of 91.13 g/L (reference range, 7–17 g/L), and IgG4 of 31.5 g/L (reference range, 0.08–1.4 g/L). Serum protein electrophoresis revealed that the percentage of γ protein was elevated at 61.8% (reference range, 9.1%–24.0%). No monoclonal proteins were found in the blood or urine immunofixation electrophoresis. Bone marrow aspiration and biopsy revealed no malignancy. In contrast to hypergammaglobulinemia, hypoalbuminemia with serum albumin of 21 g/L (reference range, 35–52 g/L) was detected, which might result in edema. Our pancreatic CT image showed a swollen pancreatic head, an atrophied pancreatic tail, and an unevenly thickened pancreatic duct and common bile duct with local stenosis (Fig. 1E). Multiple enlarged lymph nodes with elevated metabolism (standardized uptake value [SUV], 7.9), swollen bilateral lacrimal glands and submandibular glands (SUV, 3.3), and enlarged pancreatic head and thickened lower common bile duct (SUV, 3.0) were revealed in the positron emission tomography/CT.

Therefore, the patient was suspected as having possible IgG4-related AIP. Because he refused to undergo lymph node biopsy or pancreatic fine-needle aspiration to exclude malignancy, he was prescribed as prednisone 0.6 mg/kg per day for 1 month as empirical therapy and tapered down to 5 mg/d as maintenance therapy. As a result of the glucocorticoid response, the level of IgG4 decreased from 31.5 g/L to 6.25 g/L, the globulin decreased from 111 g/L to 31 g/L, and the IgG decreased from 91.13 g/L to 17.79 g/L. In the meantime, the albumin level increased, and edema disappeared. The following imaging showed that the enlarged pancreatic head and thickened bile duct normalized (Figs. 1F, G), as well as the enlarged lymph nodes. The patient was, and is still currently, being followed up.

The specific characteristic of our AIP patient is extreme hyperglobulinemia, which is uncommon. In the study by Wang et al[3] including 215 patients, the mean levels of IgG and IgG4 were 23.0 and 15.2 g/L, respectively. Based on the previous research,[4,5] high level of serum IgG4 might be related to hematologic manifestations, good response to glucocorticoid, and a high rate of relapse. According to the study from Kim et al[6] in 2010, the glucocorticoid dosage for inducing remission was 30 to 40 mg/d for 1 to 2 months, and remission maintenance was needed to prevent relapse with a dosage of 5 to 10 mg/d for at least 6 months in patients who did not achieve complete remission. Furthermore, immunosuppressive agents such as azathioprine could be used for relapsed patients with AIP. Our patient with high level of serum IgG and IgG4 had good response to glucocorticoid and no evidence of relapse with 5 mg/d prednisone for maintenance of remission.

Another special characteristic is longtime course of disease. Autoimmune pancreatitis is one type of chronic pancreatitis, but it is unknown how long the natural course is. Our patient was 78 years old and was found to have a swollen pancreatic head nearly 10 years before being diagnosed and treated with glucocorticoid. In the study by Lin et al with 118 Chinese AIP patients, the mean age at diagnosis was 53.1 years, and the mean disease duration was 26.8 months.[7] Therefore, our patient with a 108-month disease course is truly unusual.

From this AIP case, we illustrated that a high level of serum IgG4 might indicate good sensitivity to glucocorticoid, and elderly patients might endure a long course of disease without symptoms. Although this patient has a good condition at present, we still should be aware of the relapse of disease and the risk of hematologic malignancy in the follow-up.

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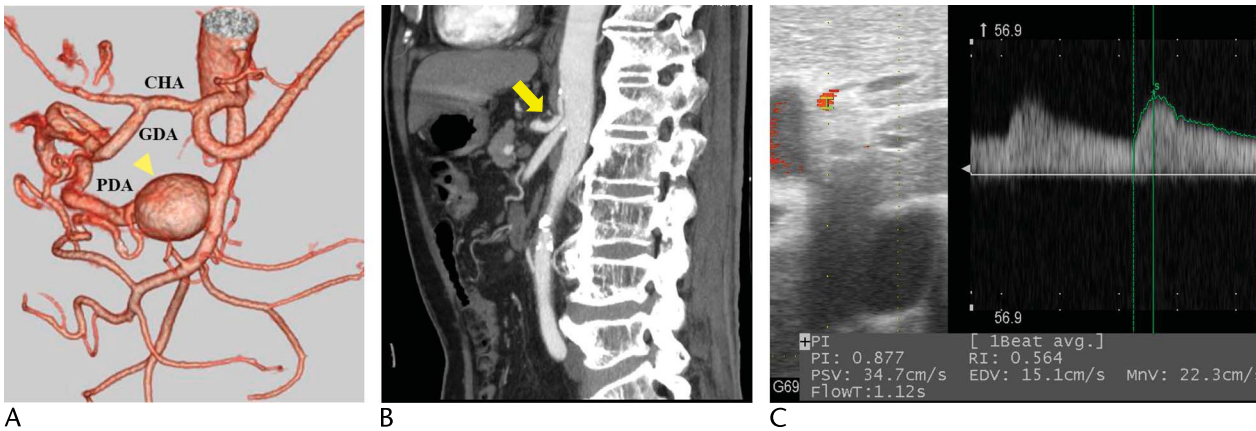
Surgical Treatment of Pancreaticoduodenal Artery Aneurysm Due to Median Arcuate Ligament Syndrome for Which Intraoperative Doppler Ultrasonography Was Beneficial
A Case Report

To the Editor:

Although the first case of a pancreaticoduodenal artery aneurysm (PDAA) was reported by Ferguson[1] in 1895, most of the publications since then have been case reports. Pancreaticoduodenal artery aneurysms are rare and account for 2% of all visceral aneurysms.[2] Almost half of all PDAAs are associated with celiac axis stenosis (CAS)[2] and median arcuate



A B C

FIGURE 1. Three-dimensional volume–rendered images and sagittal maximum-intensity projection computed tomography angiogram. A, The PDAA (33 mm in diameter, arrow head). B, Acute angulation and narrowing of the proximal celiac axis has caused poststenotic dilatation, creating a "hooked" appearance (arrow). C, After the MAL was released, the peak systolic velocity of intrahepatic blood flow was restored to 34.7 cm/s during the GDA clamping. The RI was also restored to 0.56. CHA indicates common hepatic artery; PDA, pancreaticoduodenal artery.

ligament (MAL) compression, which creates a "hooked" appearance that is characteristic of MAL syndrome (MALS), noted in 10% to 30% of such cases.[3] In these cases, division and resection of the PDAA during surgery can cause ischemic complications, including anastomotic dehiscence, abscess formation, and liver failure. Hence, a gastroduodenal artery (GDA) clamping test is mandatory for evaluating hepatic arterial blood flow before resection. Poor hepatic arterial perfusion during the GDA clamping necessitates MAL release to restore the arterial blood flow. To the best of our knowledge, few reports have described quantitative criteria for hepatic arterial blood flow restoration. Herein, we report a case of a PDAA with MALS, surgically treated after quantitatively evaluating the intrahepatic arterial blood flow using intraoperative Doppler ultrasonography.

CASE REPORT

A 79-year-old Japanese man was referred to us with anemia. Colonoscopy revealed an ascending-colon cancer (type 2, stage IIIB). Moreover, a sagittal maximum-intensity projection computed tomography angiogram and 3-dimensional volume–rendered imaging identified a PDAA (33 mm in diameter) with MALS (Figs. 1A, B). Resections of the PDAA and the ascending-colon cancer were planned. The GDA clamping test was performed by measuring the intrahepatic arterial blood flow using Doppler ultrasonography before resection (Fig. 1C). The peak systolic velocity of the intrahepatic arterial flow was 33.2 cm/s before resection; it decreased to 27.9 cm/s after the GDA clamping, suggesting the need for MAL release to minimize the risk of ischemic complications. After the MAL release, the peak systolic velocity of the intrahepatic arterial blood flow, while continuing GDA clamping, increased to 34.7 cm/s, and the resistive index (RI) was maintained within the appropriate range at 0.56. Therefore, revascularization or reconstruction of the common hepatic artery was deemed unnecessary, and the PDAA and ileocecal resections were performed. The postoperative course was uneventful. Postoperative abdominal computed tomography at 1 year 9 months showed no recurrence of the PDAA or CAS.

DISCUSSION

Pancreaticoduodenal artery aneurysms are usually asymptomatic, and a ruptured aneurysm is often fatal if untreated. The aneurysmal size is unrelated to the risk of rupture, so all PDAAs should be treated, regardless of size.[3]

Two treatment approaches, surgical resection or embolization, are currently followed. Embolization is less invasive but may cause intraoperative aneurysmal rupture or ischemic injury due to the absence of major collateral vessels.[4] In addition, without CAS repair, new aneurysms or recurrence may occur. At present, no consensus exists in the literature on the management of PDAAs with MALS. Importantly, although surgical resection of PDAAs is curative, they involve the risk of life-threatening ischemic complications.[5,6]

Doppler ultrasonography can be used to assess the blood flow qualitatively and quantitatively during liver transplantation.[7,8] The normal Doppler waveform of a hepatic artery shows a rapid systolic upstroke after continuous diastolic flow. Acceleration time and RI can serve as indicators of hepatic arterial blood flow. Acceleration time, the time from the end of diastole to the first systolic peak, should be less than 80 ms; RI, calculated as (peak systolic velocity – end diastolic velocity)/peak systolic velocity, should be between 0.5 and 0.7.[7] A tardus-parvus waveform pattern, with an acceleration time greater than 80 ms and a RI less than 0.5, indicates insufficient arterial flow due to hepatic artery stenosis during liver transplantation.[8] In our case, although the acceleration time was not measured during the clamping test, the peak and mean velocities and RI were decreased reproducibly in comparison with the baseline levels.

A reproducible decrease in hepatic arterial blood flow during the GDA clamping test necessitates MAL release. Moreover, recovery to baseline blood flow levels after MAL release eliminates the need for additional hepatic artery reconstruction. Because PDAAs with MALS are rare, the criteria may appropriately be determined using liver transplant surgery data. Large studies on hepatic artery assessment using Doppler ultrasonography are needed to define the threshold for MAL release or hepatic artery reconstruction during the resection of PDAAs with MALS.

CONCLUSIONS

The intraoperative quantitative evaluation of intrahepatic arterial blood flow using Doppler ultrasonography enabled successful resection of the PDAA because of MALS.

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Validation of the Novel Eighth Edition of American Joint Committee on Cancer Staging Manual

An In-depth Analysis for Nonfunctional Pancreatic Neuroendocrine Neoplasms

To the Editor:

Pancreatic neuroendocrine neoplasms (pNENs) are a group of tumors with a varied behavior, course, prognosis, and increasing prevalence, which consist of functional tumors (F-pNENs) and nonfunctional ones (NF-pNENs).[1] Because of the rarity and heterogeneity, the ability to stage pNENs into prognostic groups has always been challenging. In 2010, the World Health Organization classified pNENs into well-differentiated pancreatic neuroendocrine tumors (G1/G2 pNETs) and poorly differentiated pancreatic neuroendocrine carcinoma (G3 pNECs).[2] Also in 2010, the American Joint Committee on Cancer (AJCC) started to introduce a tumor-node-metastasis (TNM) system for pNENs (ie, seventh edition),[3] which derived from the staging algorithm for pancreatic exocrine adenocarcinomas (pEACs) and was proven to be convenient but oversimplified.[4–7]

In 2017, AJCC incorporated some major changes in its eighth staging manual for both pEACs and pNENs, in which the new staging system for pNENs should only be applied to G1/G2 pNETs, whereas G3 pNECs should be classified according to the new one for pEACs.[8] We have evaluated the applications of the AJCC eighth staging manual for G3 pNECs[9] and G1/G2 pNETs.[10] However, both studies enrolled a large portion of F-pNENs, especially insulinoma, which inevitably increased the heterogeneity of pNENs and influenced the accuracy of related analysis. Moreover, we have also demonstrated that F-pNENs and NF-pNENs should better be staged according to a different TNM system.[7] In order to more accurately validate the AJCC eighth staging manual, we comprehensively analyzed the distribution characteristics and survival differences of AJCC eighth and seventh staging systems for both G1/G2 NF-pNETs and G3 NF-pNECs.

Our analysis enrolled 230 consecutive patients with NF-pNENs, including 152 cases with G1/G2 NF-pNETs, and 78 with G3 NF-pNECs (Fig. 1). For G1/G2 NF-pNETs, according to the definitions of different staging systems, 52 patients were grouped in AJCC eighth edition stage I, 40 in stage II, 41 in stage III, and 19 in stage IV, with an estimated 5-year overall survival (OS) of 81.9%, 76.9%, 34.9%, and 19.2%, respectively. Survival comparisons between AJCC eighth edition stage I and stage II ($P = 0.017$), or stage III ($P < 0.001$), or stage IV ($P < 0.001$), between stage II and stage III ($P = 0.008$), or stage IV ($P < 0.001$), between stage III and stage IV ($P = 0.044$) were all statistically significant. What's more, there were, respectively, 71, 42, 20, and 19 classified from AJCC seventh edition stage I to stage IV, with an estimated 5-year OS of 79.7%, 61.6%, 39.3%, and 19.2%, respectively. Survival of patients in AJCC seventh stage I was notably better than that of patients in stage II ($P = 0.016$), or stage III ($P < 0.001$), or stage IV ($P < 0.001$), as well as those in stage II compared with stage IV ($P = 0.001$), while comparisons between stage III and stage II or stage IV were not significant ($P = 0.111$, $P = 0.133$, respectively).

For G3 NF-pNECs, there were 17 patients defined in the AJCC eighth edition as stage I, 19 in stage II, 24 in stage III, and 18 in stage IV, with an estimated 5-year OS of 66.6%, 34.6%, not applicable (NA), and NA, respectively. Survival comparisons between AJCC eighth edition stage I and stage II ($P = 0.035$), or stage III ($P < 0.001$), or stage IV ($P < 0.001$), between stage II and stage III ($P = 0.044$), or stage IV ($P < 0.001$), between stage III and stage IV ($P = 0.027$) were significant as well. Moreover, 23, 21, 16, and 18 patients were, respectively, defined from AJCC seventh edition stage I to stage IV, with an estimated 5-year OS of 57.2%, 44.2%, NA, and NA. Patients in AJCC seventh stage I present a notably longer survival than those in stage II ($P = 0.021$), or stage III ($P < 0.001$), or stage IV ($P < 0.001$), as well as those in stage II compared with stage IV ($P = 0.001$), whereas comparisons between stage III and stage II or stage IV were not significant ($P = 0.079$, $P = 0.126$; respectively).

For both G1/G2 NF-pNETs and G3 NF-pNECs, the AJCC seventh edition system failed to discriminate the survival differences when comparing stage III with stage II or stage IV. Using Cox proportional hazards model, the AJCC eighth and seventh staging system was demonstrated to be independent predictors for the OS of NF-pNENs. The Harrell's C-index of AJCC eighth system for G1/G2 NF-pNETs and system for G3 NF-pNECs was both statistically larger than that of AJCC seventh system, indicating a more informative ability about prognostic accuracy.

In conclusion, based on the results of previous studies,[9,10] our analysis revealed the 2 AJCC eighth staging systems were also

