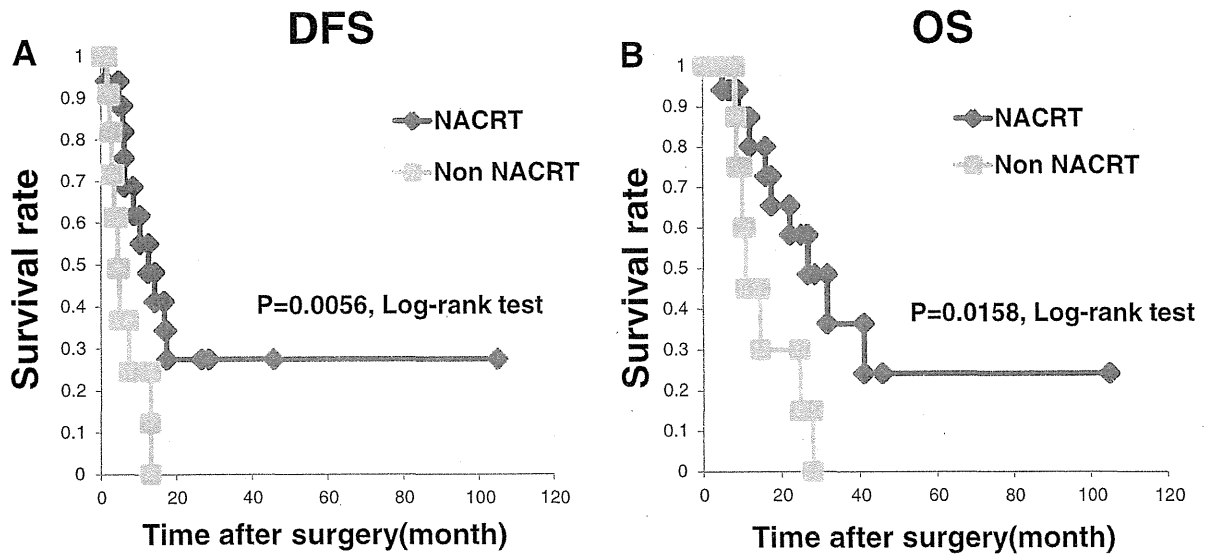

Figure 2 Prognostic analysis of NACRT. A: Disease-free survival (DFS) of the patients stratified by the treatment method. The DFS of the patients with NACRT was significantly better than that of the non-NARCT patients (median DFS 12.6 mos for the NACRT group vs. 4.3 mos for the non-NACRT group; P = 0.0056). **B**: Overall survival (OS) for patients stratified by the treatment method. The OS of the NACRT group was significantly better than that of the non-NACRT group (median OS 26.8 mos for the NACRT group vs. 10.8 mos for the non-NACRT group; P = 0.0158).

as a CSC marker in cancers of the head and neck [22], breast [30] and prostate [31]. Similar to our results, Tajima et al. [10] showed the frequencies of CD44- positive cases were increased after gemcitabine-based neoadjuvant chemotherapy and concluded CD44- positive cells were chemoresistant in pancreatic cancer.

ALDH1 is an intracellular enzyme involved in retinoic acid, and it has been characterized as a CSC marker in different types of cancer of the head and neck [22], breast [30], lung [32], and colon [33]. In pancreas cancer, ALDH1 was associated with high turmorigenic cancer cells [34], and protects pancreatic cancer cells from

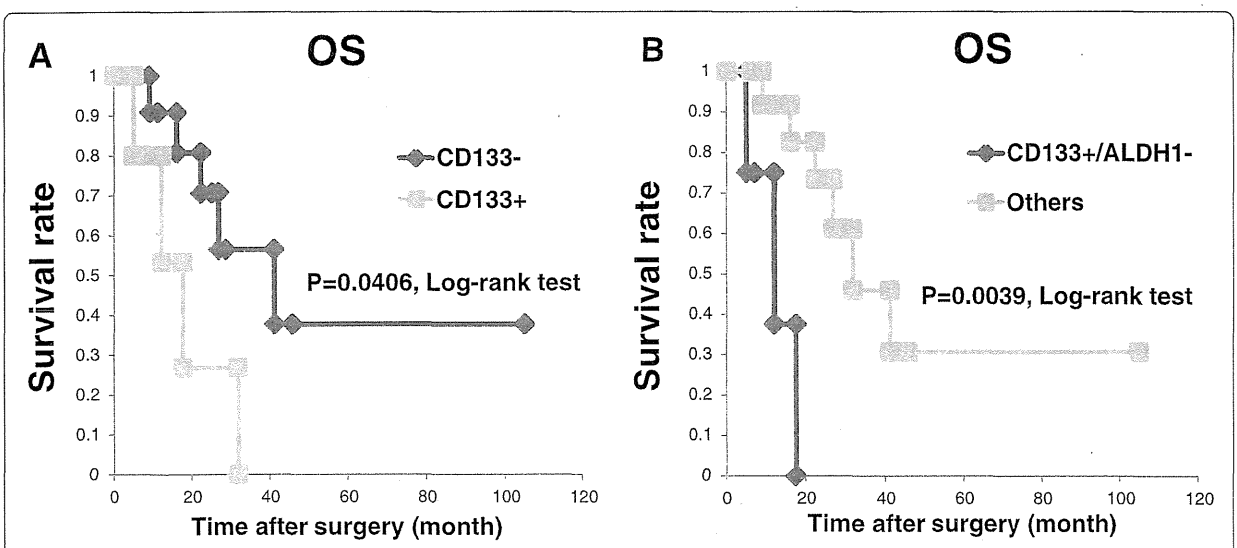

Figure 3 Positive CD133 expression correlates with poor prognosis in the NACRT group. A: The OS of the NACRT patients stratified by their CD133 expression status. The OS of the patients with positive CD133 expression was significantly worse than that of the patients with negative CD133 expression (median OS 17.6 mos for those showing positive CD133 expression vs. 41.1 mos for those showing negative CD133 expression; P = 0.0406). **B**: Overall survival for the NACRT patients stratified by their CD133 and ALDH1 expression status. The OS of the patients with CD133+/ALDH1− was significantly worse than that of the patients with the other markers' expressions (median OS 12.1 mos for those showing CD133+/ALDH1− vs. 31.8 mos for those showing the other markers' expressions; P = 0.0039).

chmothrapy-induced cell death [35]. Two immunohistochemical studies examined the prognostic significance of ALDH1 in pancreatic cancer, but their results conflict, perhaps because the evaluation methods differed (using tissue microarrays [15] vs. whole-mount tissue slides [16]). Moreover, there were also no immunohistochemical studies about the chemoradiation resistance. Our finding is a first report indicating that ALDH1-positive cells might be resistant to chemoradiation therapy.

On the other hand, our results have also showed that CD133-positive cells may have chemoradiation susceptibility. CD133 is a cell surface glycoprotein that has been widely used as a marker for CSCs in various types of solid tumours and it has been believed that the CD133-positive cells had chmoradiation resistance [36].

One of the reasons why our data are different from published literature may be related to the antibodies we used and the number of cases, as well as to the influence of NACRT.

Also, this conflicting result can be explained under the assumption that not all CD133-positive cells are characterized as the same cell population, and not all these cells are resistant to chemoradiation. It may be that clonogenicity varies among cancer cells bearing distinct cancer stem cell markers, and so does their sensitivity to altered fractionation. In fact, it has been reported regarding the susceptibility of CD133-positive cells for chemoradiation in gastric [37] and colon cancer [38]. Additional study in larger cohorts and basic research are required to clarify this result.

Regarding the prognosis in the NACRT group, there are no significant differences in DFS (Additional file 1: Figure S1) and OS (Additional file 2: Figure S2) in almost all CSCs marker expect CD133. Despite CD133-positive cells apparently may have chemoradiation susceptibility, this data is consistent with the results that the expression CD133-positive cells in pancreatic cancer without NACRT related to poor clinical outcome [12,13]. Thus, CD133 expression has a possibility to influence the prognosis on pancreatic cancer regardless of the presence or absence of NACRT. Furthermore, our results suggest that NACRT might reduce the frequency of CD133 expression and subsequently result in patient's favorable prognosis in pancreatic cancer.

With respect to the CSCs markers expression, there were almost all no associations among the co-expression of different CSCs markers used in our study. Interestingly, although its significance is unknown, CD133 expression was inversely related to ALDH1 expression after NACRT, and the patients with positive CD133 and negative ALDH1 expression had a markedly poorer OS rate compared to the other patients. A similar result was reported for head and neck cancer treated with chemoradiation, in which positive CD44 and negative ALDH1 expression was linked with significantly poor prognosis [22]. ALDH1 is an enzyme that is required for the conversion of retinol (vitamin A) to retinoic acids and retinoic acid is related to the differentiation of cells, so inhibition of ALDH1 delayed the differentiation of human hematopoietic stem cells [39].

We speculate the expression of ALDH1 is also related to the differentiation of cancer stem cells.

As a result, combination with several stem cell markers may become a more powerful prognosis prediction marker.

Conclusions

We found that CD44- and ALDH1-positive expressions were more common in the NACRT group than in the non-NACRT group, whereas CD133-positive expression was found to be common in the non-NACRT group. In addition, CD133+ expression and CD133+/ALDH1− expression were associated with a poor outcome in the NACRT group. CD133 and ALDH expressions are useful predictors of prognosis in PA patients who have received NACRT.

However, our results were obtained in a small cohort (n = 28) of PA patients, and additional studies in larger cohorts are required to clarify the predictive significance, if any, of the expressions of CSCs markers in pancreatic cancer.

Additional files

Additional file 1: Figure S1. Significance of the CSCs markers in Disease-free survival (DFS) in the NACRT group. The DFS of the NACRT patients stratified by their CSCs marker expression status. There are no significant differences in DFS in all CSCs marker.

Additional file 2: Figure S2. Significance of the CSCs markers in Overall survival (OS) in the NACRT group. The OS of the NACRT patients stratified by their CSCs marker expression status. There are no significant differences in OS in almost allCSCs marker expect CD133.

Abbreviations

CSCs: Cancer stem cells; NACRT: Neoadjuvant chemoradiotherapy; PA: Pancreatic adenocarcinoma; EPCAM: Epithelial cell adhesion molecule; ALDH1: Aldehyde dehydrogenase 1; GEM: Gemcitabine; Gy: Grays; IRS: Immunoreacting score; DFS: Disease-free survival; OS: Overall survival.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TM carried out immunohistochemistry, evaluated the immunostaining, performed statistical analysis and drafted the manuscript. HK designed the study, analyzed the data and helped to revise the draft. TM confirmed the diagnosis of the samples, evaluated the immunostaining, and helped to revise the draft. YT participated in the follow-up study. YH carried out immunohistochemistry and participated in the design of the study. TK and YM participated in the design of the study and analyzed the data. AT supervised research, analyzed the data and edited the paper. All authors read and approved the final manuscript.

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CASE REPORT

Hand-assisted laparoscopic splenectomy for sclerosing angiomatoid nodular transformation of the spleen complicated by chronic disseminated intravascular coagulation: A case report

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Keywords
Disseminated intravascular coagulation; laparoscopic splenectomy; sclerosing angiomatoid nodular transformation

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Abstract

A 36-year-old man who presented with a nosebleed and anemia was referred to our hospital. Laboratory test results showed platelet depletion, decreased levels of fibrinogen, and increased fibrinogen degeneration products. CT showed a 13-cm splenic tumor. T_2-weighted MRI revealed a high-intensity mass. We preoperatively diagnosed splenic hemangioma with chronic disseminated intravascular coagulation and scheduled an operation to relieve the disseminated intravascular coagulation. We also performed hand-assisted laparoscopic splenectomy to ensure easy handling of the splenomegaly. The resected specimen microscopically consisted of hemorrhages and hemangiomatous lesions, and multiple angiomatoid nodules were scattered and separated by fibrocollagenous stroma with inflammatory cells. Three types of vessels (capillaries, sinusoids and small veins) were contained in the angiomatoid nodules, and the pathological diagnosis was sclerosing angiomatoid nodular transformation. The results of this case suggest that we should consider sclerosing angiomatoid nodular transformation in the differential diagnosis of patients with splenic tumors, as sclerosing angiomatoid nodular transformation with hemangiomatous features may cause coagulation disorders for which splenectomy should be performed.

Introduction

The incidence of primary splenic tumors is very low. Primary splenic tumors can be categorized as those having a lymphoid origin and those having a vascular origin. Sclerosing angiomatoid nodular transformation (SANT) is a non-neoplastic vascular lesion characterized by well-circumscribed multiple angiomatoid nodules surrounded by concentric rings of collagen fibers with inflammatory cells (1). Most SANT cases are incidentally diagnosed by imaging studies, and abdominal pain is the predominant symptom (2). However, SANT rarely causes coagulation disorders.

Here we report a case of SANT complicated by chronic disseminated intravascular coagulation (DIC) treated with hand-assisted laparoscopic splenectomy (HALS).

Case Presentation

A 36-year-old man presented at a hospital with a recurrent nosebleed. Laboratory tests indicated mild anemia (hemoglobin, 12.8 g/dL), platelet depletion (93×10^3/μL), decreased fibrinogen concentration (111 mg/dL), and elevated fibrinogen degeneration products (33.4 μg/mL). The prothrombin time-international normalized

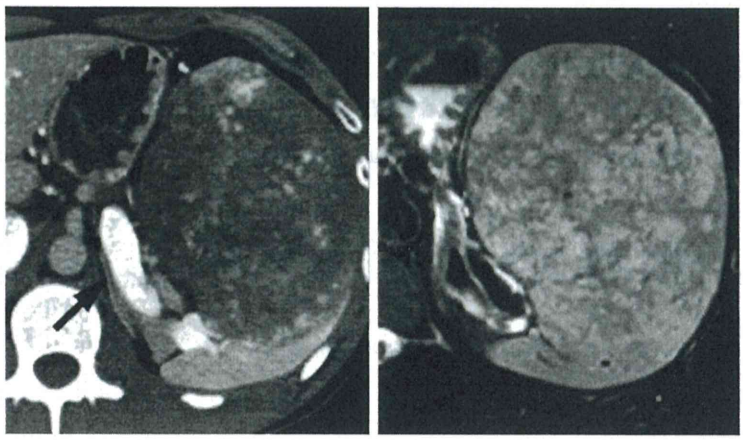

Figure 1 (a) Abdominal CT showing an enhanced splenic tumor with a gradual centripetal fill-in pattern and dilated splenic vein (arrow). (b) T_2-weighted MRI showing a high-intensity splenic tumor.

ratio was normal (1.05). An abdominal CT scan revealed an enhanced splenic tumor (13 cm in diameter) that showed peripheral globular discontinuous enhancement with a gradual centripetal fill-in pattern on delayed imaging (Figure 1a). The splenic and portal veins were dilated because of tumor-dependent blood flow. MRI indicated a low- and high-intensity splenic tumor on T_1- and T_2-weighted images, respectively (Figure 1b). The initial diagnosis was a splenic hemangioma causing chronic DIC. The patient was referred to our hospital (Hokkaido University Hospital, Sapporo, Japan), and surgical treatment was recommended because only spelectomy can relieve DIC. We planned to perform HALS for the splenomegaly. We preoperatively administered fibrinogen and nafamostat mesilate to prevent intraoperative bleeding. We also administered a pneumococcal vaccine to prevent the development of a post-splenectomy infection.

Under general anesthesia, the patient was placed in the right lateral decubitus position. One trocar was placed at the left side of the umbilicus for the camera port. Three trocars were placed at the right side of the umbilicus, the epigastric portion, and the left subcostal margin for the forceps and other instruments. Tissue dissection was performed using laparoscopic coagulation shears and a vessel sealing device at 8 mmHg under pneumoperitoneum. The splenomegaly made it difficult to mobilize the spleen (Figure 2a). A GelPort (Applied Medical, Rancho Santa Margarita, USA) for hand access was placed through an 8-cm midline incision. After hand-assisted mobilization of the spleen, the vascular pedicle was divided at the level of the splenic hilum by linear stapling devices, with attention paid to not injure the pancreatic tail. Then, the spleen was placed in a retrieval bag. After being morcellated inside the retrieval bag, the spleen was taken out through the midline incision. The operative duration was 213 min, and the blood loss was 15 mL. The spleen weighed 692 g.

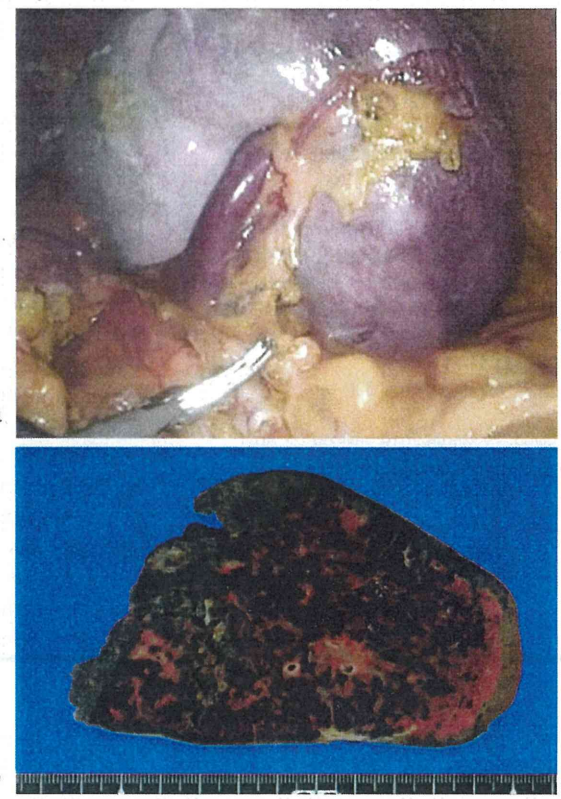

Figure 2 (a) The splenic tumor with splenic vein dilatation viewed laparoscopically. (b) Cut surface of the morcellated resected specimen showing a rust-colored tumor with white fibrous tissue.

A well-circumscribed, unencapsulated, rust-colored tumor with white fibrous scars was seen in the resected specimen (Figure 2b). Histological analysis indicated that this tumor mainly consisted of hemorrhage, hemangiomatous vascular proliferation, and sclerotic fibrous tissue (Figure 3a). Some parts of this tumor had

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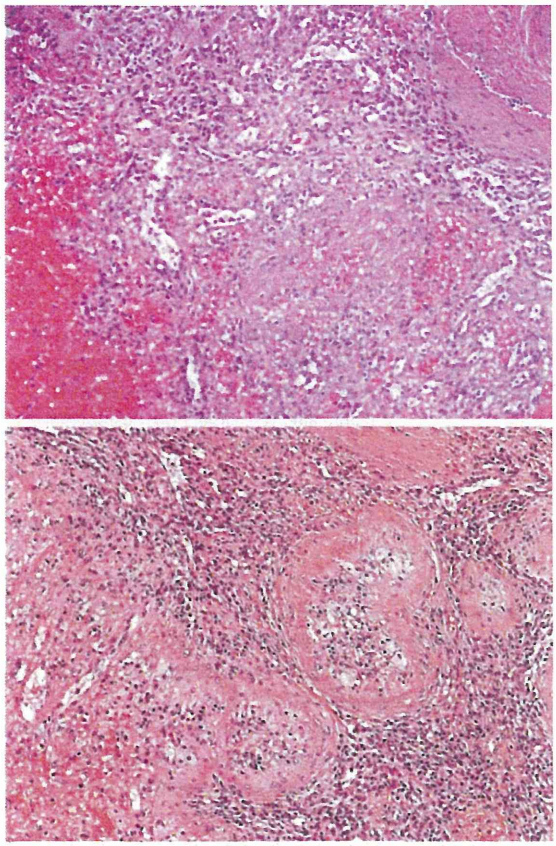

Figure 3 (a) The tumor contains hemorrhages (lower left side), hemangiomatous lesions (center), and sclerotic fibrous tissue (upper right side) (hematoxylin–eosin staining, ×100). (b) The multiple angiomatoid nodules are surrounded by fibrocollagenous stroma infiltrated with inflammatory cells (hematoxylin–eosin staining, ×100).

multiple angiomatoid nodules separated by fibrocollagenous stroma mixed with plasma cells and lymphocytes (Figure 3b). In these angiomatoid nodules, three vascular components were identified on immunohistochemical study: capillaries ($CD34^+/CD8^-/CD31^+$), sinusoids ($CD34^-/CD8^+/CD31^+$) and small veins ($CD34^-/CD8^-/CD31^+$). The pathological diagnosis was SANT.

On postoperative day 2, abdominal CT revealed portosplenic vein thrombosis (PSVT) because of sluggish blood flow in the residual splenic vein and postsplenectomy thrombocytosis. The PSVT responded to anticoagulant therapy, and the patient was discharged 16 days after the operation. At his 1-month follow-up visit, portal vein patency was maintained. Platelet count, fibrinogen levels, and fibrinogen degeneration products levels were normalized ($488 \times 10^3/\mu L$, 205 mg/dL, and 3.1 μg/mL, respectively) (Figure 4), and the patient's bleeding tendency resolved.

Discussion

Benign vascular tumors of the spleen include hemangiomas, lymphangiomas, hamartomas, littoral cell angiomas, hemangioendotheliomas and inflammatory pseudotumors. SANT, which was first described by Martel *et al.* in 2004, is a benign vascular lesion that is characterized by well-circumscribed multiple angiomatoid nodules surrounded by fibrocollagenous stroma with inflammatory cells (1). The angiomatoid nodules consist of capillaries ($CD34^+/CD8^-/CD31^+$), sinusoids ($CD34^-/CD8^+/CD31^+$) and small veins ($CD34^-/CD8^-/CD31^+$), which are normally found in splenic red pulp. The pathogenesis of SANT is uncertain. It is considered a de novo lesion, a transformation of the splenic red pulp in response to stromal proliferation, a clinical form of immunoglobulin G4-related sclerosing disease, and the final stage of inflammatory pseudotumor or hematoma (1,3).

SANT is usually asymptomatic, and approximately 50% of cases are discovered incidentally. In patients with symptoms, abdominal pain is the predominant symptom, followed by a palpable mass (2). The present case is the first report of SANT presenting with chronic DIC. Chronic DIC might occur because platelets and fibrinogen are trapped and consumed in the widespread hemangiomatous vascular bed of this tumor, just like in Kasabach–Merritt syndrome. We could not find trapped platelets or microthrombi in any of the small vessels of the SANT lesion microscopically, and the coagulation–fibrinolysis balance seemed to shift to fibrinolysis.

Typical imaging features of SANT include a solitary, well-demarcated mass; early peripheral enhancement and delayed centripetal enhancement on dynamic study; and hypointensity on T_2-weighted MRI images (4). In our case, the enhanced pattern of the tumor resembled that of hemangioma, and the tumor was hyperintense on T_2-weighted images due to extensive hemangiomatous lesions in addition to the angiomatoid nodules. A radiating central scar, which reflects fibrous tissue of the SANT, on the delayed phase on T_1-weighted dynamic MRI is one of the characteristic signs (5), but it is not always observed (4).

Splenectomy should be performed if SANT causes any symptoms. Even if the lesion is found incidentally, we believe that surgical resection is appropriate because it is difficult to make a precise diagnosis of SANT in preoperative imaging studies. There are few reports on laparoscopic approaches for SANT (6,7). HALS is an effective technique to facilitate the surgical management of massive splenomegaly because it is easy and atraumatic for manipulating enlarged spleens (8). We also selected HALS for this patient because of the splenomegaly. In one randomized control study comparing a HALS group and

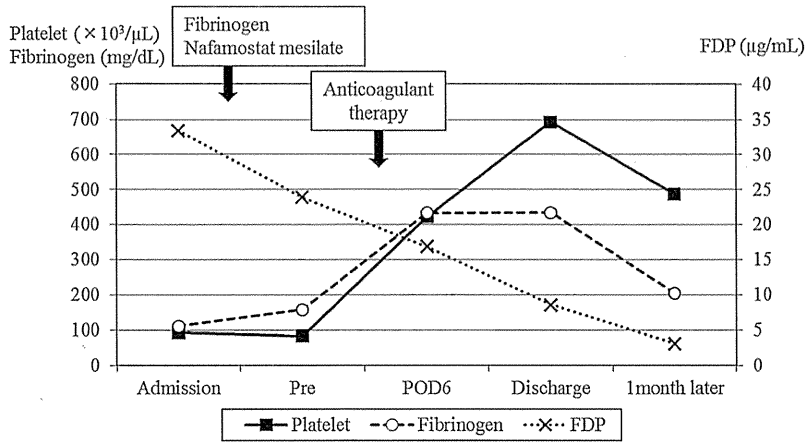

Figure 4 Time course of platelet count, fibrinogen, and fibrinogen degradation products (FDP). All factors normalized 1 month after discharge. POD, postoperative day; pre, previous day.

an open splenectomy group, the main advantages of HALS were shorter incision, less postoperative pain, and shorter hospital stay (9). The complication rate was similar between groups.

PSVT is a post-splenectomy complication. The incidence of PSVT in patients undergoing laparoscopic splenectomy is approximately 20% if routine postoperative image surveillance is performed (8,10). Splenomegaly is a significant predictive factor of postoperative PSVT (10). Appropriate anticoagulation therapy can relieve PSVT.

In summary, we reported a case of SANT complicated by DIC treated with HALS. We should consider SANT in the differential diagnoses of patients with splenic tumors. SANT with hemangiomatous features in particular may cause coagulation disorders, for which splenectomy should be performed.

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CASE REPORT

Laparoscopic gastrectomy after coronary artery bypass grafting using the right gastroepiploic artery: A report of two cases

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Abstract

We successfully executed laparoscopic distal gastrectomy in two patients who had previously undergone coronary artery bypass grafting using the right gastroepiploic artery (RGEA). A laparoscopic distal gastrectomy preserving the RGEA graft with Roux-en-Y reconstruction was performed on two men, one 69 years of age and one 73 years of age. In both cases, the RGEA was used during coronary artery bypass grafting for the posterior descending branch. The laparoscopic approach helped avoid injury to the RGEA associated with laparotomy and retractor placement. In addition, the locations of ports necessary for laparoscopy were situated away from the RGEA graft and from adhesions resulting from bypass. Using typical laparoscopic settings, we were able to easily identify the grafted RGEA. Thus, laparoscopic distal gastrectomy is not only less invasive than open gastrectomy procedures, but it is also associated with a lower risk of injury to the RGEA graft.

Introduction

Coronary artery bypass grafting (CABG) for ischemic heart disease often uses the right gastroepiploic artery (RGEA) next to the internal thoracic artery. However, problems can occur in patients who previously underwent CABG using the RGEA if they require a gastrectomy for gastric cancer in the future. Because the RGEA with should be harvested along with lymph nodes during all gastrectomies for gastric cancer, percutaneous coronary intervention or an additional bypass surgery using another vessel is necessary before gastrectomy with resection of a patent RGEA graft. In addition, in cases in which the RGEA is preserved, lymph node dissection must be carefully performed to avoid graft injury. There have been some reports of gastrectomy performed after CABG using the RGEA, but there are no reports involving laparoscopic distal gastrectomy (LDG) (1–6).

We performed LDG in two patients after CABG using the RGEA. Herein, we report our operative results.

Case Presentation

Case 1

The patient was a 73-year-old man (height, 165.5 cm; weight, 68.7 kg; BMI, 25.1 kg/m^2). In December 2004, he underwent a four-vessel CABG in which the posterior descending branch was grafted using the RGEA. In December 2011, he presented at our hospital (JA Sapporo Kosei Hospital, Sapporo, Japan) with tarry stools and was diagnosed as having early gastric cancer located in the lower anterior part of the stomach. In February 2012, endoscopic submucosal dissection was performed; according to pathologic diagnosis, both horizontal and vertical margins were positive. Based on the pathological results, additional surgery was required. Coronary CT angiography confirmed the patency of all grafts, and an echocardiogram showed that the patient's left ventricular ejection fraction was 70.0%. When surgery was performed, cardiologists and cardiovascular surgeons were on standby in case of accidental injury to the RGEA.

LDG was performed with Roux-en-Y reconstruction, with the patient receiving continuous nicorandil

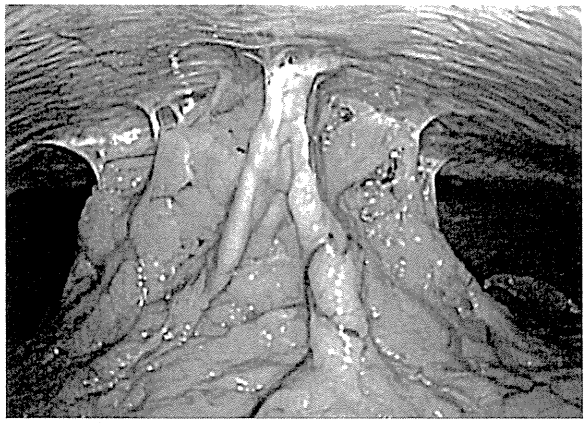

Figure 1 Overview of upper abdominal space in case 1.

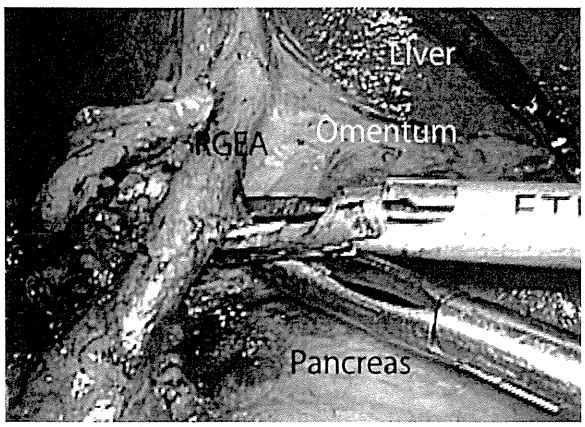

Figure 2 Skeletonization around RGEA in case 1. RGEA: right gastroepiploic artery.

injection to prevent RGEA spasm. An endoscopic surgeon with qualifications from the system established by the Japan Society for Endoscopic Surgery was the operator. The first view of the abdominal cavity revealed adhesions between the omentum and abdominal wall in the upper middle abdominal area (Figure 1). The RGEA, ascending along the falciform ligament and abdominal wall, was revealed as the adhesiotomy progressed. Skeletonization of the RGEA was easily performed with an ultrasonically activated device (USAD) (Figure 2). Fine vessels distributed from the RGEA over the pylorus and bulbs were also easily dissected using the USAD. Prophylactic no. 6 lymph node dissection preserving the RGEA was possible without injury to the RGEA or intraoperative arrhythmias. Additional lymph node dissection was performed in accordance with common LDG procedures. The Roux-en-Y method, in which gastrojejunostomy is performed away from the RGEA, was chosen for reconstruction. The

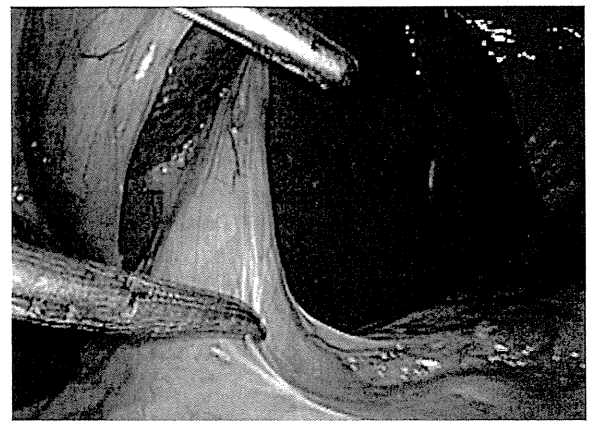

Figure 3 Overview of upper abdominal space in case 2.

operative time was 180 min, and blood loss was 11 mL. The patient was discharged on postoperative day 10 without any complications.

Currently, the patient is alive without any signs of recurrence or heart failure. The resected specimen was pathologically diagnosed (diameter, 5.4 × 3.1 cm; tub1, T1a, n0, ly0, v0, stage IA) according to the Japanese classification of gastric carcinoma (7).

Case 2

The patient was a 69-year-old man (height, 166.7 cm; body weight, 67.2 kg; BMI, 24.2 kg/m^2). In May 2006, he underwent a four-vessel CABG and left ventricular reconstruction surgery. The posterior descending branch was grafted using the RGEA. In November 2012, he presented at our hospital (JA Sapporo Kosei Hospital, Sapporo, Japan) with bloody vomiting and was diagnosed as having type 3 advanced gastric cancer located in the middle part of the lesser curvature of the stomach. The cancer was preoperatively diagnosed as stage IIB (4 × 3 cm in diameter, SS, N0) by gastroendoscopy, barium meal examination and CT. Cholecystolithiasis was also observed on echogram examination. Coronary CT angiography confirmed the patency of the other three grafts, but the RGEA bypass was closed. The patient's left ventricular ejection fraction was 46.9% according to echocardiogram results. When surgery was performed, cardiologists and cardiovascular surgeons were on standby in case of accidental injury to the RGEA.

Laparoscopic surgery was planned at the patient's request. LDG with Roux-en-Y reconstruction and cholecystectomy were performed. The same surgeon who operated in case 1 performed the procedure. The RGEA was covered with the omentum and was ascending on the lateral segment of the liver (Figure 3). The

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