patients with EHEs correctly, it is very important to perform gene testing in individual cases, but it is not realistic. By accumulating TFE3 immunostaining information on EHEs, it may become possible to predict spontaneous regression with this factor.

MTX can cause good disease control of the immune-mediated disorders through its immunosuppressive mechanisms on one hand but sometimes develops lymphoproliferative disorders [12]. We cannot elucidate the mechanism of spontaneous complete regression of the EHEs in this case. We, however, cannot deny the possibility that cessation of oral MTX therapy might have brought about the spontaneous complete regression of the multiple EHE lesions.

In conclusion, we experienced a case of spontaneous complete regression of liver EHE lesions with a possible YAP1-TFE3-fused phenotype. Physicians should note this disorder and its possible spontaneous regression in order not to overtreat it. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000531133).

Statement of Ethics

The study was approved by the Kishiwada Tokushukai Hospital Ethics Committee (IRB #Case 22-10). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shishimoto T. contributed to the design of the report. Oura S. drafted the manuscript. Motozato K. actually treated the patient. Tanaka H. and Takamatsu S. evaluated the pathological findings. Ono W. revised the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in this article and its online supplentary material files. Further inquiries can be directed to the corresponding author.

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