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Correlation between Gd-EOB-DTPA-enhanced MR imaging findings and OATP1B3 expression in chemotherapy-associated sinusoidal obstruction syndrome

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Abstract

We report a female case of sinusoidal obstruction syndrome (SOS) diagnosed pathologically after chemotherapy (Pmab + m-FOLFOX6) for ascending colon cancer with multiple liver metastases, focusing on the findings of gadoxetic acid-enhanced MRI (EOB-MRI) and the organic anion transporting polypeptide 1B3 (OATP1B3) expression of in the liver. The patient was a 75-year-old female. She had received chemotherapy (Pmab + m-FOLFOX6) as six cycles for preoperative chemotherapy. After the preoperative chemotherapy, tumor sizes of hepatic metastases were reduced and hepatobiliary phase of EOB-MRI clearly depicted diffuse reticular hypointensity in the background liver. On the other hand, dynamic CT and/or other sequences of EOB-MRI did not show definite abnormality in the background liver. After the operation, this patient was pathologically confirmed as SOS demonstrating centrilobular congestion, sinusoidal dilatation, and perisinusoidal fibrosis. In normal liver parenchyma, OATP1B3 (uptake transporter of the EOB-MRI) expression is observed predominantly in centrilobular hepatocytes (zone 3). On the other hand, OATP1B3 expression was remarkably reduced because of the damages in the centrilobular (zone 3) hepatocytes in this SOS case. This indicated that EOB-MRI might be extremely sensitive in diagnosing SOS in its early stage.

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Sinusoidal obstruction syndrome (SOS) was previously termed hepatic veno-occlusive disease (VOD). A recent study indicated that the primary damage site in VOD is the centrilobular (zone 3 of liver parenchyma) sinusoidal endothelial cell. It was accordingly renamed as SOS [1]. SOS is believed to occur because of sinusoidal obstruction due to endothelial detachment after damage to sinusoidal endothelial cells. SOS has a variety of causes, such as hematopoietic cell transplantation (HCT), chemotherapy, alkaloid toxins, high dose radiation therapy, and liver transplantation. Recently, chemotherapy-associated SOS has been increasingly reported, in particular, as an adverse side effect in patients with colorectal liver metastasis treated with oxaliplatin [2–4]. Imaging diagnosis of SOS is important because it can be a cause of intra- and post-operative complications [5–9].

Gd-EOB-DTPA-enhanced MRI (EOB-MRI) has been more and more frequently used for detecting and evaluating liver lesions [10, 11]. Gd-EOB-DTPA is a hepatobiliary contrast agent for MRI and is incorporated into hepatocytes mainly by organic anion transporting polypeptide (OATP). It has been clarified that there was a highly significant correlation between Gd-EOB-DTPA uptake and OATP1B3 expression in HCC cells and/or normal hepatocytes and also between the

grade of OATP1B3 expression and enhancement ratio (signal intensity) on hepatobiliary (HB) phase of EOB-MRI [12–14]. Recently, Shin et al. reported that hepatobiliary phase (HB phase) of EOB-MRI sensitively visualized SOS as diffuse reticular hypointense areas in the liver but without analyzing OATP1B3 expression [15].

We herein report a case of chemotherapy-associated SOS diagnosed pathologically after preoperative chemotherapy (Pmab + m-FOLFOX6: panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin) for ascending colon cancer with multiple liver metastases, focusing on the findings of EOB-MRI and OATP1B3 expression in SOS liver.

Case report

Case

A 75-year-old female was diagnosed with ascending colon cancer by colonofiberscopy and detected multiple liver metastases on computed tomography (CT) in local hospital. Liver metastasis were not confirmed by the histological examination before surgery and diagnosed by the only imaging finding. She admitted to our hospital to receive preoperative chemotherapy for ascending colon cancer and multiple liver metastases. There was a family history of gastric cancer in the father and older and younger brothers, and parotid cancer in the mother. Her past history included acute appendicitis at 27 years and hypertension at 50 years. She had no history of alcohol abuse or smoking. Laboratory data showed decreased hemoglobin (10.4 g/dL) and albumin (3.4 g/dL), elevation of ductal enzymes (alkaline phosphatase 479 IU/l, γ-glutamyl transpeptidase 100 IU/l), C-reactive protein (4.8 mg/dL), and tumor markers (carcinoembryonic antigen 71.5 ng/dL, carbohydrate antigen 19-9 625U/mL). She had received six cycles of chemotherapy (Pmab + m-FOLFOX6) as preoperative chemotherapy. After the preoperative chemotherapy, the size of the hepatic metastases was reduced. Mean size of metastasis before and after chemotherapy was 59.1 and 27.5 mm, respectively. Estimation of the chemotherapy effect was partial response. Worsening of the liver function was not observed during chemotherapy. She underwent surgery 4 and half months after induction of chemotherapy. Right hemicolectomy and partial hepatectomy (five portions) were performed.

Contrast-enhanced CT imaging was performed with a CT system. After precontrast scanning, contrast material with 600 mg of iodine per kilogram was injected with an injection duration of 30 s. The arterial dominant phase was determined using the bolus-tracking method and obtained 36 s after injection. Portal dominant phase (70 s after injection) and equilibrium phase (150 s after injection) were obtained. Dynamic contrast-enhanced CT revealed ascending colon cancer with multiple hepatic metastases showing multiple hypovascular mass at the initial visit. Multiple metastases were detected segment 2, 4, 6, 7, and 8 of the liver. Total ten metastases were detected. There were no particular findings in the background liver on the dynamic CT after chemotherapy, and almost no change was observed in spleen size before and after chemotherapy.

Preoperative EOB-MRI was performed 22 days before surgical resection for the detecting correct number of the hepatic metastasis. MR images were obtained with 1.5T MR system. Precontrast images were obtained in a transverse plane with a fat-suppressed three-dimensional (3D) T1-weighted gradient echo (GRE) sequence (TR, 3.3 ms; TE, 1.6 ms; flip angle 12; matrix, 288 × 192; field of view, 42 × 42 cm^2; section thickness, 4.2 mm). Patient received a dose of 0.1 ml/kg Gd-EOB-DTPA (Primovist; Bayer Schering Pharma, Berlin, Germany) intravenously at a speed of 1 mL/s. The line was flushed with 20 ml of saline. Immediately after the start of the Gd-EOB-DTPA injection, dynamic studies with a fat-suppressed 3D T1-weighted GRE sequence were performed using the test injection method (1.5 mL of Primovist + 8 mL saline flush), and arterial phase timing was determined as the peak time of the abdominal aorta plus 10 s minus half of imaging time. Portal dominant and transient phase images were obtained at 60–90 and 120–180 s after injection. T2-weighted fast spin echo (T2 W) with fat suppression sequences (TR, 9230; TE, 86; flip angle 90; matrix, 288 × 192; field of view, 40 × 40 cm^2; section thickness, 4 mm) and diffusion-weighted spin eho planar (DWI) sequence (TR, 10000; TE, 64.2; flip angle 90; matrix, 128 × 160; field of view, 40 × 40 cm; section thickness, 6 mm) were taken after the dynamic images. HB phase images were taken at 20 min after the end of injection with T1 W images with fat suppression. The HB phase images of preoperative EOB-MRI showed diffuse reticular hypointensity in the background liver (Fig. 1 B). Other MRI sequences did not detect any abnormalities clearly in the background liver (Fig. 2). A follow-up EOB-MRI was performed 3 months after operation, and this reticular hypointensity finding on HB phase of EOB-MRI improved and became inconspicuous. (Fig. 1c).

After the operation the patient was pathologically diagnosed as having SOS. Macroscopically, patchy and reticular brown areas intermingled with whitish normally looking areas were observed throughout the background liver (Fig. 3a). These brown areas demonstrated severe centrilobular (zone 3) congestion with sinusoidal dilatation and perisinusoidal fibrosis consistent with SOS microscopically (Fig. 3b). The microscopic specimen from the intermingled whitish liver parenchyma demonstrated no definite abnormality (Fig. 3c left). Immunohistochemical staining for OATP1B3 showed its expression in centrilobular zone 3 hepatocytes in this area (Fig. 3c right). OATP1B3 has been known to be predominantly expressed zone 3 hepatocytes in normal

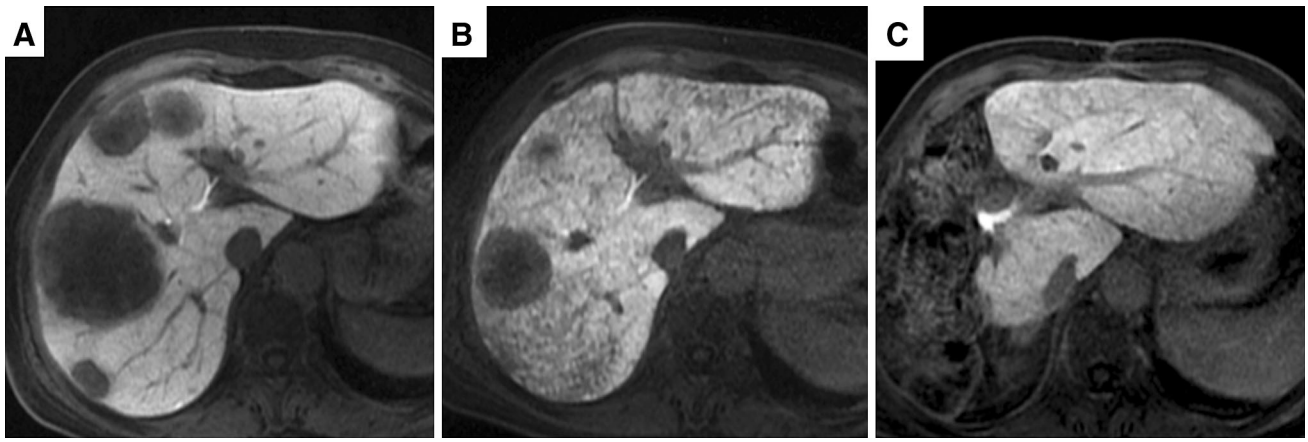

Fig. 1. HB phase of the EOB-MRI findings before and after six-cycle chemotherapy (Pmab+m-FOLFOX6) and 3 months after operation. HB phase of EOB-MRI before (**A**) and after six-cycle chemotherapy (**B**), 3-month follow-up image after operation (**C**). Before chemotherapy, multiple hepatic metastases show hypointensity on HB phase of EOB-MRI (**A**). There is no definite abnormality in the background liver (**A**). After chemotherapy, tumor sizes are reduced, and there are diffuse reticular hypointense areas in the background liver on the HB phase of EOB-MRI (**B**). A follow-up EOB-MRI was performed 3 months after operation, and diffuse reticular hypointense area in the background liver on the HB phase of EOB-MRI (**C**) was improved and became inconspicuous.

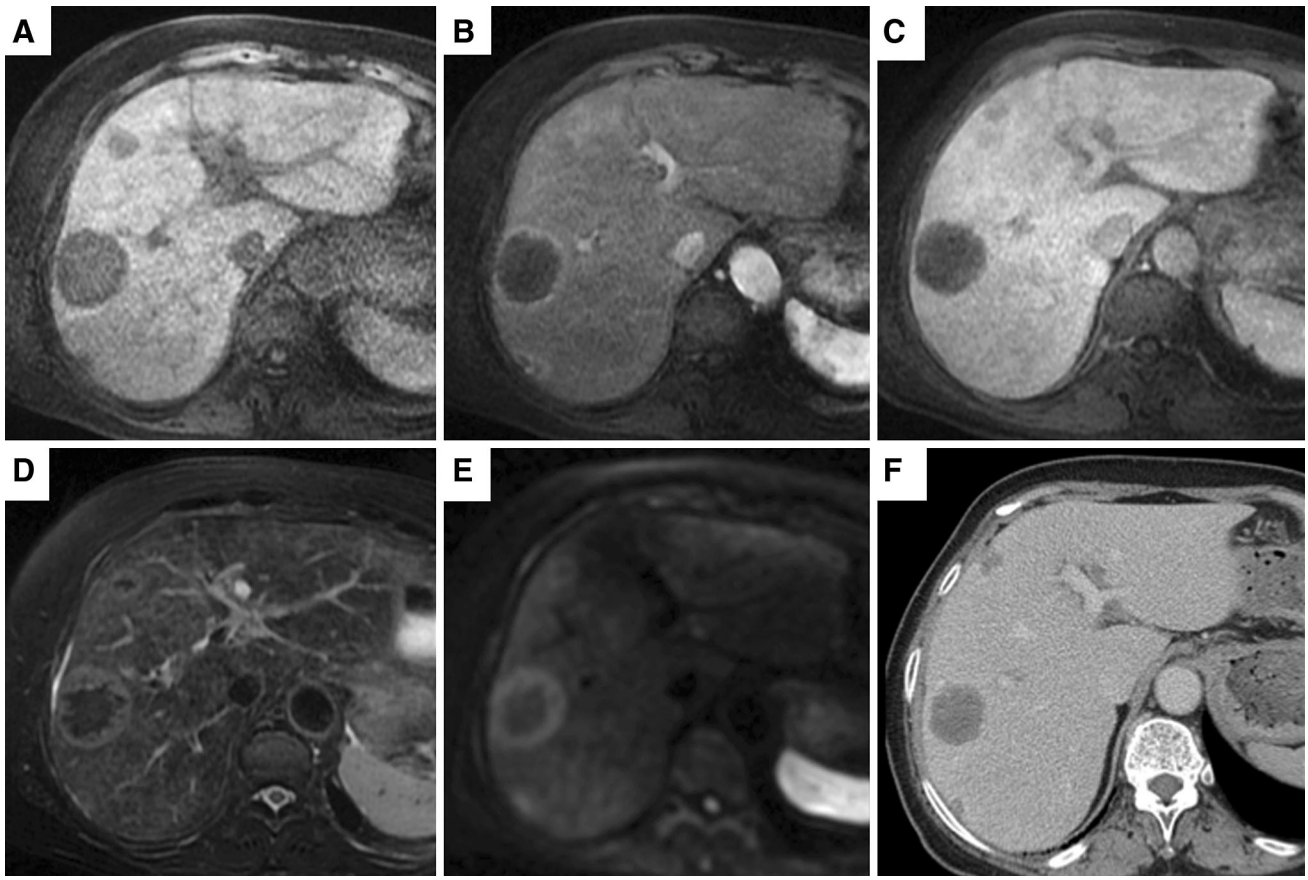

Fig. 2. The other MRI sequence findings and delayed phase of contrast CT findings after chemotherapy. Precontrast T1-weighted image with fat suppression (**A**), arterial phase (**B**), transitional phase (**C**) of dynamic MRI, T2-weighted image with fat suppression (**D**), diffusion image (b value = 800) (**E**), and delayed phase of contrast CT (**F**). The other MRI sequences show mild signal change in the background liver (**A**–**E**). However, these sequences cannot reveal the lesion clearly compared with HB phase of EOB-MRI. Delayed phase of contrast CT shows no abnormalities in the background liver after chemotherapy (**F**).

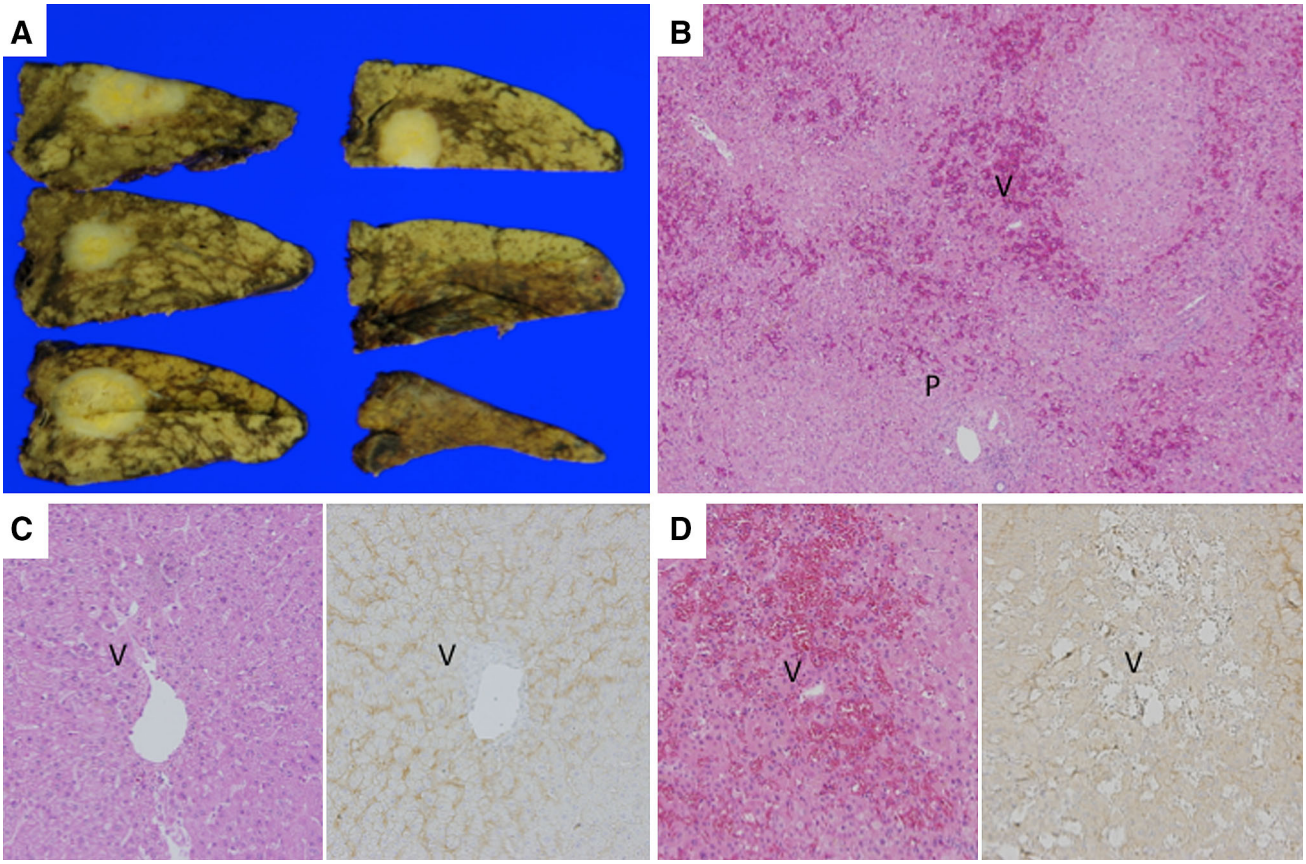

Fig. 3. Pathological findings. *Left upper* panel shows gross impression of the lesion (**A**). Macroscopically reticular and patchy brown areas intermingled with whitish normally looking areas were observed in the background liver. Microscopically hematoxylin–eosin staining showed centrilobular (zone 3) congestion and sinusoidal dilatation in the background liver consistent with sinusoidal obstruction syndrome (SOS) (**B**). The microscopic specimen from the intermingled whitish liver parenchyma demonstrated no definite abnormality (**C** *left*). Immunohistochemical staining for OATP1B3 showed its expression in centrilobular zone 3 hepatocytes (**C** *right*). The microscopic specimens taken from the brown area demonstrated severe congestion with sinusoidal dilatation (**D** *left*) with markedly attenuated and lost in part of OATP1B3 expression (**D** *right*) in centrilobular (zone 3) area. Original magnifications ×40 (**B**), ×100 (**C**, **D**).

liver parenchyma [16]. In contrast, the microscopic specimens taken from the brown area showed severe congestion in zone 3 as described above (Fig. 3d left) and markedly attenuated OATP1B3 expression (Fig. 3d right). This difference of the expression of OATP1B3 in zone 3 hepatocytes between the intermingled damaged and almost normal-looking liver parenchyma was considered to be an etiology of diffuse reticular hypointense areas in the liver on HB phase of EOB-MRI seen in this case. In addition, no definite deterioration of liver function on laboratory data observed in this case may be due to the intermingled less damaged or normal-looking liver parenchyma, resulting in earlier diagnosis of SOS by EOB-MRI than laboratory data.

Discussion

We reported a case with ascending colon cancer and chemotherapy-associated SOS. Recently, the frequency of chemotherapy-associated SOS has increased in colorectal cancer (the incidence was between 42 % and 51 %). In particular, oxaliplatin has been associated with a higher incidence of SOS (51 %–79 %) [2–4]. The present case had similarly received a chemotherapy protocol (Pmab + m-FOLFOX6) that included oxaliplatin. Severe SOS may be associated with the following signs: hepatomegaly with pain, ascites, and rise of bilirubin. However, chemotherapy-associated SOS is usually asymptomatic [2–4]. Our patient had no symptoms either, and there was no exacerbation of liver dysfunction during the preoperative chemotherapy. However, several cases treated with oxaliplatin for colorectal metastasis have been described as developing severe hepatic dysfunction and even death in one [17, 18]. In addition, when SOS arises in preoperative chemotherapy, it may cause a decrease in the residual liver function and increase the amount of bleeding during surgery [5–9]. This makes the preoperative detection of SOS very important clinically. No consensus has been obtained on the optimal length of the waiting period for hepatectomy after chemotherapy, but Welsh reported a sig-

nificant reduction in surgical complications with increasing time interval between the cessation of chemotherapy and surgical hepatectomy [19]. A recent study noted that chemotherapy-associated SOS improved during the 3- to 7-month period after drug cessation [2]. Present case also showed an image on a certain degree of improvement 3 months after operation. Determination of the optimal interval between the cessation of chemotherapy and surgical hepatectomy is an important subject for future investigations.

Radiologically, a previous report showed the ability of SPIO-enhanced MRI to detect SOS by demonstrating diffuse or patchy reticulations [20]. However, after the introduction of EOB-MRI, it has largely been abandoned in clinical practice. Increased spleen size has also been reported as a predictor of sinusoidal injury [15, 21]. However, almost no change was observed in spleen size before and after chemotherapy in this case.

A recent study showed that the presence of reticular hypointensity on HB phase of EOB-MRI is highly specific for the diagnosis of SOS [15] as also demonstrated in this case. However, its pathological background has not been clarified yet. In normal liver parenchyma, OATP1B3 which is the main uptake transporter of Gd-EOB-DTPA into hepatocytes is almost exclusively expressed in the zone 3 hepatocytes with the absence of OATP1B3 expression in periportal (zone 1) hepatocytes. [16]. On the other hand, the primary site of the damages in SOS is also in zone 3 area with the histologic features of sinusoidal congestion and dilation, hepatocellular necrosis, periosis, and perisinusoidal fibrosis. In this case, similar changes were observed in zone 3 area in the damaged liver parenchyma resulting in markedly impaired OATP1B3 expression. However, these damaged areas with SOS were intermingled with less damaged or almost normal liver parenchyma throughout the entire liver with patchy and/or reticular distribution. Because the intermingled less damaged areas showed enough OATP1B3 expression, it was considered to be reasonable that the unique reticular hypointense pattern was visualized on HB phase of EOB-MRI in this case as also reported previously [15]. This is a case report analyzed in only one case, but the result obtained in this analysis can be applied to explain the reason why EOB-MRI is highly sensitive in the detection of SOS as compared with other imaging modalities.

In conclusion, we reported a case of chemotherapy-associated SOS that was clearly visualized on the HB phase of EOB-MRI. In SOS, centrilobular hepatocytes (zone 3), which mainly express OATP1B3 in the liver, are damaged. Therefore, it was considered that EOB-MRI may be a very useful tool in detecting and depicting SOS in its relatively early stage.

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