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Effectiveness of Intraoperative Indocyanine Green Fluorescence-Navigated Surgery for Superior Mesenteric Vein Thrombosis that Developed During Treatment for Intravascular Lymphoma: A Case Report

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 70-year-old
Final Diagnosis: Intravascular lymphoma • superior mesenteric vein thrombosis
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: Small intestine resection
Specialty: Gastroenterology and Hepatology

Objective: Unusual setting of medical care

Background: Superior mesenteric vein thrombosis (SMVT) is a relatively rare form of acute abdominal disease; less than 0.1% of laparotomy surgeries are performed for SMVT. In the presence of severe intestinal ischemia or necrosis caused by SMVT, immediate surgical intervention is required. Macroscopic diagnosis of intestinal viability is sometimes difficult; its over-resection may carry the risk of short bowel syndrome. A near-infrared fluorescence imaging system with indocyanine green (ICG) has recently been developed for intraoperative, real-time evaluation of intestinal perfusion. This is the first report on the use of ICG fluorescence imaging during surgery for intestinal ischemia caused by venous thrombosis.

Case Report: A 70-year-old man presented with a general feeling of weariness. On examination, he was diagnosed with intravascular large B cell lymphoma. R-CHOP therapy was initiated. On day 3 of initial R-CHOP therapy, the patient experienced sudden severe abdominal pain while in the hospital. Contrast-enhanced computed tomography revealed SMVT and loss of contrast effect in the small intestine. We diagnosed small bowel necrosis caused by SMVT, and exploratory laparotomy was performed, which revealed a continuous ischemia of 150 cm. Intraoperative ICG fluorescence imaging was utilized, and the color boundary was consistent with the ischemic area detected by visualization. The necrotic small intestine was excised and anastomosed. The patient was transferred to the hematology department on postoperative day 10 with no severe complications such as anastomotic leakage or re-thrombosis, and re-embolization was not observed 6 months later.

Conclusions: Venous thrombosis should be listed as a differential diagnosis when acute abdominal disease presents during chemotherapy for malignant lymphoma. ICG fluorescence imaging may be useful in the evaluation of intestinal blood flow for venous thrombosis.

Keywords: Indocyanine Green • Lymphoma, B-Cell • Venous Thrombosis

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Background

Superior mesenteric vein thrombosis (SMVT) is a relatively rare form of acute abdominal disease; less than 0.1% of laparotomy surgeries are performed for SMVT. The etiology of SMVT can be divided into idiopathic and secondary, with approximately 80% of cases being secondary [1]. The pathophysiology of secondary SMVT encompasses several features, including reduced portal blood flow, a hypercoagulable state, and vascular endothelial injury. Intravascular lymphoma (IVL), one of the primary lymphoproliferative disorders, is a subtype of malignant lymphoma in which lymphoma cells selectively proliferate in small blood vessels of various organs. IVL accounts for less than 1% of all malignant lymphomas and can be a risk factor of SMVT [2]. In the presence of severe intestinal ischemia or necrosis, immediate surgical intervention involving intestinal resection and anastomosis is required. A near-infrared fluorescence imaging system with indocyanine green (ICG) has recently been developed for intraoperative, real-time evaluation of intestinal perfusion. It has been utilized in the field of gastrointestinal surgery as it may be useful in reducing the risk of anastomotic leakage after surgery for malignant tumors. Even in the context of benign acute abdominal diseases, there have been reports of its usefulness in intraoperative assessment of intestinal blood flow for arterial embolism, especially superior mesenteric artery (SMA) embolism and ischemia [3,4]. This is the first report on the use of ICG fluorescence imaging during surgery for intestinal ischemia caused by venous thrombosis.

Case Report

A 70-year-old man presented with a general feeling of weariness. On examination, he was 170 cm tall and weighed 79.4 kg (body mass index 27.5 kg/m^2). His lactate dehydrogenase (LDH) level was 920 U/L, and soluble interleukin-2 receptor (sIL-2R) was remarkably high at 8809 U/mL. His Child-Pugh score was 6 (non-hepatic encephalopathy; no ascites; total bilirubin, 0.97 mg/dL; albumin, 2.8 g/dL; prothrombin activity, 79%; prothrombin normalized ratio, 1.12). Tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were negative. He had diabetes mellitus (DM) and was on medication for the same.

Fluorodeoxyglucose-positron emission tomography revealed systemic proliferation, particularly in the right parietal bone, left frontal sinus, liver, bilateral humerus, and right forearm. Skin biopsy revealed CD20-positive, CD3-negative large atypical lymphocytes in blood vessels, so he was therefore diagnosed with intravascular large B cell lymphoma. Combination chemotherapy using Rituxan, Endoxan, Adriacin, Oncovin, and Predoninbut (R-CHOP) was initiated. On day 3 of initial R-CHOP therapy 1 month after the initial medical examination, the

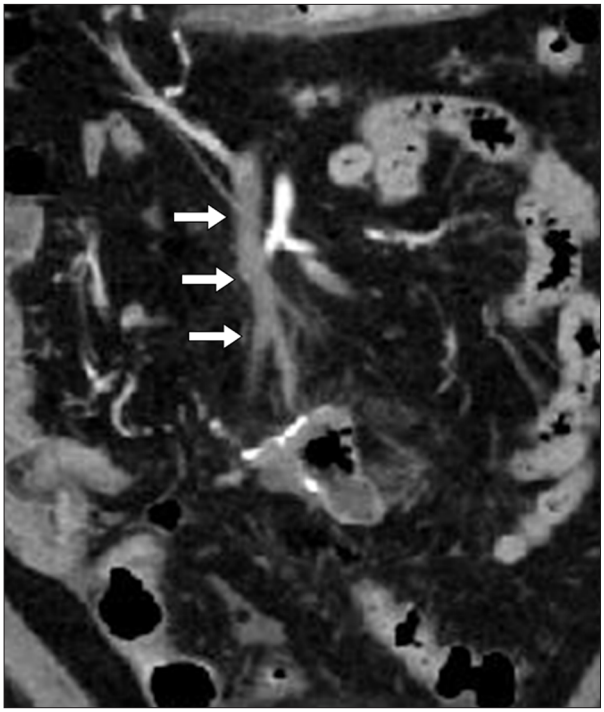

Figure 1. Contrast-enhanced computed tomography reveals thrombosis in the SMV (white arrow head).

patient experienced sudden severe abdominal pain while in the hospital. Contrast-enhanced computed tomography (CT) revealed thrombosis in the SMV and loss of contrast effect in the small intestine (**Figure 1**). A diagnosis of small bowel necrosis caused by SMVT was made, and exploratory laparotomy was performed, which revealed a continuous ischemia of 150 cm. Intraoperative ICG fluorescent imaging was done using the VISERA ELITE II system (OLYMPUS), with 10 mg ICG (2.5 mg/mL) injected via the peripheral vein. The non-ischemic areas had a luminous mild green color. Approximately 30 s after the injection, the color boundary was consistent with the ischemic area detected by visualization (**Figure 2**). Equipment and chemical preparation for the ICG fluorescence method only took several minutes. The necrotic small intestine was excised, and anastomosis was performed.

The surgery duration was 101 min, with estimated blood loss of 80 mL, and no intraoperative complications. Permanent pathological examination confirmed ischemic necrosis due to thrombosis in the artery, with no signs of lymphoma in the samples. Immediately after surgery, anticoagulation therapy using continuous heparin infusion was started. On postoperative day (POD) 5, the heparin infusion was switched to oral apixaban. From POD 6 to 9, administration of granulocyte colony stimulating factor (G-CSF) was needed for neutropenia, which seemed to be caused by the R-CHOP therapy. The patient was transferred to the hematology department on POD 10 with no severe complications such as anastomotic leakage or

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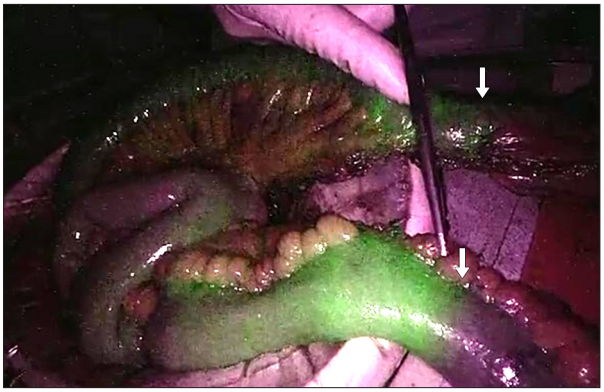

Figure 2. Indocyanine green (ICG) fluorescent imaging reveals a color boundary consistent with the ischemic area detected by visualization (white arrow).

re-thrombosis, and re-thrombosis was not observed 6 months after the surgery.

Discussion

SMVT is a relatively rare form of acute abdominal disease; less than 0.1% of laparotomy surgeries are performed for SMVT [5]. The etiology of SMVT can be divided into idiopathic and secondary, with approximately 80% of cases being secondary [1]. The pathophysiology of secondary SMVT encompasses several features, including reduced portal blood flow, a hypercoagulable state, and vascular endothelial injury. A hypercoagulable state may be due to inherited prothrombotic disorders; factor II gene mutation, factor V Leiden mutation, anti-thrombin III deficiency, protein C or S deficiency, and acquired thrombophilic disorders; paroxysmal nocturnal hemoglobinemia, primary myeloproliferative disorders, hyperhomocysteinemia, antiphospholipid syndrome, thrombin-activatable fibrinolysis inhibitor gene mutation, and increased factor VIII levels [6]. A previous report proposed that 2.7% of SMVT cases (3/111) were caused by malignant lymphomas [7]. IVL, one of the primary lymphoproliferative disorders, is a subtype of malignant lymphoma in which lymphoma cells selectively proliferate in small blood vessels of various organs. IVL accounts for <1% of all malignant lymphomas [2] and can be a risk factor of SMVT. In fact, there was a case report of acute abdomen due to thrombosis of the mesenteric artery and vein, which required small bowel resection in a patient with intravascular large B cell lymphoma [8].

In addition, chemotherapy with antitumor drugs can further enhance the tendency toward thrombosis. The reasons for this are, firstly, the release of tissue factors following the destruction of tumor cells, along with the vascular endothelium damage caused by antitumor drugs; and secondly, clotting tendencies are specific adverse effects of certain antitumor drugs, particularly thalidomide and its derivatives, all-trans retinoic acid (ATRA), tranexamic acid, and L-asparaginase [9]. In this case, no drugs associated with specific thrombogenic tendencies were used, but the possibility of tissue factor release could not be ruled out.

In very recent portal vein thrombosis, thrombolytic therapy may be performed by indirect intra-arterial infusion into the SMA or by direct catheter insertion into the portal vein, either through the transhepatic or transjugular approach, which can improve regional clot lysis [10-13]. Selective catheterization of the SMA and intra-arterial infusion of thrombolytic drugs, such as urokinase, streptokinase and recombinant tissue plasminogen activator have been shown to have adequate results [14,15]. However, in the presence of severe intestinal ischemia or necrosis, immediate surgical intervention involving intestinal resection and anastomosis is required. Macroscopic diagnosis of intestinal viability is sometimes very difficult, and over-resection, particularly when the residual bowel is less than 200 cm, carries the risk of short bowel syndrome [16]. Methods of assessing bowel viability during surgery include intraoperative angiography, laser Doppler flowmetry, and fluorescence angiography [17-20]. Moreover, the rate of correct diagnosis of laparoscopic observation in acute abdominal diseases, including SMA embolisms, is 81-93%, and is considered to be as accurate as that of open surgery [21,22]. A near-infrared fluorescence imaging system with ICG has recently been developed for intraoperative, real-time evaluation of intestinal perfusion. This technology is reasonably priced, easily reproducible, and not time-consuming. Intraoperative ICG fluorescence imaging is beneficial in several surgical fields (foregut, hepatobiliary, plastic surgeries, and transplant) [23,24]. It has also been utilized in the field of gastrointestinal surgery as it can be useful in reducing the risk of anastomotic leakage during surgery for malignant tumors [25]. There have been cases in which the initial resection line, which was demarcated by visual inspection and palpation, required shifting toward either the oral or anal side for viable intestine following the use of ICG fluorescence imaging. Even in the context of benign acute abdominal diseases, there have been reports of its usefulness in intraoperative assessment of intestinal blood flow for arterial embolism, especially SMA embolism and ischemia, to prevent short bowel syndrome due to over-resection [3,4]. There have no reports on the use of ICG fluorescence imaging during surgery for intestinal ischemia caused by venous thrombosis. In the present case, the intestinal resection line was determined by visualization, palpation, and ICG fluorescence imaging, and there were no postoperative anastomotic leakages, suggesting that ICG fluorescence imaging may be useful in the evaluation of venous thrombosis. Importantly, ICG contains iodine, which can cause allergic reactions in patients with iodine hypersensitivity. Cases of intraoperative anaphylactic shock following ICG administration have been reported at a frequency

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ranging from 0.05% to 0.07% [28-30]. Furthermore, equipment and chemical preparation for the ICG fluorescence method only require several minutes; extension of surgery time for use of the ICG method would therefore be acceptable. The use of ICG may prevent both anastomotic leakage due to inadequate resection and short bowel syndrome arising from over-resection.

Conclusions

Venous thrombosis should be listed as a differential diagnosis when acute abdominal disease is present during chemotherapy for malignant lymphoma. ICG fluorescence imaging can be useful in the evaluation of intestinal blood flow for venous thrombosis.

Acknowledgements

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Conflict of Interests

None.

Abbreviations

SMVT – superior mesenteric vein thrombosis; **ICG** – indocyanine green; **SMV** – superior mesenteric vein; **POD** – postoperative day; **IVL** – intravascular lymphoma; **SMA** – superior mesenteric artery; **LDH** – lactate dehydrogenase; **sIL-2R** – soluble interleukin-2 receptor; **CEA** – carcinoembryonic antigen; **CA19-9** – carbohydrate antigen 19-9; **DM** – diabetes mellitus; **G-CSF** – granulocyte colony stimulating factor; **ATRA** – all-trans retinoic acid.

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