Oxaliplatin-related Portal Hypertension Complicated with Esophageal Varices and Refractory Massive Ascites

Tomotaka Yazaki¹, Kousaku Kawashima², Norihisa Ishimura³, Masatoshi Kataoka¹, Mai Fukunaga², Ryoji Hyakudomi¹, Yoshitsugu Tajima¹, Ichiro Moriyama³, Asuka Araki¹, Kyuichi Kadota¹, Kotaro Shibagaki⁶, Hiroshi Tobita¹ and Shunji Ishihara²

Abstract:
Oxaliplatin, widely used as a chemotherapy drug for colorectal cancer, is known to cause various adverse reactions. In particular, special attention for the development of portal hypertension associated with porto-sinusoidal vascular disease is necessary, as it is a serious adverse life-threatening reaction, although rare. We herein report a case of oxaliplatin-related portal hypertension that developed several years after oxaliplatin administration and led to esophageal varices and refractory massive ascites. Clinical physicians should be aware of the possibility of oxaliplatin-induced portal hypertension and its possible development over a long period after discontinuation of the drug.

Key words: oxaliplatin, portal hypertension, esophageal varices, refractory ascites, porto-sinusoidal vascular disease

(Intern Med 61: 3225-3231, 2022)
(DOI: 10.2169/internalmedicine.9266-21)

Introduction

In recent years, hepatectomy for liver metastasis of colon cancer has been reported to contribute to a prolonged survival rate in affected patients (1). For successful radical resection of liver metastasis, preoperative chemotherapy is performed for tumor size reduction (2-4), with an oxaliplatin-based chemotherapy regimen widely utilized prior to such resection.

It is well known that the most frequent adverse reactions to oxaliplatin administration are peripheral neuropathy, hematologic toxicity, and gastrointestinal tract toxicity, although oxaliplatin-related portal hypertension without cirrhotic change has also been reported as a relatively well-known complication (5). While oxaliplatin may cause hepatic sinusoidal endothelial cell injury and obstruction leading to portal hypertension, details regarding the pathological mechanisms have not been fully clarified. In general, oxaliplatin-related portal hypertension is treated by discontinuation of the drug, but the resultant therapeutic effects and disease prognosis remain unclear.

We herein report a case of oxaliplatin-related portal hypertension that was exacerbated several years after the administration of the drug, leading to the development of esophageal varices and refractory ascites.

Case Report

The patient was a 71-year-old man with controlled hypertension. He was a former smoker, with no history of heavy alcohol drinking or diabetes mellitus. Nine years earlier, the patient had been diagnosed with advanced ascending colon cancer with a single metastatic lesion of the liver (S6, 55×45 mm), for which right hemicolectomy was initially performed because of intestinal obstruction. A total of five...
courses of XELOX plus bevacizumab therapy were given as preoperative chemotherapy for the liver metastasis, which led to a reduction in the size of the liver tumor. Thereafter, the patient underwent laparoscopic-assisted S6 partial hepatectomy. For postoperative adjuvant chemotherapy, a total of six courses of XELOX therapy and two of Xeloda monotherapy were given, and no recurrence of colorectal cancer or liver metastasis was observed.

At a checkup examination five years after the end of chemotherapy, regular abdominal computed tomography (CT) findings revealed esophageal varices and marked splenomegaly. However, no evidence of hepatic marginal irregularities or atrophy was demonstrated, indicating the absence of liver cirrhosis. Point shear wave elastography (pSWE) was performed to evaluate liver fibrosis, which showed a mean value for the shear wave velocity (Vs), known to increase in parallel with the progress of liver fibrosis (6), of 1.35 m/s, indicating a lack of progression.

Esophagogastroduodenoscopy (EGD) indicated grade 2 esophageal varices with red color signs, as shown in Fig. 1 (7, 8). Therefore, the patient was admitted to our department for endoscopic treatment of esophageal varices to avoid gastrointestinal bleeding. At the time of admission, the patient’s height and weight were 156 cm and 62 kg, respectively, and his body mass index (BMI) of 25.5 indicated a slightly overweight condition. His body weight had increased by approximately 1 kg compared to the value at hepatectomy, although the change was not significant.

The laboratory findings upon admission are presented in Table. Hepatobiliary enzymatic activities were nearly normal, and no findings of hepatitis B and C virus were noted. In contrast, the platelet count had gradually decreased from $20.9 \times 10^4$ to $8.3 \times 10^4/\mu L$ during the approximately 5-year postoperative clinical course (Fig. 2). In addition, a review of previously obtained abdominal CT images showed splenomegaly at one year after hepatectomy, with gradual enlargement over time (Fig. 3), although neither portal vein

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**Figure 1.** Endoscopic findings before endoscopic therapy for esophageal varices. Esophagogastroduodenoscopy (EGD) showed grade 2 esophageal varices colored red.

**Table.** Laboratory Findings on Admission.

| <Blood count> | <Biochemistry> | <Hepatitis virus> |
|---------------|----------------|------------------|
| WBC 3,560 /μL | TP 7.5 g/dL | HBs antigen Negative |
| RBC 506 ×10^4/μL | Alb 4.3 g/dL | HBe antibody Negative |
| Hb 12.6 g/dL | T-Bil 1.1 mg/dL | HBs antibody Negative |
| Ht 41% | AST 27 U/L | HCV antibody Negative |
| Plt 8.3 ×10^4/μL | ALT 26 U/L | |
| ALP 81 U/L | γ-GTP 95 U/L | Anti-nuclear antibody <40 |
| LDH 227 U/L | ChE 277 U/L | IgA 353 mg/dL |
| PT 92.5% | AMY 104 U/L | IgM 139 mg/dL |
| APTT 31 s | BUN 11.4 mg/dL | IgG 1,450 mg/dL |
| D-dimer 1.5 μg/mL | Cre 1.09 mg/dL | |
| Type 4 collagen 7S 7.7 mg/mL | Na 141 mEq/L | <Tumor markers> |
| K 4.2 mEq/L | CEA 2.2 ng/mL |
| Cl 107 mEq/L | CA19-9 22.1 U/mL |
| Ca 8.6 mg/dL | AFP 2.1 ng/mL |
| CRP 0.73 mg/dL | PIVKA 25 mAUM/L |
| NH₃ 44 μg/dL | HbA1c 6.2% |

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, ChE: choline esterase, AMY: amylase, BUN: blood urea nitrogen, Cre: creatinine, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, CRP: C-reactive protein, NH₃: ammonia, HbA1c: hemoglobin A1c, HBs: hepatitis B surface, HBe: hepatitis B core, HCV: hepatitis C virus, IgA: immunoglobulin A, IgM: immunoglobulin M, IgG: immunoglobulin G, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, AFP: alpha fetoprotein, PIVKA: prothrombin induced by vitamin K absence
Figure 2. Clinical course. The vertical and horizontal axes show the platelet count and years, respectively. EIS: endoscopic injection sclerotherapy, EVL: endoscopic variceal ligation

Figure 3. Coronary section computed tomography imaging in accordance with the vertebra position. (A) Before hepatectomy. (B) One year after hepatectomy. (C) Six years after hepatectomy. Marked splenomegaly appeared following hepatectomy, and the positioning of abdominal organs was changed by the procedure.

Figure 4. The comparison of abdominal magnetic resonance imaging (MRI) findings. (A) Obvious evidence of nodular lesions was not noted in the liver at the time of hepatectomy. (B) Two years after hepatectomy, multiple nodular lesions appeared in the liver (arrowheads). (C) Five years after hepatectomy, the number of nodular lesions in the liver had increased (arrowheads).

thrombosis nor stenosis was shown. In addition, multiple liver tumors in both lobes of the liver appeared two years after surgery in abdominal ultrasonography results. Since those were visualized as high intensity tumors in the hepato-
biliary phase of Gd-EOB-DTPA in enhanced magnetic resonance imaging (MRI) findings, they were considered to be consistent with focal nodular hyperplasia (FNH). Follow-up examinations revealed gradual increases in the size and number, as shown in Fig. 4. To distinguish those from malignant neoplasms, such as hepatocellular carcinoma, samples were obtained from the liver tumors and subjected to biopsy examinations.

At the same time, a liver parenchymal biopsy was performed to investigate the cause of progressive portal hypertension. However, there were no marked differences between the nodules and parenchymal tissue seen in histological findings. In addition, no evidence of malignant cells or cirrhotic changes was found. As shown in Fig. 5, histological findings of liver parenchyma demonstrated dilated sinusoids and aggregation of abnormal blood vessels around the central vein, similar to idiopathic portal hypertension (IPH). Furthermore, aggregation of reticular tissue was observed following silver impregnation staining, suggesting that the hepatocytes had been damaged for a long period. Since oxaliplatin-based chemotherapy was performed before and again after surgery, it was considered that oxaliplatin-induced injury to the sinusoidal endothelial cells had occurred and caused portal hypertension, resulting in the exacerbation of splenomegaly and esophageal varices. Furthermore, histological findings of a liver biopsy specimen showed steatoses in the liver parenchyma. Similar findings were also noted in surgical specimens obtained at the time of hepatectomy. However, the histological findings did not meet the diagnostic criteria for non-alcoholic steatohepatitis (NASH), as there was no evidence of cirrhotic changes or hepatocyte ballooning. In this regard, the patient had no history of heavy alcohol drinking and was thus considered to have a history of nonalcoholic fatty liver disease.

Endoscopic injection sclerotherapy (EIS) for esophageal varices was performed with a total of 9 mL of 5% ethanolamine oleate with iopamidol. Radiographic imaging findings obtained during endoscopic injection sclerotherapy confirmed that some of the ethanolamine oleate had reached the afferent veins of the varices. Endoscopic findings after endoscopic therapy for esophageal varices showed complete eradication of esophageal varices.
nusoidal injuries were described as SOS, veno-occlusive disease (SOS), including sinusoid dilatation, fibrosis of the central vein, and formation of perisinusoidal fibrosis, indicating that subclinical pathological liver injury had occurred in most of their patients who received oxaliplatin-based chemotherapy. In addition, several reports regarding SOS related to the administration of drugs, such as thiopurines, busulfan, and cyclophosphamide, as well as oxaliplatin, have been presented (13-15). Previously, such sinusoidal injuries were described as SOS, veno-occlusive disease, or IPH (16). More recently, as part of an attempt to produce unified diagnostic criteria to reflect these conditions, the Vascular Liver Disease Interest Group (VALDIG) proposed the term “porto-sinusoidal vascular disease” (PSVD), since these lesions are found in the portal venules or sinusoids (17). The definition of PSVD is based on the absence of cirrhosis with or without signs of portal hypertension or histologic lesions, and the condition is characterized by obliterator portal venopathy, nodular regenerative hyperplasia (NRH), non-cirrhotic portal fibrosis, hepatoportal sclerosis, and incomplete septal cirrhosis. PSVD can be induced by various causative factors, such as drugs, including oxaliplatin, genetic and hematological diseases, and immunological disorders. The presence of known causes of chronic liver injury must be excluded in suspected cases.

Oxaliplatin-induced PSVD has also been shown to be characterized by hepatocyte atrophy, perisinusoidal fibrosis, centrilobular necrosis, and NRH (12, 18). Furthermore, based on the major etiological mechanisms of oxaliplatin-induced PSVD, it has been proposed that oxaliplatin administration may induce sinusoidal endothelial cell injury and the formation of gaps between sinusoidal endothelium cells, resulting in obstruction due to sinusoidal endothelial cell detachment (16, 18). Furthermore, a report noted that glutathione depletion of sinusoidal endothelial cells, nitric oxide depletion, the increased expression of matrix metalloproteinases and vascular endothelial growth factor in sinusoidal endothelium, and activation of coagulating factors are related to the pathogenesis of PSVD (19). Such sinusoidal endothelial cell-related injuries typically show a patchy distribution in the liver and thus may not be able to be confirmed when only a limited resected specimen is available (20).

In the present case, similar histological findings were confirmed by an examination of a liver biopsy specimen obtained six years after the end of oxaliplatin administration but were not seen in a hepatectomy specimen, which is comparable to PSVD. In the present case, no etiological factor indicating chronic liver injury was confirmed nor were any cirrhotic changes detected. Following the end of the administration of oxaliplatin in the present case, various symptoms related to portal hypertension were noted over time, such as increased splenomegaly, thrombocytopenia, exacerbation of esophageal varices, and massive ascites; we therefore concluded that oxaliplatin induced the development of PSVD in our patient. The appearance of multiple liver tumors after chemotherapy in this case is consistent with NRH seen in association with PSVD and suggests a long-term portal hypertension state. Another study of NRH associated with PSVD noted heterogeneity in size and patchy distribution throughout the liver, differing from the characteristics of classical NRH that were previously reported (21).

The prognosis of oxaliplatin-induced PSVD has yet to be fully investigated, possibly because diagnostic criteria and assessment methods have differed among presented reports (22-25). However, a recent retrospective study conducted by Satta et al. revealed that 5.7% of patients who re-
ceived oxaliplatin-based chemotherapy developed apparent esophageal varices (EGVs), although PSVD was not confirmed in those cases because of a lack of a histological evaluation of the liver (26). Importantly, their results also showed that a decreased platelet count and splenomegaly were predictive markers of EG formation caused by oxaliplatin-based chemotherapy that appeared from three to six months following treatment. As noted above, a review of previous laboratory records and images related to the present case showed a decreased platelet count and splenomegaly at one year after the patient underwent hepatectomy. Therefore, the results obtained at a one-year follow-up examination after hepatectomy should be analyzed carefully, and upper gastrointestinal endoscopy should be used to check for the possible development of esophageal varices, although the varices in the present case did not lead to gastrointestinal bleeding. The attending physician should be alert for any change in platelet count and development of splenomegaly after beginning oxaliplatin administration, particularly within the initial 6- to 12-month post-treatment period. However, there was a recent report of 4 patients who presented with portal hypertension from 3.9 to 11.8 years after the administration of oxaliplatin (27). Of those, one developed refractory massive ascites. In the present case, refractory ascites developed eight years after oxaliplatin discontinuation, although esophageal varices were completely eradicated. However, the development of massive ascites in our patient may have been influenced by the eradication of afferent esophageal varices by EIS and EVL. When oxaliplatin-induced portal hypertension occurs, clinical observations for the possible development of various complications over the long term are necessary.

At present, no treatment for PSVD has been established. For patients with oxaliplatin-induced PSVD, discontinuation of medication is likely necessary, although the therapeutic effect of that approach is controversial. In a study presented by Yakushijin et al. regarding SOS following hematopoietic stem cell transplantation (HSCT), which is strictly different from PSVD, defibrotide was found to be effective in approximately half of the treated patients (28). Defibrotide might be a potential treatment option for PSVD, while ursoodeoxycholic acid (UDCA) may prevent the development of SOS after HSCT (29). Furthermore, another report presented successful cases of partial splenic embolization among patients with thrombocytopenia associated with oxaliplatin-induced PSVD (30). However, even though several potential treatments for PSVD have been described, as mentioned above, they are insufficient. It will be necessary to accumulate additional evidence in future studies concerning possible effective treatments for PSVD.

In conclusion, we encountered a case of oxaliplatin-induced portal hypertension that developed six years after oxaliplatin administration and led to esophageal varices and refractory ascites. Clinical physicians should be aware of the possibility of oxaliplatin-induced portal hypertension and note that it can develop several years after discontinuation of the drug.

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

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